STUDY NAME

CLINICAL INVESTIGATION PLAN

VERSION: 1.0 (11/15/19)

CIP No.: HC#1902

IU IRB #: 1910647251

Study Title:
Medela INVIA Motion NPWT system for prophylactic use on surgical incision after cesarean delivery

Study Device	**Medela INVIA Motion**
Manufacturer	Medela AG Lättichstrasse 4b, 6340 Baar Switzerland
PI contact	Name: Methodius Tuuli, MD, MPH Title: Professor, Vice Chair for Obstetrics Phone: 678 558 2874 Email: mtuuli@iu.edu

REVISION HISTORY

Version	Date	Summary
1.0	***15 November 2019***	***Approved version for study initiation***

Table of contents

Site Principal Investigator Statement

I have read the protocol entitled, "Medela INVIA Motion NPWT system for prophylactic use on surgical incision after cesarean delivery" and I agree to participate and comply with the procedures and requirements as outlined in this protocol. I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor.

_____ _____

Signature of Principal Investigator Date

1 Synopsis

Study title	Short Title: **The Invia Motion at Cesarean Study** Full Title: Medela INVIA Motion NPWT system for prophylactic use on surgical incision after cesarean delivery
Coordinating investigator(s)	Methodius Tuuli, MD, MPH Division of Maternal Fetal Medicine Department of Ob/Gyn Indiana University School of Medicine 550 N. University Boulevard, UH 2440 Indianapolis, IN 46202
Study objective	To assess patient centered outcomes of the Medela INVIA Motion prophylactic NPWT system at cesarean delivery
Study design	A two-center feasibility case series. This study is designed to be performed in accordance with the Declaration of Helsinki, ISO 14155:2011(E), ICH-GCP, Local and National Regulations.
Study duration	First subject enrolled: **December, 2019** Expected time of enrolment: **6 Months** Last Follow Up Visit: **May, 2019** (1 month follow up)
Study sites	Up to 2 sites
Study population	Women undergoing cesarean delivery
Inclusion criteria	1. Scheduled/non-labor or unscheduled/labor cesarean delivery 2.Gestational age ≥ 23 weeks
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
Primary endpoint	Patient centered outcomes • Pain scores (scale of 0 - 10) at discharge and postoperative day 30 (+/-2 days) • Patient satisfaction scores (scale of 0 - 10) at discharge and postoperative day 30 (+/- 2 days) • Patient satisfaction with aesthetic appearance (scale of 0 - 10) at postoperative day 30 (+/- 2 days)
Secondary endpoint	Efficacy outcome • Composite wound complication including wound infection, would separation, seroma, antibiotics prescribed for presumed SSI within 30 days (+/- 2 days) Safety outcomes: • Skin blistering, allergic reaction, wound bleeding
Study device	Invia Motion
Reference device	Not applicable

2 Contact information

Contacts could be updated during the study independently from the CIP.

Coordinating investigator(s)	
Company name: Indiana University Address: Department of Obstetrics and Gynecology 550 N. University Boulevard, UH 2440 Indianapolis, IN 46202	Name: Methodius Tuuli, MD, MPH Title: Professor, Vice Chair for Obstetrics Phone: 678 558 2874 Fax: 317 944 7417 Email: mtuuli@iu.edu

3 Participating institutions

Participating institutions could be updated during the study independently from the CIP.

Principal investigator(s)	**Participating institution**
Methodius Tuuli, MD, MPH Department of Obstetrics and Gynecology 550 N. University Boulevard, UH 2440 Indianapolis, IN 46202	IU Health Methodist Hospital
Methodius Tuuli, MD, MPH Department of Obstetrics and Gynecology 550 N. University Boulevard, UH 2440 Indianapolis, IN 46202	Eskenazi Hospital

4 Abbreviations

SSI	Surgical Site Infection
NPWT	Negative Pressure Wound Therapy
HAI	Hospital Associated Infection

5 Introduction

Surgical site infections (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]

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.[6-16] Three brands of a modified, single-use, battery-powered, portable NPWT devices Prevena™ (KCI USA, San Antonio, TX), PICO™ (Smith & Nephew, Hull, UK) and Invia Motion (Medela) have been 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.[17 - 21] 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.[22]

Increasing data suggest potential efficacy of prophylactic NPWT for prevent SSI and other wound complications after cesarean. This is supported by a recent systematic review and meta-analysis which included use of the PICO or Prevena, but was limited by the inclusion of studies with small sample sizes or retrospective design [23]. Two large retrospective studies are underway to define the role of prophylactic NPWT at cesarean. However, none of the studies to date have included use of the Medela Invia Motion device. This study is a prospective case series to assess patient centered outcomes of the Medela INVIA Motion prophylactic NPWT system at cesarean delivery

6 Study device(s)

This study will be a prospective study involving the use of 30 FDA-approved Invia Motion devices.

6.1 Study device description

The Invia Motion NPWT system is comprised of the Invia Motion pump, Invia Motion Canister/Tubing Set with 150ml capacity, Invia Motion Power Supply and Invia Motion Carrying Case. Additionally, several separately cleared accessories and kits are compatible with the Invia Motion NPWT System.

