# Non-invasive bioELEctroniC Treatment foR pOst-cesarean paiN (ELECTRON)

IRB Protocol Number: 2022H0046

National Clinical Trial (NCT) Identified Number: NCT05250830

Funded by:
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# 1 Protocol Summary

## *1.1 Synopsis*

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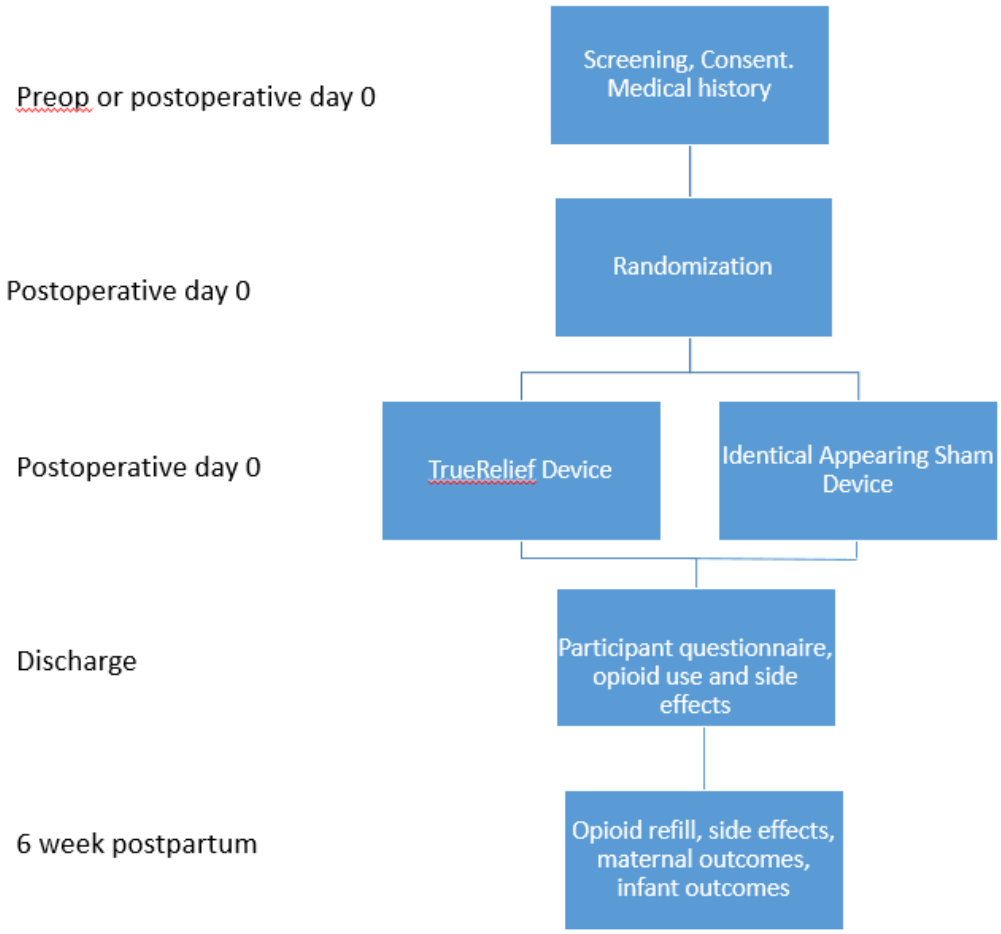
|---|---|
| **Title:** | **Non-invasive bioELEctroniC treatment foR pOst-cesareaN (ELECTRON)** |
| **Study Description:** | This is a randomized trial of 134 individualized post-cesarean delivery who will be randomized to three times use of non-invasive bioelectronic treatment with TrueRelief device or identical appearing sham device for post-cesarean pain management. |
| **Objectives:** | Primary: To evaluate whether post-cesarean use of non-invasive bioelectronic treatment reduces inpatient postoperative opioid consumption in morphine milligram equivalents (MME). Secondary: To evaluate whether post-cesarean use of non-invasive bioelectronic treatment 1) improves pain management defined as the presence/absence of moderate to severe pain on post-operative day 2. Moderate to severe pain is defined as a value of 4 or higher on the Brief Pain Inventory worst pain scale (0-10) at discharge, 2) decreases the total amount of opioid tablets prescribed, 3) decreases an opioid refill prescription 4) reduces adverse maternal and infant outcomes. |
| **Endpoints:** | Total inpatient opioid consumption in morphine milligram equivalents. Brief Pain Inventory pain severity (worst, least, average, current) in last 24 hours on post-operative day 2, Brief Pain Inventory pain interference during the past week, number of opioid tablets prescribed at discharge, number of opioid prescriptions filled beyond that prescribed at discharge, maternal and infant outcomes. |
| **Study Population:** | Individuals with a cesarean delivery who deliver at The Ohio State Wexner Medical Center |
| **Description of Study Intervention:** | Non-invasive bioelectronic treatment with TrueRelief device for post-cesarean pain management. |
| **Study Duration:** | Recruitment between April 2022 -November 2022. Follow-up, closeout and data analysis by December 2022. |
| **Participant Duration:** | 6 weeks postpartum |

