Management of Pain After Cesarean: A Randomized Control (MOPAC) Trial

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Protocol Title:
Management Of Pain After Cesarean: A Randomized Control (MOPAC) Trial

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1.0 Objectives

1.1 Study Objectives

To compare the efficacy of a multimodal pain regimen of both ibuprofen with acetaminophen dispensed on schedule vs a regimen of ibuprofen with placebo dispensed on schedule to control pain experienced by women after scheduled, uncomplicated Cesarean delivery.

1.2 Primary Study Endpoints

a. Pain score mid-day (12 pm – 4 pm) on the second post-operative day (POD), as assessed on a 10-point scale obtained as part of routine vital signs

1.3 Secondary Study Endpoints

a. Pain scores assessed through hospitalization on a 10-point scale mid-day (12 pm – 4 pm) on the first post-operative day, on the morning (4 am – 8 am) of the second and third post-operative days, and the evenings (6 pm – 10 pm) of the first and second post-operative day.

b. Total opiate consumption while admitted in total number of oxycodone 5 mg tablets

c. Total opiate consumption one week after discharge

d. Total opiate consumption two weeks after discharge

e. Scores on the WHOQOL-BREF survey two weeks after discharge measured and recorded in each of four domains of quality of life (physical health, psychological, social relationships, and environment) scaled to the WHOQOL-100 using procedure outlined in the provided manual from the World Health Organization

2.0 Background

2.1 Scientific Background and Gaps

In July 2017, the ACOG "Green Journal" published several papers which looked at the opiate epidemic from different angles in relation to obstetrics. In the editorial, Dr. Patrick made note that "by 2012, 259 million prescriptions were written annually in the United States for opioid pain relievers-more than one for every American adult," and that nearly a third of women of reproductive age had been prescribed opiates according to the CDC. However, a growing body of evidence has found that in post-operative women after a Cesarean section, opiates are often prescribed in excess (1–3) and that when educated and given the option, patients tended to opt for less pills of narcotic pain medication at discharge (4). Especially concerning is that some women may have a genetic predisposition to opioid addiction, with the risk of addiction increasing with total exposures to opiate medication (5). NSAIDs appear to be safe, even in a population of women with pre-eclampsia with severe features (6), and may not increase incidence of postpartum hypertension in women with hypertensive disease of pregnancy (7). Additionally, evidence is beginning to accumulate suggesting non-opiates may not be non-inferior to opiates (8). Furthermore, synergism has been found between NSAIDs and acetaminophen (9). More high-quality evidence is needed to re-examine opiate prescribing habits in an effort to provide guidelines for patients after Cesarean delivery.

We therefore propose a double-blinded, placebo-controlled randomized, controlled trial to compare a standardized pain regimen of scheduled ibuprofen and acetaminophen to scheduled ibuprofen and placebo. In both arms, the patient will have the ability to ask for medication for breakthrough pain which will be oxycodone. By standardizing and scheduling the administration of ibuprofen with acetaminophen, we hypothesize we can decrease the amount of opiate medication requested and

decrease total narcotic exposure in this population. We will primarily assess pain as reported on a 10-point scale mid-day on the second post-operative day. Secondarily, we will collect reported pain scores and total opiate consumption while in the hospital, opiate consumption after discharge, and quality of life as assessed by the WHOQOL-BREF. This information will be obtained via chart review and an at-home survey administered via email on the Research Electronic Data Capture (REDCap) system one and two weeks after surgery.

2.2 Previous Data

See. 2.1

2.3 Study Rationale

To collect high quality data in order to propose a standardized pain regimen for the average-risk woman after an uncomplicated Cesarean delivery, which minimizes narcotic usage and exposure.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- All pregnant women
- Planned delivery via C-section
- Pfannenstiel skin incision
- Lower uterine segment transverse hysterotomy
- English speaking
- Access to electronic mail (email) to be checked at least daily since this project relies heavily on automated computer software to send survey invitations and reminders via email. Crafting a methodology to communicate with participants manually without email would add undue burden to research staff. This criteria should not affect the equitability of research participants given the general accessibility of email in our study population.