The Invia Motion pump is a rechargeable battery powered, maintenance-free pump for Negative Pressure Wound Therapy which incorporates a DC-motor with membrane aggregate power actuation in its housing. A user friendly interface, based on 4 tactile buttons and a display, facilitates use and information handling. The Invia Motion NPWT pump provides treatment status through a display and acoustic signals. It is a single patient use pump which provides continuous or intermittent operation and multiple negative pressure selection options. The Invia Motion NPWT pump is portable and its rechargeable battery duration generally exceeds 10 hours, supporting various activities of the patient during the day. Acoustic and optical signals are triggered for variances from the set values as well as for faults.

The Invia Motion NPWT system provides convenience to the patient and provider. Every patient receives their own personal pump for the duration of therapy. The small size and

light weight promote mobility for the patient. The pump is quiet and replacement of the canister is quick and easy.
The Invia Motion NPWT system comes with a discrete carrying case and battery autonomy of up to 10 hours to promote mobility of the patient.

6.2 Accessory(ies) description

The Quick-connector interface provides easy and secure attachment between the dressing tubing and the canister tubing.

Invia Foam Dressing Kit with FitPad suction interface consists of:

- Charcoal foam, manufactured using a reticulated polyether and polyurethane hydrophobic material
- FitPad suction interface with Quick-connector
- Transparent film (one or more pieces depending on the kit size)
- All components are packaged together and sterilized using ethylene oxide (EO)
- Invia Foam Dressing Kit is available in four sizes: Small, Medium, Large and X-Large

Invia Gauze Dressing Kit with FitPad suction interface consists of:

- Sterile Kerlix Gauze with PHMB
- Sterile Saline
- Sterile packaged FitPad suction interface with Quick-connector
- Sterile packaged Transparent film (one or more pieces depending on the kit size)
- All components placed together in a plastic bag

Y-connector: Allows treatment of two wound sites on the same patient with a single device.

Transparent film (single sterile item) available as a separate item. Size is 26cm x 32cm.

Invia Silverlon NPWT Antimicrobial Wound Contact Dressing. Provides a barrier to bacterial penetration using silver ions activated by moisture delivered in the dressing which can help reduce infection. Available in two sizes:

- 4” x 5” (10 x 12 cm)
- 5” x 8” (12 x 20 cm)

Not all accessories will be used on all enrolled patients.

6.3 Study device intended use

Invia Motion Devices

The Invia Motion NPWT system is intended to be used by healthcare professionals or adequately trained lay users. Healthcare professionals are responsible to train lay users according to the patient instructions for use and explain all related safety information.

Intended patient population

The Invia Motion NPWT system is intended to be used on patients only exhibiting conditions as described in the indications for use. The device has not been studied in pediatric patients.

Intended environment

The Invia Motion NPWT system is intended for use in acute, extended and home care settings.

Indications for use
The Invia Motion Negative Pressure Wound Therapy (NPWT) system is indicated for patients who would benefit from a suction device (NPWT) as when used on open wounds it creates an environment that promotes wound healing by secondary or tertiary (delayed primary) intention by preparing the wound bed for closure, reducing edema, promoting granulation tissue formation and perfusion, and by removing exudate and infectious material. When used on closed surgical incisions, the Invia Motion NPWT system is also intended to manage the environment of surgical incisions that continue to drain following sutured or stapled closure by maintaining a closed environment and removing exudate via the application of NPWT.

The Invia Motion NPWT system is appropriate for the following indications:
– Acute or subacute wounds
– Chronic wounds
– Dehisced wounds
– Pressure injuries, Pressure ulcers
– Diabetic/Neuropathic ulcers – Venous insufficiency ulcers – Traumatic wounds
– Partial thickness burns
– Flaps and grafts
– Closed surgical incisions

Contraindications
The Invia Motion NPWT system is contraindicated in the presence of:
– Necrotic tissue with eschar present – Untreated osteomyelitis
– Non-enteric and unexplored fistulas – Malignancy in the wound
– Exposed vasculature
– Exposed nerves
– Exposed anastomotic site of blood vessels or bypasses – Exposed organs

Dressing Kits
The Invia Foam Dressing Kit with FitPad is intended for use in conjunction with the Invia Motion and Invia Liberty NPWT systems. The Invia Motion and Invia Liberty NPWT systems are intended for use in acute, extended and home care settings. Users are directed to the Invia Motion and Invia Liberty NPWT system labeling for additional safety information and instruction for use. To help ensure safe and effective use, the Invia Foam Dressing Kits with FitPad are to be used only with the approved therapy units.
The components of the Invia Foam Dressing Kit with FitPad are packaged sterile and are for single use only. Do not use if sterile package is damaged or opened prior to use. To apply Invia Foam Dressing Kit with FitPad, use clean/aseptic or sterile techniques in accordance with local protocol.
Important: Failure to consult a physician and carefully read and follow all therapy unit and dressing instructions for use and safety information prior to each use may lead to inadequate performance of the product and/or potential for serious or fatal injury. Do not adjust therapy unit settings or use unit without directions from or supervision by the prescribing physician.