## *1.2 Schema*


Preop or postoperative day 0
Screening, Consent. Medical history
Postoperative day 0
Randomization
Postoperative day 0
TrueRelief Device
Identical Appearing Sham Device
Discharge
Participant questionnaire, opioid use and side effects
6 week postpartum
Opioid refill, side effects, maternal outcomes, infant outcomes

## *1.3 Schedule of Activities*

| Measure | Visit 0:<br>Screening & randomization | Visit 1:<br>Discharge | Visit 2:<br>6-wk postpartum in-person or virtual visit |
|---|---|---|---|
| Informed consent | X | | |
| Demographics | X | | |
| Medical history | X | | |
| Randomization | X | | |
| Number of inpatient opioids used (MME) | | X | |
| BPI pain severity | | X | |
| Edinburgh Postnatal Depression Scale | | | X |
| Number of opioids prescribed (MME) | | X | |
| Opioid prescription refilled (or initially filled if not prescribed at discharge) | | | X |
| Opioid-related side effects | | X | |

| Measure | Visit 0:<br>Screening & randomization | Visit 1:<br>Discharge | Visit 2:<br>6-wk postpartum in-person or virtual visit |
|---|---|---|---|
| Breastfeeding | | X | X |
| Maternal & infant outcomes | | X | X |

# 2 Introduction

## 2.1 Study Rationale

Cesarean delivery is the most commonly performed major surgical procedure in the United States. Systemic opioids have been universally used for post-cesarean analgesia management, with the number of tablets prescribed varying significantly among providers and institutions. Pain thresholds and analgesic requirements vary among patients, but studies suggest that most women are given prescriptions at discharge for at least 10 more tablets than needed.[1,2] The consequence of over-prescribing opioids for 1.2 million cesareans annually is at least 12.5 million unused tablets. These unused tablets often go unguarded, and undisposed, providing an important reservoir of opioids that may be misused, diverted or accidentally ingested, contributing to the opioid crisis. Growing recognition of the role that post-cesarean opioid prescribing plays in the opioid crisis has led to a search for alternative methods to control postoperative pain.

## 2.2 Background

In 2017, approximately 1 in 3 women (32%) in the US gave birth by cesarean delivery.[3] More than 80% of women take at least one opioid medication for pain after cesarean.[1] Recent studies show that up to 75% of women who have a cesarean delivery and fill their opioid prescription after their discharge from hospital have unused tablets. The majority of women do not dispose of the excess tablets appropriately.[2,4-6] These unused opioids are then available for diversion, non-medical use, overdose and development of chronic dependence.

Between 2007 and 2016, the rate of pregnancy-associated mortality involving opioids more than doubled (1.3 to 4.2 per 100,000), as did the percentage of all pregnancy-associated deaths (4% to 10%).[8] It is becoming clear that opioid overprescribing plays a significant role in maternal mortality. Surgery contributes to the ongoing opioid crisis in two ways. First, opioids provided to treat acute post-surgical pain may lead to chronic opioid use (defined by continued use at 90 days, which occurs in approximately 3-6% of post-surgical patients).[9,10] 1 in 300 to 1 in 50 opioid-naïve women in the US will develop a persistent opioid use at one year after a cesarean delivery.[1,11] Secondly, surgeons tend to provide more opioids than patients use postoperatively, leading to excess opioids in a patient's possession. As approximately 60% of adults report that they obtained opioids for nonmedical use from a friend or relative,[10] decreasing the number of excess opioids available to the general population is critical to combating the opioid crisis in the US.

Physicians today struggle to balance the need for adequate control of acute pain after surgery with the desire to limit opioid use and avoid overprescribing, development of dependence and diversion. This had led to a search for effective pain control methods with less short and long-term risks than opioids.