3.2 Exclusion Criteria

- Major intra-operative or post-operative complication such that clinician recommends patient should not receive non-steroidal anti-inflammatory drugs or that patient requires acetaminophen to treat other condition (ie to treat fever if suspected endometritis)
- Unplanned surgery (hysterectomy, bowel/bladder repair)
- Allergy or contraindication to study medication
- Non-English speaking
- Inability to provide informed consent
- History of opioid, other illicit substance, or alcohol use disorder either before or during pregnancy
- History of chronic pain requiring medication
- Multifetal gestation
- Severe renal or hepatic impairment

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

- Physician determines that continuing the research would be harmful to the participant
- Complication of C-section such that participant cannot receive NSAIDs or requires acetaminophen for indication other than pain
- Inability to tolerate pain regimen
- Post-operative complication such that clinician recommends patient should not receive non-steroidal anti-inflammatory drugs or that patient requires acetaminophen for indication other than pain (ie: fever)

3.3.2 Follow-up for withdrawn subjects

Subjects may withdraw at any time after enrollment by contacting the PI in writing. Subjects who withdraw will be asked if information can continue to be obtained from their medical records. Subjects who do not complete the surveys will also be asked if information can continue to be obtained from their medical records.

4.0 Recruitment Methods

4.1 Identification of subjects

Study staff will review the Labor and Delivery (L&D) unit schedule for planned Cesarean sections 1-7 days in advance, and certain patient data will be collected and stored in a REDCap database used for screening, which is separate from the primary project database. The patient's name, medical record number, phone number, and scheduled date of surgery will be entered into the REDCap database in a HIPAA-compliant fashion.

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

Study staff will review the Labor and Delivery (L&D) unit schedule for planned Cesarean sections 1-7 days in advance, and certain patient data will be collected and stored in a REDCap database used for screening, which is separate from the primary project database. The patient's name, medical record number, phone number, and scheduled date of surgery will be entered into the REDCap database in a HIPAA-compliant fashion.

Patients will then be contacted via telephone, read a standardized script regarding our study, and be invited participate. They will also be offered to have an electronic copy or paper copy of the consent sent to them. They will be informed that they will be approached again on date of surgery and that we will plan to obtain written consent on the date of surgery if they are interested in participating. Please see supporting documentation for an example of the telephone script and the REDCap tool which will be used to track patient enrollment.

Being allowed to review the L&D schedule and contact patients in advance offers significant logistical benefits and will help promote successful enrollment. Speaking to the patient outside of the hospital will afford the opportunity to introduce our project in a relaxed atmosphere without the added stress and anxiety typical of the morning of surgery. Additionally, she will be allowed the opportunity to receive a copy of our consent form to review at her leisure. On the date of surgery, patients are often presented with tremendous information, paper forms to sign, and new people they are meeting who will comprise their surgical and support staff. The

process of preparing and getting the patient to the operating room leaves little time to allow study staff to speak with patients ahead of time, and may add increased burden and stress to the patient.

Since it's not possible to know when a patient would start requiring oral pain medication after surgery, enrollment prior to surgery would be ideal and best accomplished by contacting patients by telephone in advance. Additionally, the REDCap database will be utilized to manage patient phone calls and enrollment.

We will register the study on the Penn State Clinical and Translational Science Institute (CTSI) "Study Finder" website. Additionally, a supplemental advertisement sheet (generated by printing services at Penn State University Hershey Medical Center) will be included in the "36 Week Informational Packet" which is handed out to all women at 36 weeks undergoing a planned, scheduled C-section. We will also place the fliers in conspicuous locations on the second floor of the OB clinic located at 35 Hope Drive. The advertisement will contain a QR code which will link back to the "Study Finder" website. This will allow patients to contact study staff with any questions. Please see provided supplementary material.

4.2.2 Where potential subjects will be recruited.

On the third floor of the Penn State Hershey Medical Center Hospital Labor and Delivery Unit.

4.2.3 When potential subjects will be recruited.

Potential patients will be approached on their scheduled Cesarean date.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Patient medical records will be reviewed for eligibility prior to study enrollment. The patient's name, medical record number, phone number, and scheduled date of surgery will be entered into the REDCap database. The entries for patients who do decide not to participate in the study or who are not approached about participating will be deleted from the REDCap database no later than 30 days after their scheduled C-section date.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Informed consent will be obtained in the patient's room on the Labor and Delivery Unit at Penn State Hershey Medical Center.