The Invia Foam Dressing Kit with FitPad in conjunction with Invia Motion and Invia Liberty NPWT systems is indicated for patients who would benefit from a suction device (NPWT) as when used on open wounds, it creates an environment that promotes wound healing by secondary or tertiary (delayed primary) intention by preparing the wound bed for closure, reducing edema, promoting granulation tissue formation and perfusion, and by removing exudate and infectious material.
When used on closed surgical incisions, the Invia Foam Dressing Kit with FitPad is also intended to manage the environment of surgical incisions that continue to drain following sutured or stapled closure by maintaining a closed environment and removing exudate via the application of Negative Pressure Wound Therapy.

The Invia Foam Dressing Kit with FitPad is appropriate for use for the following indications:

- Acute or sub-acute wounds
- Chronic wounds
- Dehisced wounds
- Pressure injuries, Pressure ulcers
- Diabetic/neuropathic ulcers
- Venous insufficiency ulcers
- Traumatic wounds
- Partial thickness burns
- Flaps and grafts
- Closed surgical incisions

6.4 Procedure

Primary or repeat cesarean delivery

6.5 Training

The Invia Motion Endure NPWT system is an equivalent system to NPWT devices widely used at this Facility.

Onsite, face-to-face training will be provided by Medela representatives to research staff who will be involved in the study.

Research and/or clinical staff will instruct the patient on what to do during the treatment. Patient will be provided with Invia Motion Endure NPWT system Patient IFU and NPWT APP.

Research and clinical staff trained by Medela representatives will be allowed to train any additional staff for the study.

6.6 Study device management

6.6.1 Device complaints/malfunction of device

Complaints are any deficiencies with regards to the study device, instructions for use, operator's manual and other product related documentation. Device complaints may or may not involve a clinical event/in this case an adverse device effect to the patient in which case the definitions in the section of adverse event reporting of this clinical investigation plan shall also apply.

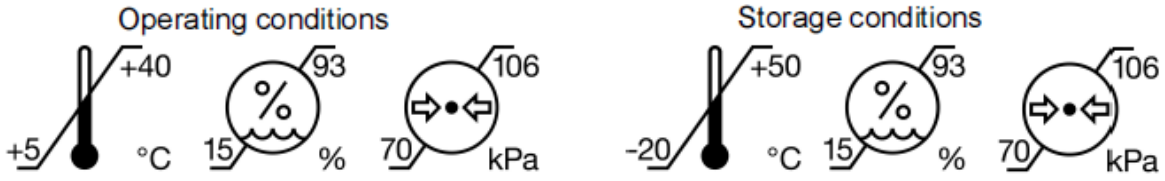
6.6.2 Reporting of complaints

Any complaints on the device, instructions for use, operator's manual and other product related documentation shall be reported to the CRA using the appropriate reporting forms. Whenever possible in case of malfunction of the study device or part of study device, the product in question shall be returned to the Sponsor for investigation. The appropriate procedure for such return shall be provided by the Sponsor prior to starting the clinical investigation.

6.6.3 Inventory and accountability records

Adequate records of study product and disposition will be maintained by the research staff at both study sites. The purpose of these records is to ensure regulatory authorities that the study product will not be distributed to any person who is not a study subject under the terms and conditions set forth in the protocol. The study product is to be prescribed by the Investigator or designees and may not be used for any purpose other than that described in this protocol. At study completion, all study products must be returned to Medela USA.

6.6.4 Device storage
Devices will be stored in a secure storage location at the site.



6.6.5 Device return
Upon completion of the study, all unused devices must be returned to Medela USA according to the local agents' instruction.

7 Risk analysis
7.1 Risks
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. 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.[24, 25] Moreover, adverse events noted with NPWT after cesarean were minor and comparable in frequency to standard dressing.[26]

7.2 Benefits
The study is not designed to provide direct benefits to research participants. Nonetheless, if our hypothesis that women will have lower rates of SSIs after cesarean with use of prophylactic NPWT than with standard care is correct, then patients will have the benefits lower rates of SSIs. More importantly, results from this study have the potential to improve outcomes for women undergoing cesarean delivery.

7.2.1 Risk-to-benefit rationale
Because the anticipated risk to participants is minimal, the risk-benefit ratio is very favorable.

8 Investigational plan
8.1 Study objectives
To assess patient centered outcomes of the Medela INVIA Motion prophylactic NPWT system at cesarean delivery.

8.2 Study hypotheses
We test the hypothesis that the Medela INVIA Motion prophylactic NPWT system will be feasibly used at cesarean delivery with significant patient satisfaction.

8.3 Claims to verify
Feasibility of the Medela INVIA Motion prophylactic NPWT system at cesarean delivery with significant patient satisfaction.