The use of multimodal analgesia to control postoperative pain can decrease opioid requirements postoperatively. Multimodal analgesia protocols typically emphasize timed and consistently administered non-opioid analgesics (such as non-steroidal anti-inflammatory drug (NSAIDs) and acetaminophen), with opioid analgesics as needed for breakthrough pain. Use of local treatments and novel devices remains an under-explored adjunct for postoperative pain control as part of a multimodal protocol.

Electrical nerve stimulation represents a promising adjunctive therapy. Originally utilized for chronic pain, transcutaneous electrical nerve stimulation has recently been shown to reduce acute pain and opioid requirements postoperatively, including after total knee arthroplasty and hernia repair.[12,13] TrueRelief is a novel FDA-cleared bioelectronic device that delivers high-frequency (20,000 Hz) pulsed direct electrical current transcutaneously via stainless steel probes. Efficacy of this technology for pain control after cesarean delivery has not been studied, but it may represent an important adjunct to improve pain control while reducing opioid use.

## *2.3 Risk /Benefit Assessment*

### 2.3.1 Known Potential Risks

Risks of electroceutical treatment in the postoperative period are minimal. The treatment itself is painless and takes only a few minutes. Treatment with the TrueRelief device or sham device will be administered three times beginning on postoperative day zero until discharge. Aside from the treatment itself, patients will receive usual inpatient care postoperatively, including standard non-opioid and opioid pain medications available as needed.

### 2.3.2 Known Potential Benefits

Use of the TrueRelief device may improve pain control after cesarean delivery. If treatment successfully decreases opioid requirements, patients may benefit from decreased risk of tolerance, dependence and diversion.

### 2.3.3 Assessment of Potential Risks and Benefits

As described above, potential risks are not more than encountered in usual care after cesarean delivery. Treatment with the TrueRelief device may improve pain control and reduce opioid requirements.

# 3. Study Design

This is a blinded randomized trial of 134 individuals undergoing a cesarean delivery who are randomized after cesarean to three times use of non-invasive bioelectronic treatment with TrueRelief device or identical appearing sham device for post-cesarean pain management.

The primary endpoint is the total inpatient morphine milligram equivalents used during hospital admission. The primary hypothesis is that three times use of non-invasive bioelectronic treatment with TrueRelief device decreases the total inpatient morphine milligram equivalents used during hospital admission compared to use with identical appearing sham device. Consenting women will be assigned in a 1:1 ratio to one of the two arms using a secure internet based randomization system. Individuals will be followed through 6 weeks postpartum.

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# 4. Objectives and Endpoints

| OBJECTIVES | ENDPOINTS |
|---|---|
| Primary | |
| To evaluate whether non-invasive bioelectronic treatment reduces inpatient post-cesarean opioid consumption. | Total inpatient postoperative opioid consumption in morphine milligram equivalents (MME). |
| Secondary | |
| To evaluate whether non-invasive bioelectronic treatment post-cesarean decreases opioid refill prescriptions. | Opioid prescription filled (beyond that prescribed at discharge) between discharge and six weeks postpartum. |
| | Total number of opioid prescriptions filled by six weeks postpartum (beyond that prescribed at discharge). |
| To evaluate whether non-invasive bioelectronic treatment post-cesarean decreases the total amount of opioid tablets prescribed at discharge. | Number of opioid tablets prescribed at discharge. |
| To evaluate whether non-invasive bioelectronic treatment post-cesarean reduces pain intensity pain scores | Pain severity scores (worst, least, average, current) in last 24 hours assessed on the Brief Pain Inventory numeric scale from 0 to 10 at discharge |
| To evaluate whether non-invasive bioelectronic treatment post-cesarean reduces opioid related side effects, wound disruption and increases rates of breastfeeding | • Opioid related side effects including nausea and constipation<br>• Surgical site would disruption/infection<br>• Breastfeeding rates at discharge and 6 weeks postpartum<br>• Maternal depression score ≥ 13 at 6 weeks postpartum |

# 5. STUDY POPULATION

### *5.1.1 Inclusion Criteria*

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

Post cesarean delivery (combined vaginal/cesarean deliveries are not eligible)

Singleton, or twin gestation

### *5.1.2 Exclusion Criteria*

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

- Fetal or neonatal death prior to randomization
- Inability to randomize on postoperative day 0
- Inability to complete all three non-invasive bioelectronic treatment during inpatient stay as assessed by research staff
- Language barrier (non-English or Spanish speaking)

- Participation in another intervention study that influences the primary outcome in this trial

## *5.2 Lifestyle Considerations*

There are no lifestyle considerations specific for this study. General post-cesarean instructions will be given to participants during admission and prior to discharge.