5.2.2 Coercion or Undue Influence during Consent

Informed consent will be obtained in the patient's room. Patients will be informed verbally and in writing that participating in this study is entirely voluntary and that her medical care is not contingent on agreeing to participate in this study.

5.3 Waiver of Written Documentation of Consent

Not applicable

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Not applicable

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Not applicable

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

The inclusion of non-English speaking participants is not planned.

5.6.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

The study team members will rely on the assessments of other providers. If the patient was able to sign the inpatient general consent, she will be considered capable of consenting to participate in this research study.

5.6.2.2 Adults Unable to Consent

Adults unable to consent will not be included in this study.

5.6.2.3 Assent of Adults Unable to Consent

Assent will not be required in this study. Only patients who are able to provide written informed consent will be included.

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

By Pennsylvania law, pregnant minors are allowed to consent and receive medical care without approval or permission from a parent/guardian. Therefore, parental permission is not required for minors to participate in this study.

5.6.3.2 Assent of subjects who are not yet adults

Not applicable as in 5.6.3.1.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Study data will be collected and managed using REDCap. Data will be de-identified with the removal of PHI when abstracted and stored onto this secure system and there will be no PHI for statistical analysis. We will also need to access the patient's medical record throughout the study to obtain information regarding opiate administration and pain scores while in the hospital and rates of medical

complications and comorbidities. Additionally, we will review her Cesarean operative report to ensure no unexpected complications were encountered. Identifiers will include medical record number, patient name, and date of birth.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Without PHI, it would not be possible to identify patients eligible to participate in this study. Additionally, it would not be possible to review their charts to obtain information on opiate consumption, prescription, and operative complications.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Without the ability to access the medical records of patients, it would be impossible to identify eligible patients to participate in the study in advance. As detailed previously, being able to speak with patients prior to obtaining consent allows us to introduce the study without the added anxieties associated with the day of surgery. We will also offer the patient the opportunity to receive an electronic version of our consent to review at her leisure.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This is a prospective, double-blinded, placebo-controlled randomized controlled trial

7.2 Study Procedures

7.2.1 Date of Patient Cesarean Section

Patients who verbally express an interest over the phone will be approached on the date of surgery for enrollment. If interested, consent would be thoroughly explained and her questions would be answered.

After thoroughly reviewing the consent, if the patient volunteers to participate, written informed consent will be obtained. Two copies of the signed consent will then be made with one given to the participant, another placed on the medical record, and the original to be stored in a secured cabinet in the Maternal-fetal Medicine Division office.

We will then collect demographic and other information which will be stored in the REDCap system. The questionnaire will be administered by study staff using an iPad or other tablet-style mobile device connected to the PSU network.

Participants will then be randomized by Investigational Drug Services (IDS) using our REDCap randomization table generated by our biostatistician in the Department of Public Health Sciences to receive either the single (with placebo) or multimodal (with acetaminophen) regimen. If the online interface is not available, a backup paper system will be utilized and entries entered into the database later by IDS staff once back online. By design, the module does not allow the randomization assignment to be edited.

After randomization assignment, the subject will then undergo her Cesarean section by the labor and delivery assigned team. Her oral post-operative pain regimen will be dispensed as follows: the clinical pharmacy will dispense scheduled ibuprofen 600 mg every 6 hours and oxycodone 5 mg every 4 hours 1-2 tablets as needed for breakthrough pain. IDS will then dispense 40 tablets of either acetaminophen (325 mg each) or placebo based on the participant's assignment to be administered by the nurse caring for the patient along with the scheduled ibuprofen. In the immediate post-operative period, she may receive analgesia as prescribed by the obstetric and/or anesthesia team, which would be beyond the control of this trial.