8.4 Risks to assess
<10% device related adverse events including skin blistering, allergic reaction and wound bleeding.

8.5 Study design
This study will be a two center case series of women undergoing caesarean delivery conducted at two medical centers in Indianapolis, Indiana.
All patients meeting inclusion criteria will be included. All enrolled patients will receive the Medela INVIA Mation prophylactive NPWT device.

8.6 Primary Endpoint
Patient centered outcomes
- Patient satisfaction scores (scale of 0 - 10) at discharge and postoperative day 30 (+/- 2 days)
- Pain scores (scale of 0 - 10) at discharge, at removal and postoperative day 30 (+/- 2 days)
- Patient satisfaction with aesthetic appearance (scale of 0 - 10) at postoperative day 30 (+/- 2 days)

8.6.1 Secondary endpoints
Efficacy outcome
- Composite wound complication including wound infection, would separation, seroma, antibiotics prescribed for presumed SSI within 30 days (+/- 2 days)

Safety outcomes:
- Skin blistering, allergic reaction, wound bleeding

9 Subject selection
Patients will be enrolled at any time after 23.0 weeks gestation and prior to cesarean

9.1 Inclusion criteria
1. Scheduled/non-labor or unscheduled/labor cesarean delivery
2. Gestational age ≥ 23 weeks

9.2 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

9.3 Withdrawal criteria and procedure
Patients will be withdrawn from the study for any of the following reasons:
1. Patient requests early discontinuation.
2. Patient undergoes removal of the study device
3. Patient is lost to follow up.

The patient can leave the investigation at any time, at the patient’s request. The reason for withdrawal will be investigated and carefully documented in the Patient’s Medical file and the appropriate section of the Case Report Form. When a patient withdraws or is withdrawn from the study, the final evaluation and the follow up will be performed as completely as possible. In addition, any comments (spontaneous or elicited) or complaints made by the patient or any other physician not related to the investigation but taking care of the patient

subsequently will be carefully recorded in the Patient's Medical File and related section of the Case Report Form.

9.4 Patient Identification and Confidentiality

Patients will be identified on all CRFs by a unique number. CRFs are confidential documents and will only be available to the sponsor (including sponsor delegates, like CRAs), the Investigator, the investigation statistician, and if requested to the advisory committee and regulatory authorities. The Principal Investigator for each centre will maintain as part of the investigation file a list identifying all patients entered into the trial.

10 Enrollment and Procedures

Patients will be enrolled at any time after 23.0 weeks gestation and prior to cesarean delivery. Enrollment activities may occur at prenatal appointments or upon admission to the Labor and Delivery unit. 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 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 (see Flow Chart below).

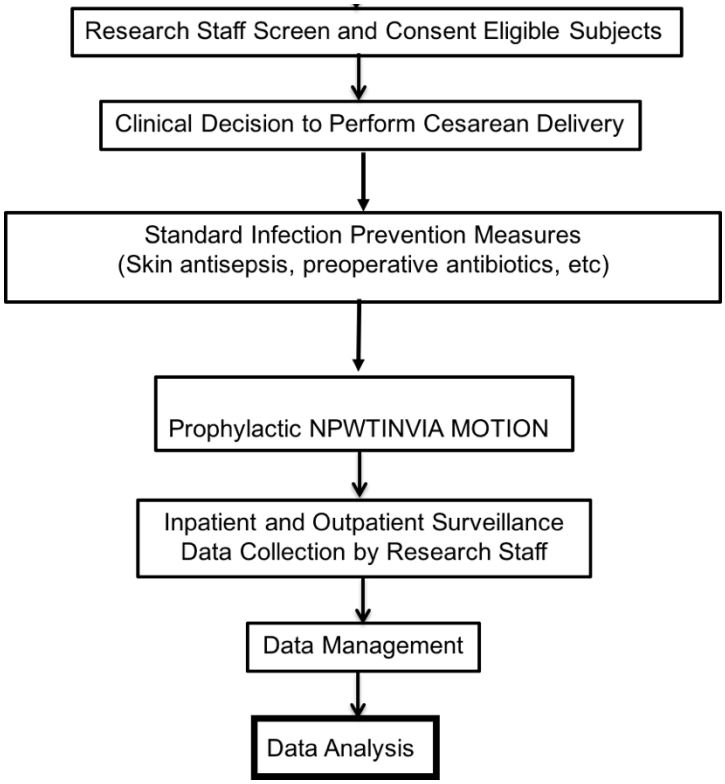
10.1 Enrollment

Patients will be considered enrolled in the study once they have provided documented consent. Consent from patients will be obtained in a private setting, such as a quiet conference area or the patient's private room. All subjects will be provided a copy of the signed informed consent form to take home. The informed consent process will be documented. There will be no randomization. All patients enrolled will receive the Medela INVIA Motion system.

10.2 Data collection

We will collect detailed antepartum, intrapartum, and postpartum information from study participants into a comprehensive database. 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 Indiana University School of Medicine

- Trained research staff in obstetric and perinatal outcomes abstraction 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
- Data on these forms devoid of personal identifiers will be securely sent to the data management center through web-based entry



10.3 Visit A: Interventional Procedure

All enrolled patients will receive the Medela INVIA Motion device placed by the patient's surgeon after the skin is closed with subcuticular suture or staples. Research staff and clinicians (labor & delivery and postpartum nurses, OR technicians, physicians, etc.) involved in the study will receive formal training on how to place and remove the prophylactic NPWT device.