## *5.3 Screen Failures*

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes screen failure details, eligibility criteria, and any serious adverse event.

## *5.4 Strategies for Recruitment and Retention*

### 5.4.1Recruitment Plan

Good recruitment will depend on access, promotion, education and clinical staff buy-in. Research staff will view the daily schedule to review who has had a cesarean. If eligible by medical record review, research staff will approach participants preoperatively or post-operative day 0 to inform them about the study. Randomization should occur on postoperative day 0, but not earlier.

Care providers will be educated about the study via targeted information sessions. It has been found to be helpful to provide in-person informative sessions with specific groups of providers, for example faculty, residents and fellows.

The Ohio State Wexner Medical Center is a large academic medical center with over 5000 deliveries per year. Assuming a 30% rate of cesarean deliveries this is approximately 1500 cesarean deliveries per year. Not every day has 24/7 coverage; therefore it is conservatively assumed that approximately 4 individuals daily are potentially available to enroll on a weekday. It is expected that the number of women who meet the exclusion criteria will be less than 1 percent. Even if 20% of physicians are reluctant to allow their patients to participate (relevant in the setting of private physician deliveries within a hospital) and 60% of women refuse consent for the trial, over 360 women could be enrolled annually.

We are currently conducting a randomized trial in women undergoing cesarean delivery. The aim of the trial is to determine whether an individualized opioid prescription protocol (IOPP) at discharge after cesarean delivery is non-inferior to a prescription for a fixed amount of opioid tablets which approximates current standard of care has similar pain control.

Women are randomized after cesarean delivery and research staff has to be present on day of discharge for randomization. Even with these major barriers to recruitment, sites have been able to recruit approximately 24 participants/ month. While these barriers do not apply to this trial, this study does require a medically trained individual to administer the intervention. Thus the study should conservatively be able to enroll at least 24 participants per month.

# 6. Study Intervention

## *6.1 Study Intervention Administration*

### 6.1.1 Study Intervention Description

Women will be randomized on post-operative day 0 to receive treatments with non-invasive bioelectrical device or identical appearing sham device. Three treatments will be given to each patient. The first treatment should be given as soon as is practical after the cesarean section and not longer than two hours after the procedure. The second treatment will be administered 12 hours after the first treatment, but can be given within a range of 10-14 hours after the first treatment to avoid having to wake the patient when sleeping or otherwise disrupt other care being given to the patient. The third and final treatment will be administered 12 hours after the second treatment, but can be given within a range of 10-14 hours after the second treatment to avoid having to wake the patient when sleeping or otherwise disrupt other care being given to the patient.

#### 6.1.1.1 Inpatient opioid consumption (morphine milligram equivalents [MMEs])

Opioid use will be converted to equianalgesic doses of morphine sulfate (morphine milligram equivalents [MMEs]) using standard ratios. Table 1 demonstrates opioid conversions.

**Table 1. Opioid Conversion Table**

| Opioid (mg/day) | Conversion factor |
|---|---|
| hydrocodone 5mg | 1 |
| hydrocodone 20mg | 1 |
| oxycodone 5mg | 1.5 |
| oxycodone 20mg | 1.5 |

Prior to discharge, participants will complete a brief pain inventory questionnaire. The number of opioid pills prescribed at discharge will be at the discretion of the discharging provider.

### 6.1.2 Administration

Trained clinic research nurses will apply device three times after cesarean section before discharge (at least 10-14 hrs apart) for duration of 12 minutes each.

## *6.2 Measures to Minimize Bias: Randomization and Blinding*

Selection bias is minimized by the randomized design. However, adequate concealment of the assignment and a clear definition of the point of randomization are also important. Eligible and consenting women will be randomized by certified research staff using a secure internet based randomization system. Once the randomization program has been run by the staff member and the assignment revealed, the participant will be considered randomized even if the woman reneges. Assignment to device or sham device will be in a 1:1 ratio according to a randomization sequence. The simple urn method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis to be conducted with relative ease.[37]

Research staff will be responsible for randomization and for administering the intervention or sham device. Clinicians will be blinded to the patient's group assignment.

## *6.3 Concomitant Therapy*

Medications for postoperative pain management will be at the discretion of the clinical team. Our institution uses standardized postoperative medication order sets that include oxycodone, acetaminophen and/or ibuprofen.

## *6.4 Discontinuation of Study Intervention*

Since the intervention is a treatment with device during inpatient stay, participants may choose to not continue with intervention. Women will be followed through 6 weeks postpartum regardless of their treatment assignment.