"Breakthrough" pain is defined as pain that is present at a time which no scheduled pain medication is due (in other words, the pain "broke through" the scheduled medication and additional medication may be needed). Scheduled medication, either ibuprofen + placebo or ibuprofen + acetaminophen, will be administered to the patient every 6 hours on schedule regardless of their reported pain on the pain scale without oxycodone. Oxycodone will be given if the patient has pain (4 or greater; 1 pill if pain 4-6 or 2 pills if pain 7-10) at a time when no scheduled medication is due.

Here is a schedule:
0000 - Pain assessed; scheduled medication given
0400 – Pain assessed; may receive oxycodone if pain score 4+
0600 – Pain assessed; Scheduled medication given
0800 – Pain assessed; may receive oxycodone if pain score 4+
1200 - Pain assessed; scheduled medication given
1600 – Pain assessed; may receive oxycodone if pain score 4+
1800 - Pain assessed; scheduled medication given
2000 - Pain assessed; may receive oxycodone if pain score 4+

In the event that the participant receives patient-controlled analgesia (PCA; typically a narcotic such as morphine or hydromorphone), she may not receive oral oxycodone until the PCA is discontinued. This is to prevent over-sedation that may occur if a participant receives excess opioid medication, since oxycodone too is a narcotic. Typically, a patient may receive a PCA after surgery if they did not receive long-acting morphine through an intrathecal and/or epidural catheter. This usually is the case if a patient requires general anesthesia. The PCA administers a low-dose basal rate of medication, and patients are allowed to request additional medication by pressing a button. PCAs have a "lockout" feature with parameters pre-set by the anesthesia team to prevent over-sedation, and they are stopped after 12-24 hours which is the typical time of action of long-acting intrathecal morphine. While receiving PCA analgesia, our participants will receive other study medication (ibuprofen and placebo/acetaminophen), since they are non-narcotic. They will then be ordered for oral oxycodone once the PCA is discontinued.

7.2.□2 Post-Operative Day 0 Until Discharge

Patient will receive pain regimen as prescribed: one tablet of ibuprofen and two tablets of either placebo or acetaminophen 325 mg (for total of 650 mg) every 6 hours.

7.2.3 Hospital Discharge

Pain scores and opiate consumption will be recorded based on chart review. The patient will receive a prescription for narcotic by physician study team staff which is currently the standard of the "OB Providers" group at PSHMC: 20 tablets of oxycodone 5 mg with instruction to take 1-2 tablets every 6-8 hours as needed for breakthrough pain.

7.2.4 One Week Post-Surgery

The patient will receive an invitation via email to complete a survey via REDCap to assess opiate consumption.

7.2.5 Two Weeks Post-Surgery

Patient will receive an invitation to complete another survey to assess opiate consumption, as well as the WHOQOL-BREF survey on the REDCap system. The invitations will be sent by email.

7.2.5 Other Considerations

Subjects will be sent daily reminders for 3 days by REDCap via email to complete surveys. After the third day, the subject will not be eligible to complete the assigned survey. If subject still does not complete the survey, data that we collected from the subject until this time will still be utilized and incorporated into the data analysis.

Please see supplements provided for the sample surveys to be administered.

7.3 Duration of Participation

Patients will participate for two weeks.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.□1 Description

We will dispense acetaminophen 325 mg or placebo as study medication. Both will be dispensed as tablets and will be identical in appearance. Acetaminophen has been approved by the FDA for use to treat pain.

7.4.2 Treatment Regimen

Patient will receive ibuprofen 600 mg every 6 hours standing and oxycodone 5 mg 1-2 tablets every 4 hours as needed for break through pain. In addition, to be dispensed with scheduled ibuprofen, the patient will also receive either two tablets of placebo or acetaminophen 325 mg (total dose of 650 mg; tablets coated to be identical in appearance to placebo). There will be no dose adjustments.

7.4.3 Method for Assigning Subject to Treatment Groups

After enrollment, Investigational Drug Services (IDS) will randomize the participant using the REDCap module which was built using tables designed by our biostatistician in the Department of Public Health. A backup system has also been designed and will be available to IDS staff to use in the event that REDCap is offline (randomization entries are then entered manually into REDCap once back online by IDS). IDS will then dispense either acetaminophen 325 mg or placebo tablets to the caring registered nurse. Total number of tablets dispensed will be 40 so that medication is available for the entire hospitalization.