10.4 Visit B: Post Procedure until Discharge

- Patients will be monitored daily while in the hospital by clinical staff and/or research staff for complications.
- The negative pressure wound therapy dressing will be removed on the day of discharge. If the patient remains hospitalized for more than 7 days, the dressing will be removed on postoperative day 7.
- 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 if these should arise.
- Research staff document inpatient course regarding SSI.
- Management of surgical site infections will follow the Practice Guidelines of the Infectious Diseases Society of America.

10.5 Visit C: Postpartum Follow Up

We will use active surveillance by research staff to ascertain surgical site infections:

- Research staff will follow-up with the research participant at time of discharge or within 48 hours post discharge (postpartum day 1-9) to assess for adverse events, assess the participant's pain, obtain their satisfaction with their dressing and aesthetic appearance of the incision.
- A $25 gift card will be disbursed to the participant.

- Research staff will call subjects on approximately postoperative day 30 (±2 days). They will ask the patient standardized questions regarding wound complications, patient satisfaction, pain and aesthetic appearance. 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.
- Medical records from postpartum clinic visits as well as records of unscheduled visits (to any hospital clinic or ER) will be sought to ascertain study outcomes.
- At the time of the subject's standard of care postpartum appointment about 4-6 weeks after inpatient hospital discharge research staff will collect information on outcomes, pain and patient satisfaction. If the patient does not attend the clinical postpartum visit, the study staff will contact the subject by phone to collect the data. A $50 gift card will be disbursed to the participant once this postpartum visit is complete.

10.5.1 Chart Abstraction

Data from the subject's prenatal record, delivery admission, and all clinic or hospital visits through the 6 week postpartum period, including medications and procedures will be collected.

10.5.2 Schedule of Events

	Enrollment	At Discharge or Within 48 hours Post Discharge (PP Day 1-9)	Post-Op Day 30 (+/- 2 days)	Post-Op ~4-6 Weeks Postpartum Visit
Eligibility	X			
Interview: Maternal Demographic Characteristics	X			
Chart abstraction: Prenatal Records		X		
Chart abstraction: Labor & Delivery		X		
Patient Satisfaction Survey		X	X	X
AE/SAE Form (if applicable)		X	X	X
Chart abstraction: Outcome Assessment		X		X
Disburse gift card		X		X
Chart abstraction: Postpartum				X

10.6 Discontinuation of subjects

If a patient develops a wound complication the Principal Investigator or patient's provider will determine if the NPWT device should be discontinued.

11 CIP administration

The Principal Investigator has a legal responsibility to the regulatory authorities to fully report all the results of sponsored clinical studies. No investigative procedures other than those stated in this CIP shall be undertaken on the enrolled clinical investigation subjects without the agreement of the IRB and PI.

11.1 Amendments

Amendments to the CIP can be made by the investigator and will be communicated to Medela AG. All changes must be documented in a signed CIP amendment. All amendments must be submitted to the IRB for approval prior to implementation.

11.2 Deviations

Any deviation from the CIP shall be recorded together with an explanation for the deviation. Medela shall be informed about deviations. Investigator is responsible for analysing them and assessing their significance.
Significant deviations defined as compromising or potentially compromising the safety of the patients, enrollment of non-eligible patients and any deviation which compromises

significantly the outcomes of the study, shall be subject to reporting by Investigator to the IRB within the appropriate deadlines indicated by the IRB.
Note: Where relevant, Competent Authorities should be informed.

11.3 Study termination

Medela AG will be allowed to monitor the progression of the clinical investigation. Medela and the Institution shall jointly agree on the scope and plan of the monitoring. If warranted, the clinical investigation may be suspended or discontinued by Investigator early if there is an observation of serious adverse reactions presenting an unreasonable risk to the clinical investigation population.
In the event of clinical investigation termination or suspension, Investigator will send a report outlining the circumstances to the IRB, and all I investigators. A suspended or terminated clinical investigation may not be re-initiated without approval of the reviewing IRB.

12 Safety

NPWT is currently used in clinical obstetric practice. Further, the adverse events reported with the use of prophylactic NPTW at cesarean were minor. 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.

12.1 Adverse Event Reporting

During the course of this clinical investigation adverse events might occur. For the purposes of this study the following categories of adverse events are relevant for reporting:

- Adverse Event of Special Interest (AESI)
- Serious Adverse Event (SAE)
- Adverse Device Effect (ADE)
- Serious Adverse Device Effect (SADE)

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.
- Patients will be scheduled for standard of care follow-up with their provider at 1-2 weeks and 4-6 weeks postpartum. Research staff will review the subject's EMR after 6 weeks postpartum.
- Medical records will be sought for any patient or provider-reported complications.