# 7. Study Assessments and Procedures

## *7.1 Study Assessments*

### 7.1.1 Screening & Randomization

All women with a cesarean delivery will be screened for eligibility. If appropriate, study personnel will invite the patient to serve as a study participant. The initial approach will occur pre-operatively or on post-operative day 0 to ensure individual care is not modified as a result of the study design prior to randomization. Study personnel will describe the study in detail and review the study protocol with the participant. Women agreeing to participate will sign the consent form.

### 7.1.2 Baseline Procedures

If the patient is eligible and signs the consent form, participants be randomized to TrueRelief device or identical appearing sham device:

In addition to information collected for eligibility, the following information will be obtained from an interview with the participant and/or through the electronic medical record:

- Demographic factors (e.g., maternal date of birth, age, BMI, race/ethnicity, education, employment status, marital status, household income, insurance)
- Factors related to persistent opioid use including tobacco use, history of mental health conditions (e.g., depression, anxiety), use of anti-depressants or benzodiazepines, chronic pain conditions (e.g., back pain, migraines, fibromyalgia).

Medical history including obstetrical outcomes from the current delivery (e.g., indication for cesarean, repeat cesarean, labor prior to cesarean, operative time, type of anesthesia, peri-operative complications, gestational age, birth weight, neonatal outcomes).

- Opioid and non-opioid analgesics (e.g., acetaminophen, ibuprofen) use post cesarean through discharge

### 7.1.3 Follow-up

Participants will be followed through 6 weeks postpartum.

## *7.2 Adverse Events and Serious Adverse Events*

### 7.2.1 Definition of Adverse Events (AE)

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug related.

Events should be reported also if they are unexpected in nature, severity, frequency, or fit the single IRB definition of adverse event. The unexpected nature of the event is determined based on the research procedures and the characteristics of the subject population being studied. If the event is not one that is usually seen in this context or reported in the principal investigator / participant brochure, it should be considered unexpected.

### 7.2.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is one of the following that occurs in the mother, neonate, or infant through 90 days postpartum:

- Death
- Life-threatening event
- Inpatient re-hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Other important medical event may meet the definition of serious if it jeopardizes the participant

### 7.2.3 Classification of an Adverse Event

7.3.3.1 Relationship to Study Intervention

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

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or

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

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

7.3.3.2 Expectedness

The Center PI, or designee will be responsible for determining whether an adverse event is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

### 7.2.4 Time Period and Frequency for Event Assessment and Follow-up

Adverse events will be recorded from randomization through 6 weeks postpartum. If a serious adverse event occurs after the consent is signed and before randomization, it will also be reported.

Participants will be instructed to contact research staff to report an adverse event that occurs during study participation. In addition, research staff will ask participants at each study visit if they have experienced any side effects or adverse events since the last study visit.

Adverse and Serious Adverse Events will be reported on the Adverse Event Form.

### 7.2.5 Adverse Event Reporting

### 7.2.6 Non-serious adverse events must be entered into the study database within 7 days of being notified. Adverse events are reviewed in real-time by PI. Serious Adverse Event Reporting

Any maternal death, neonatal death, or life threatening maternal event must be entered into the adverse events database within 24 hours of being notified, but no later than 72 hours from the onset of the event if it occurs prior to delivery discharge. If a death is reported, a copy of the

participant's de-identified medical record will be uploaded to the adverse events database. Other serious adverse events must be entered into the study database within **7 days** of being notified.

Serious adverse events are reviewed in real-time by PI.

### 7.2.7 Reporting Events to Participants

Participants will not be informed about adverse events, serious adverse events, or study-related results unless the PI decides such information should be reported to participants. As noted in Section 7.2, an Edinburgh depression score of 13 or higher, or a value other than 'never' on the Edinburgh question 10 (harming oneself), will be reported to the participant and the clinical provider.

## *7.3 Unanticipated Problems*

### 7.3.1 Definition of Unanticipated Problems (UAP)

An investigator may not initiate a change in research activity without single IRB approval unless the change is necessary to eliminate apparent immediate hazards to human subjects, in which case it should be reported to the single IRB as an unanticipated problem (UAP).

The Office of Human Research Protections (OHRP) and the single IRB defines an unanticipated problem as an event that:

- Is unexpected (in terms of nature, severity, or frequency) given the research procedures and the characteristics of the subject population being studied; and
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 7.3.2 Unanticipated Problem Reporting

For an event that a PI considers to be an unanticipated problem that is also an adverse event, the AE should be entered into the database within the timeframes established above.

In addition, regardless of whether the UAP is an adverse event or not, a report should be emailed by the PI. The email should contain the following information:

- Protocol identifying information
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP
- A description of any corrective actions that are proposed in response to the UAP

Potential unanticipated problems will be reviewed by PI to determine whether changes to the protocol or consent form should be considered. UAP reports should be submitted through the online IRB system no later than 2 weeks (10 business days) from the notification.

### 7.3.3 Reporting Unanticipated Problems to Participants

An unanticipated problem will be reported to the specific participant involved. Changes to the protocol or consent form, or the event itself, may also warrant reporting to participants who are currently on study as well as those who have completed the study. In this case, the PI will recommend the course of action (for example, a letter to participants) which will be submitted to the single IRB.

## *7.4 Participant Discontinuation/Withdrawal from the Study*

Participants are free to withdraw from participation in the study at any time upon request.

# 8 Statistical Considerations

## *8.1 Statistical Hypotheses*

The primary endpoint is the amount of inpatient opioid consumed post-cesarean measured by total morphine milligram equivalents used. The null hypothesis is that there is no difference in amount of inpatient MME in the non-invasive bioelectrical device intervention group compared to sham device group. The alternative hypothesis is that the amount of inpatient MME in the non-invasive bioelectrical device intervention group is less then MME in the sham device group.

Key secondary endpoints include:

- Worst pain score assessed at discharge measured by presence or absence of moderate to severe pain at 1 week post-discharge, defined as a value of 4 or more on the BPI worst pain in the last 24 hours numeric scale (0 to 10).
- Opioid prescription beyond that prescribed at discharge within 6 weeks postpartum
- Opioids prescribed at discharge
- Opioid side effects, wound complications and breastfeeding rates

For the secondary endpoints, the null hypothesis is there is no true difference between the two groups. The alternative hypothesis is there is a difference between the groups. For the key secondary outcomes, the level of significance will be adjusted for multiple comparisons using the false discovery rate method.[41]

## *8.2 Sample Size Determination*

Review of inpatient post-operative data, showed that from post-operative day 0 to 2 our patients consume on average MME 42 with SD 15. For 20% reduction in MME to 33.6 and 90% power would need total sample size of 134. Resulting in 67 intervention group and 67 participants in control group.

## *8.3 Population for Analyses*

All statistical analyses will be based upon the total cohort of participants randomized into the trial. Although data on some patients may be missing, all relevant data available from each participant will be employed in the analyses. Patients will be included in the treatment group to which they were randomly assigned regardless of compliance.

## *8.4 Statistical Analyses*

### 8.4.1 General Approach

In general, summaries of categorical data will be presented as number of observations and a percentage. Summaries of continuous data will be presented as means with standard deviation if the variable follows a normal distribution, or else as the median and 95% confidence interval.

Binary or categorical will be reported as a proportion with relative risk and 95% confidence intervals as appropriate. For normally distributed continuous outcomes, least squares means general linear regression will be used to estimate means and 95% confidence intervals. For continuous outcomes that are not normally distributed and cannot be transformed to approximate normality, the Wilcoxon test and the Hodges-Lehmann estimators of the median will be reported.

### 8.4.2 Analysis of the Primary Endpoint

The primary outcome is continuous and defined as MME consumed inpatient post-cesarean not normally

distributed and cannot be transformed to approximate normality, the Wilcoxon test and the Hodges-Lehmann estimators of the median will be reported. If normally distributed then paired t-test and mean with standard deviations will be reported.

**Analysis of Secondary Endpoint**

Secondary outcomes that are binary or categorical will be reported as a proportion with relative risk and 95% confidence intervals as appropriate. For normally distributed continuous outcomes, least squares means general linear regression will be used to estimate means and 95% confidence intervals. For continuous outcomes that are not normally distributed and cannot be transformed to approximate normality, the Wilcoxon test and the Hodges-Lehmann estimators of the median will be reported.

### 8.4.3 Baseline Descriptive Statistics

Baseline factors will be compared by treatment group. If the treatment groups are found to differ on a key pre-treatment factor known to be a risk factor for the outcome, the statistical analyses will adjust for these differences.

### 8.4.4 Planned Interim Analyses

No interim analyses are planned given the short duration of enrollment and follow-up.

### Subgroup Analyses

Interactions will be evaluated and subgroup analyses conducted to determine whether the effect or lack thereof prevails throughout particular subgroups of participants. The following factors will be considered for subgroup analysis, if there is a significant interaction between the factor of interest and the treatment effect:

- Race/ethnicity
- BMI category (obese vs non-obese)
- Type of labor (labor vs no labor)
- Type of anesthesia
    - General, spinal, combined spinal-epidural, epidural
    - Neuraxial morphine administration
- Skin incisional type (low transverse vs vertical midline)
- Primary vs repeat cesarean

- Time from delivery to discharge (<48 hours, ≥ 48 hours).