12.2 Adverse Events of Special Interest (AESI)

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 Adverse Events of Special Interest (AESI) defined below will be recorded on the CRFs and in the subject's chart.

For this study, AESIs refer to:

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

Any current condition that is recorded as a pre-existing condition in the medical history, unless there is a change in nature, severity, or degree of incidence, is not an AE.

Relation to the clinical investigation device will be assessed by help of the following criteria:

- Related
- Not related

Relation to the procedure will be assessed by help of the following criteria:

- Related
- Not related

12.3 Serious Adverse Events (SAE)

A serious adverse event (SAE) is any adverse event that results in any of the following outcomes:

- Maternal death
- Serious deterioration in the health of the subject, that either resulted in
  1) A life-threatening illness or injury, or
  2) A permanent impairment of a body structure or a body function, or
  3) In-patient or prolonged hospitalization, or
  4) Medical or surgical intervention to prevent life-threatening illness or
  5) Injury or permanent impairment to a body structure or a body function

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

This also applies to adverse events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

The assessment of 'seriousness' is independent from any relation to the investigational device.

Hospitalization is defined by a medical need for in-patient hospitalization overnight. For procedures that are commonly performed in out-patient clinic but yet requires hospitalization solely based on non-medical needs (e.g. logistical reasons) this criterion could be considered

not applicable by the Investigator. Proper documentation of the reasons for decision is required in this case.

Events that are planned (e.g. elective surgery) and documented prior to clinical investigation entry will not be recorded if the procedure is performed without any complications. Medication received during this activity may be recorded.

12.4 Adverse Device Effects (ADE) & Serious Adverse Device Effects (SADE)

An adverse device effect is an adverse event related to the use of a study medical device

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition also includes any event resulting from user error or from intentional misuse of the investigational medical device.

An ADE is classified as serious if it has resulted in any of the consequence characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

If an ADE or SADE has occurred any retrievable part of the Invia® Motion™ Endure NPWT system should be returned to Medela AG for analysis. If there is also a suspected relation to accessory material (guide wire etc.) the accessory material in question should also be sent to Medela AG for analysis.

12.5 Reporting Adverse Events

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 AESIs and ADEs will be reported to the Sponsor every 6 months, and to the IRB at renewal.**
    - **SAEs and USADEs will be reported within 24 hours of discovery to the IRB and the Sponsor.**

Relationship of Reportable Events:

An Investigator must make the determination of relationship to the drug for each AESI/ADE. The relationship to the 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.

13 Data management

Qualified study staff at the investigational site will perform primary data collection. Paper source will be used to collect all subject data during the study. All study data will then be entered into REDCap in electronic case report forms (eCRFs). The investigator is responsible for the accuracy and completeness of all data on the eCRFs. Site personnel will review completed eCRFs at regular intervals throughout the study.
Information on the eCRFs will be compared for completeness, validity, and consistency 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.

The PI/data manager is responsible for providing a clean data set at the end of the clinical investigation. Queries should be resolved by the investigator or a person designated by the investigator in a timely manner. When all data is complete the database will be locked and the data analyzed.

Quality control audits of all key performance and safety data in the database will be made after 90% of all data have been entered and processed. Prior to database lock, the entire database will be re-validated to ensure that there are no outstanding errors. When all queries have been resolved, the database will be locked. Any changes to the database after that time will require joint written agreement between the PI and Sponsor.
The Investigator is responsible for reporting appropriately and in a legible manner the requested information in the CRFs.
The medical/ subject record (source document) must contain but is not limited to the following information:

- Date of informed consent
- Subject participation in the clinical investigation
- Demographics
- Dated reports of the discharge
- Documentation of medical/ surgical history and current medication
- Description of device procedure (material used, date, time, complications etc.)
- All AESI, SAE, ADE, or SADEs: Diagnosis and symptom(s), onset and end date, severity, action taken, outcome
- Concomitant medication
- Date of clinical investigation completion or withdrawal

13.1 Clinical data system management

Data will be managed at Indiana University. 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 IU. 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).

13.2 Data retention

All clinical investigation records and reports must remain on file at the clinical investigation centers for the minimum time given by the national legislation.

The investigator must contact Medela AG before destruction of any records and reports related to the clinical investigation. Medela AG must be informed if the investigator plans to leave the

clinical investigation site. In such case the site must name a new contact person before the investigator parts from the clinical investigation site.

Medela AG will retain the Trial Master File (TMF) according to national legislation and Medela AG Standard Operating Procedure (SOPs).

Medela AG is responsible for instructing all involved parties to maintain clinical investigation records according to national regulations.

14 Monitoring

Monitoring will be performed by Medela AG or by Medela AG designees and the PI to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the CIP, Declaration of Helsinki, ISO 14155:2011(E), ICH-GCP and applicable regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

The monitor will verify that records on the clinical investigation conduct and data collection are complete and present, and that the device accountability is complete

15 Statistical Analysis

Descriptive statistics will characterize the group of individuals recruited into the study. Categorical variables will be reported and proportions while continuous variables will be reported as mean and standard deviation or median and interquartile range as appropriate. The primary outcome and other categorical secondary outcomes will be reported as proportions with 95% confidence intervals. As this is a two-site trial, subgroup analyses will be performed by site as well as body mass index.