### 8.4.7 Tabulation of Individual Participant Data

Participant data will only be reported in aggregate in study abstracts, presentations or manuscripts.

# 9 Supporting Documentation and Operational Considerations

## *9.1 Data Regulatory, Ethical, and Study Oversight Considerations*

### 9.1.1 Informed Consent

A single IRB will be used for this study. A HIPAA Waiver of Consent for recruitment purposes will be obtained to allow clinical sites to review electronic medical records to identify potentially eligible participants.

Prior to cesarean delivery or within first 24 hours after cesarean delivery, women will be approached for participation into the study. Full disclosure of the nature and potential risks of participating in the trial is to be made. Women that elect to participate in the study will sign the study consent. The consent form describes in detail the study intervention, study procedures, and risks is given to the participant and written documentation of informed consent is required prior to randomization.

The following consent materials are submitted with this protocol: study consent and assent, participant completed questionnaire..All participant materials will be IRB approved.. Both verbal and written informed consent and authorization will be obtained in the participant's fluent language. Participants not fluent in English will be excluded.

### 9.1.2 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and persons or organizations working with the sponsor. All research activities will be conducted in as private a setting as possible. The following individuals and/or agencies will be able to review medical and research records:

- The study doctor, study staff and other medical professionals who may be evaluating the study.

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

Additional details are provided in the full study consent form and authorization.

### 9.1.3 Clinical Monitoring

Clinical monitoring is performed by PI.

### 9.1.4 Data Handling and Record Keeping

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the principle investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

### 9.1.5 Protocol Deviations

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

### 9.1.6 Conflict of Interest Policy

All investigators will have conflict of interests reviewed by the single IRB. The single IRB requires that a series of questions be answered at the time of initial submission related to financial and non-financial COI relevant to the research protocol. These questions apply to the investigator, the study staff, and their

immediate families inclusive of spouse and each dependent child. Any new financial interests or increased value of a previously reported financial interest that occurs during the course of the study, must be reported to the single IRB within 30 business days of the change.

# References

1. Osmundson SS, Schornack LA, Grasch JL, Zuckerwise LC, Young JL, Richardson MG. Postdischarge Opioid Use After Cesarean Delivery. Obstetrics and gynecology 2017;130:36-41.
2. Bateman BT, Cole NM, Maeda A, et al. Patterns of Opioid Prescription and Use After Cesarean Delivery. Obstetrics and gynecology 2017;130:29-35.
3. Dinis J, Soto E, Chauhan SP, Sibai B. 42: Non-opioid versus opioid analgesia after hospital discharge from a cesarean delivery: a randomized clinical trial. American Journal of Obstetrics & Gynecology 2019;220:S34.
4. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies--tackling the opioid-overdose epidemic. The New England journal of medicine 2014;370:2063-6.
5. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. The New England journal of medicine 2015;372:241-8.
6. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. Jama 2013;309:657-9.
7. Gemmill A, Kiang MV, Alexander MJ. Trends in pregnancy-associated mortality involving opioids in the United States, 2007-2016. American journal of obstetrics and gynecology 2019;220:115-6.
8. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA surgery 2017;152:e170504.
9. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. Bmj 2014;348:g1251.
10. Lessenger JE, Feinberg SD. Abuse of prescription and over-the-counter medications. Journal of the American Board of Family Medicine : JABFM 2008;21:45-54.
11. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final Data for 2017. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 2018;67:1-50.
12. Peahl AF, Dalton VK, Montgomery JR, Lai YL, Hu HM, Waljee JF. Rates of New Persistent Opioid Use After Vaginal or Cesarean Birth Among US Women. JAMA network open 2019;2:e197863.
13. Corso E, Hind D, Beever D, et al. Enhanced recovery after elective caesarean: a rapid review of clinical protocols, and an umbrella review of systematic reviews. BMC pregnancy and childbirth 2017;17:91.
14. Wilson RD, Caughey AB, Wood SL, et al. Guidelines for Antenatal and Preoperative care in Cesarean Delivery: Enhanced Recovery After Surgery Society Recommendations (Part 1). American journal of obstetrics and gynecology 2018;219:523 e1- e15.
15. Caughey AB, Wood SL, Macones GA, et al. Guidelines for intraoperative care in cesarean delivery: Enhanced Recovery After Surgery Society Recommendations (Part 2). American journal of obstetrics and gynecology 2018;219:533-44.
16. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. JAMA surgery 2017;152:691-7.
17. Nelson G, Altman AD, Nick A, et al. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations--Part II. Gynecologic oncology 2016;140:323-32.

18. Gerrish AW, Fogel S, Lockhart ER, Nussbaum M, Adkins F. Opioid prescribing practices during implementation of an enhanced recovery program at a tertiary care hospital. Surgery 2018;164:674-9.

19. Brandal D, Keller MS, Lee C, et al. Impact of Enhanced Recovery After Surgery and Opioid-Free Anesthesia on Opioid Prescriptions at Discharge From the Hospital: A Historical-Prospective Study. Anesthesia and analgesia 2017;125:1784-92.

20. Schmidt P, Berger MB, Day L, Swenson CW. Home opioid use following cesarean delivery: How many opioid tablets should obstetricians prescribe? The journal of obstetrics and gynaecology research 2018;44:723-9.

21. Prabhu M, McQuaid-Hanson E, Hopp S, et al. A Shared Decision-Making Intervention to Guide Opioid Prescribing After Cesarean Delivery. Obstetrics and gynecology 2017;130:42-6.

22. Hill MV, McMahon ML, Stucke RS, Barth RJ, Jr. Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures. Annals of surgery 2017;265:709-14.

23. AAPM et al. (American Academy of Pain Medicine NPF, American Pain Foundation, and National Hospice and Palliative Care Organization). Recommendations to Physicians Caring for Katrina Disaster Victims on Chronic Opioids2005.

24. Kral LA JK, Uritsky T. A practical guide to tapering opioids. Ment Health Clin 2015;5(3):102-8.

25. Inturrisi CE LA. Opioid analgesics. In Fishman SM, Ballantyne JC, Rathmell, JP, editors. Bonica's management of pain. 4th ed. Philadelphia: Wolters Kluwer Lippincott Williams and Wilkins; 2010.

26. Werner RM, Goldman LE, Dudley RA. Comparison of change in quality of care between safety-net and non-safety-net hospitals. Jama 2008;299:2180-7.

27. Garcia MC, Heilig CM, Lee SH, et al. Opioid Prescribing Rates in Nonmetropolitan and Metropolitan Counties Among Primary Care Providers Using an Electronic Health Record System - United States, 2014-2017. MMWR Morbidity and mortality weekly report 2019;68:25-30.

28. Lyon A, Solomon MJ, Harrison JD. A qualitative study assessing the barriers to implementation of enhanced recovery after surgery. World journal of surgery 2014;38:1374-80.

29. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. The New England journal of medicine 2012;366:780-1.

30. Clever SL, Ford DE, Rubenstein LV, et al. Primary care patients' involvement in decision-making is associated with improvement in depression. Medical care 2006;44:398-405.

31. Loh A, Leonhart R, Wills CE, Simon D, Harter M. The impact of patient participation on adherence and clinical outcome in primary care of depression. Patient education and counseling 2007;65:69-78.

32. Loh A, Simon D, Wills CE, Kriston L, Niebling W, Harter M. The effects of a shared decision-making intervention in primary care of depression: a cluster-randomized controlled trial. Patient education and counseling 2007;67:324-32.

33. Osmundson SS, Raymond BL, Kook BT, et al. Individualized Compared With Standard Postdischarge Oxycodone Prescribing After Cesarean Birth: A Randomized Controlled Trial. Obstetrics and gynecology 2018;132:624-30.

34. Chen EY, Marcantonio A, Tornetta P, 3rd. Correlation Between 24-Hour Predischarge Opioid Use and Amount of Opioids Prescribed at Hospital Discharge. JAMA surgery 2018;153:e174859.

35. Salazar A, Tolivaisa S, Allard D, et al. What we have learned about best practices for recruitment and retention in multicenter pregnancy studies. Seminars in perinatology 2016;40:321-7.

36. Calculating Total Daily Dose of Opioids [Internet]. 2019. Available from: https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

37. Rosenberger W L, JM. Randomization in Clinical Trials. New York: Wiley; 2012.

38. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. Pain medicine 2005;6:432-42.

39. The Pain Catastrophizing Scale: Development and validation. American Psychological Association, 1995. 7,

40. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. The British journal of psychiatry : the journal of mental science 1987;150:782-6.

41. Benjamini Y HY. Controlling the false discovery rate: a practical and powerful approach to multiple testing. R Stat Soc [B] 1995;57:289-300.