15.1 Determination of Sample Size

As this is a feasibility study, no formal sample size estimation is performed. A sample of 30 will be sufficient to test feasibility and patient reported outcomes.

16 Investigator Responsibilities

The Investigator will be able to publish and/or present the data generated from the study after mutual agreement between the Investigator and Sponsor. The Investigator will provide the sponsor with a manuscript copy of the abstract and paper at least 60 days in advance of presentation to editors for publication or presentation.

16.1 Ethics Committee Approval/IRB

The investigator/co-investigator is responsible for the submission to the central/local IRB.

The content of the submitted documents must be documented in writing. A copy of this document will be provided to Medela AG. A copy of the IRBopinion/approval together with the

list of IRB voting members will be provided to Medela AG (or designee) prior to initiating the clinical investigation at a particular site.

The investigator is obliged to submit the appropriate documentation if any necessary extension or renewal of the IRB approval has to be obtained.

The investigator must report to the IRB any new information that may affect the safety of the subjects or the conduct of the clinical investigation.

Upon completion of the clinical investigation, the investigator shall provide the IRB with a brief report of the outcome of the clinical investigation as required by the local IRB.

16.2 Study conduct

Prior to shipment of the first clinical investigation device and first implantation, the investigator must read and sign this CIP as well as the Investigator's Agreement, to document that he/she has accepted to conduct the clinical investigation according to all agreed conditions and follow the CIP.

Prior to enrolling any subjects in the clinical investigation, all national and local regulatory requirements must be fulfilled.
Each clinical investigation site must have, but is not limited to, the following documents:

- Competent authority approval, if applicable
- Ethics committee approval
- Signed investigator's agreement
- Signed and dated CVs for all investigators participating in the clinical investigation.
- Laboratory Accreditation and the normal ranges

16.3 Regulatory Reporting

The investigator is obliged to report in writing to the IRB, any Serious Adverse Event whether device related or not within the timelines required by the IRB. Investigator is obliged to report in writing to the CA if applicable, any Serious Adverse Event whether device related or not within the timelines required by the CA and inform Medela about this report.

17 Sponsor Responsibilities

Investigator is responsible to apprehend the approval from the Competent Authority (CA), if applicable, prior to any site initiation. Investigator must report to the CA any new information that may affect the safety of the subjects or the conduct of the clinical investigation and inform Medela about this report

17.1 Subject Insurance

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. Medela AG has issued clinical trial liability insurance with appropriate coverage for the continuation of the entire study.

17.2 Compliance statements

This clinical investigation is designed to be performed in accordance with the Declaration of Helsinki 2008, ISO 14155:2011(E), ICH-GCP, Local and National regulations.

Any corrections to the CIP that might become necessary to be in conformity with new standards and regulations will be issued as amendments to this CIP. This clinical investigation shall not begin until the required approvals from the IRBs and the applicable regulatory

authorities have been obtained. Any specific requirement imposed by the IRBs or the regulatory authority shall be followed.

18 Audits and inspections

An internal audit is performed by the Institution and its employees. Prior to the internal audit, Medela and the Institution shall jointly agree on the scope and plan of the audit. During the internal audit, the Institution shall gather and evaluate all records, information and documentation within the scope of the audit and, if necessary, conduct interviews with the Institution's and/or subcontractor's employees. It shall inform Medela regularly about progress and developments of the audit. At the end of the audit, the Institution shall issue a final report and hand it over to Medela.

An external audit is performed by Medela or third parties acting on behalf of Medela with confidentiality obligations, i.e. auditors and external counsel. Prior to the external audit, Medela and the Institution shall jointly agree on the scope and plan of the audit. During the external audit, the Institution has comprehensive obligations to cooperate, including but not limited to making available all records, information and documentation within the scope of the audit, handing over documents (hard copies and electronic documents) and allowing Medela or the third party acting on behalf of Medela to conduct interviews with the Institution's employees.

19 Publication policy

The Institution has the sole right to the primary presentation and publication of the Study Results, including articles, papers, posters, abstracts, presentations, etc. ("Publication"). Before Publication of the Study Results, the Institution or the Principal Investigator shall submit the manuscript to Medela and Medela shall have a period of sixty (60) days to review the proposed Publication for the disclosure of patentable inventions of interest to Medela and for any information considered proprietary or Confidential Information by Medela. If a patentable invention of interest to Medela is to be disclosed, the Publication shall be delayed to permit Medela to prepare and file a patent application in timely manner. Publication may not be delayed more than an additional ninety (90) days to permit the preparation and filing of a patent application. If proprietary or Confidential Information of Medela are in the manuscript, the Publication shall require approval by Medela before submission to the presenter or publisher. The Institution and the Principal Investigator shall have sole responsibility for the scientific content of the Publications. The Parties agree that Publications should be made in the first place in prestigious scientific periodicals (peer reviewed), in books or at congresses and conferences.

20 Bibliography

1. Anderson DJ, Podgorny K, Berrios-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 2014;35 Suppl 2:S66-88.
2. Gibbs RS. Clinical risk factors for puerperal infection. Obstetrics and gynecology 1980;55:178S- 84S.
3. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. World psychiatry : official journal of the World Psychiatric Association 2016;15:53-8.
4. Kolliakou A, Ball M, Derczynski L, et al. Novel psychoactive substances: An investigation of temporal trends in social media and electronic health records. European psychiatry : the journal of the Association of European Psychiatrists 2016;38:15-21.
5. Conroy K, Koenig AF, Yu YH, Courtney A, Lee HJ, Norwitz ER. Infectious morbidity after cesarean delivery: 10 strategies to reduce risk. Reviews in obstetrics & gynecology 2012;5:69-77.

6.Hasan MY, Teo R, Nather A. Negative-pressure wound therapy for management of diabetic foot wounds: a review of the mechanism of action, clinical applications, and recent developments. Diabetic foot & ankle 2015;6:27618.
7. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Annals of plastic surgery 1997;38:553-62.
8. Morykwas MJ, Faler BJ, Pearce DJ, Argenta LC. Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. Annals of plastic surgery 2001;47:547-51.
9. Schintler MV. Negative pressure therapy: theory and practice. Diabetes/metabolism research and reviews 2012;28 Suppl 1:72-7.
10. Timmenga EJ, Andreassen TT, Houthoff HJ, Klopper PJ. The effect of mechanical stress on healing skin wounds: an experimental study in rabbits using tissue expansion. British journal of plastic surgery 1991;44:514-9.
11. Timmers MS, Le Cessie S, Banwell P, Jukema GN. The effects of varying degrees of pressure delivered by negative-pressure wound therapy on skin perfusion. Annals of plastic surgery 2005;55:665-71.
12. Greene AK, Puder M, Roy R, et al. Microdeformational wound therapy: effects on angiogenesis and matrix metalloproteinases in chronic wounds of 3 debilitated patients. Annals of plastic surgery 2006;56:418-22.
13. Gustafsson R, Johnsson P, Algotsson L, Blomquist S, Ingemansson R. Vacuum-assisted closure therapy guided by C-reactive protein level in patients with deep sternal wound infection. The Journal of thoracic and cardiovascular surgery 2002;123:895-900.
14. Patmo AS, Krijnen P, Tuinebreijer WE, Breederveld RS. The Effect of Vacuum-Assisted Closure on the Bacterial Load and Type of Bacteria: A Systematic Review. Advances in wound care 2014;3:383-9.
15. Noble-Bell G, Forbes A. A systematic review of the effectiveness of negative pressure wound therapy in the management of diabetes foot ulcers. International wound journal 2008;5:233-42.
16. Seo SG, Yeo JH, Kim JH, Kim JB, Cho TJ, Lee DY. Negative-pressure wound therapy induces endothelial progenitor cell mobilization in diabetic patients with foot infection or skin defects. Experimental & molecular medicine 2013;45:e62.
17. Xia CY, Yu AX, Qi B, Zhou M, Li ZH, Wang WY. Analysis of blood flow and local expression of angiogenesisassociated growth factors in infected wounds treated with negative pressure wound therapy. Molecular medicine reports 2014;9:1749-54.
18. Chen SZ, Li J, Li XY, Xu LS. Effects of vacuum-assisted closure on wound microcirculation: an experimental study. Asian journal of surgery / Asian Surgical Association 2005;28:211-7.
19. Gouttefangeas C, Eberle M, Ruck P, et al. Functional T lymphocytes infiltrate implanted polyvinyl alcohol foams during surgical wound closure therapy. Clinical and experimental immunology 2001;124:398-405.
20. Malmsjo M, Gustafsson L, Lindstedt S, Gesslein B, Ingemansson R. The effects of variable, intermittent, and continuous negative pressure wound therapy, using foam or gauze, on wound contraction, granulation tissue formation, and ingrowth into the wound filler. Eplasty 2012;12:e5.
21. Wilkes RP, Kilpad DV, Zhao Y, Kazala R, McNulty A. Closed incision management with negative pressure wound therapy (CIM): biomechanics. Surgical innovation 2012;19:67-75.
22. Echebiri NC, McDoom MM, Aalto MM, Fauntleroy J, Nagappan N, Barnabei VM. Prophylactic use of negative pressure wound therapy after cesarean delivery. Obstetrics and gynecology 2015;125:299-307.
23. Yu L, Kronen RJ, Simmon LE, Stoll CRT, Colditz GA, Tuuli MG. Prophylactic negative pressure wound therapy after cesarean is associated with reduced risk of surgical site infection: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2017 Sep 23.

24. Dragu A, Schnurer S, Unglaub F, et al. Wide topical negative pressure wound dressing treatment for patients undergoing abdominal dermolipectomy following massive weight loss. Obesity surgery 2011;21:1781-6.
25.Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2014;59:147-59.