7.4.4 Subject Compliance Monitoring

Compliance will be assessed by review of the "eMAR" function available on the Powerchart system, which records when and how patients are dispensed and receive medication.

7.4.5 Blinding of the Test Article

The acetaminophen 325 mg tablets will be blinded with a coating to be applied to the tablet by IDS staff which will match the size, shape, and color of a corresponding placebo tablet.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

A total of 40 tablets (of either acetaminophen 325 mg or placebo) will be dispensed by IDS to the nurse caring for the patient. The medication will be transported in a prescription bottle labeled with the patient's name and medical record number.

7.4.6.2 Storage

Medication bottles will be stored in either the Pyxis or within locked cabinets on the nursing "Workstation On Wheels." The tablets can be stored at room temperature without additional considerations.

7.4.6.3 Preparation and Dispensing

Study drug (two tablets of either either acetaminophen 325 mg or placebo tablet) will be dispensed by the nurse caring for the participant on the postpartum unit at the same time as scheduled ibuprofen 600 mg.

7.4.6.4 Return or Destruction of the Test Article

All unused study medication will be returned to IDS.

7.4.6.5 Prior and Concomitant Therapy

Participant will continue to receive pain medication of ibuprofen 600 mg every 6 hours and can also ask for additional medication, which will be oxycodone 5 1-2 tablets every 4 hours as needed. Participants can continue to receive other therapies and medications typically prescribed while

postpartum, including prenatal vitamin, stool softener, and iron supplement.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Our target sample size is 144 patients.

8.2 Sample size determination

The primary outcome of this randomized, double-blind trial is the mid-day pain score as assessed using a 10-point scale that will be collected on the second post-operative day. Factoring in 10% subject attrition and assuming the pain score standard deviation will be 4.0 points, a sample size of 144 subjects (72 per group) will provide 80% statistical power to detect a pain score difference of 2 points between the two treatment groups using a two-sided test having a significance level of 0.05.

8.3 Statistical methods

A linear mixed-effects model, which is a subject-specific model, will be used to compare pain scores between the two treatment groups. This methodology will account for the correlation due to repeated pain measurements collected over time for each participant. For this model, the dependent variable will be the pain score and the independent variables will be the treatment group, time, and the interaction of treatment group and time. For the primary outcome, a contrast will be constructed from this model to compare the two treatment groups at the mid-day POD 2 time point. Similarly, contrasts will be constructed from the mixed-effects model to compare the treatment groups at the additional secondary time points as well. For the mixed-effects model, a first-order antedependence covariance matrix will assess the residual error associated with the repeated measurements over time per participant. If the antedependence covariance structure fails to provide model convergence then other covariance structures will be considered such as unstructured, heterogeneous compound symmetry, and compound symmetry. Residual diagnostics will be used to determine the appropriateness of model fit and, if necessary, transformations (e.g., logarithmic) of the outcome will be performed to meet modeling assumptions. Following our assessment of the initial fit of the model, we will add total opiate consumption while admitted (e.g., in MEUs) as a covariate to the model to assess its impact, if any, on the intervention effect.

A mixed-effects model also will be used to compare the two treatments with respect to total opiate consumption (i.e., in MEUs) collected over time: while admitted, one week after discharge, and two weeks after discharge. Two-sample t-tests, or Wilcoxon Rank-Sum tests if the data are not normally distributed, will be used to compare the treatment groups with respect to the secondary continuous endpoints such as the WHOQOL-BREF survey scores and demographic information such as patient's age. Chi-square tests, or Fisher's exact tests if the expected cell counts are small, will be used to compare the treatment groups for any categorical demographic variables collected.

9.0 Data and Safety Monitoring Plan

This study involves minimal risk to subjects as it involves standard methods for pain control in patients undergoing cesarean section.

9.1 Periodic evaluation of data

Not applicable

9.2 Data that are reviewed

Not applicable.

9.3 Method of collection of safety information

On the REDCap "1 week" and "2 week" survey modules, participants will be queried regarding serious adverse events (SAEs). Specifically, they will be asked if they experienced any complications requiring hospitalization. By answering "yes," that will trigger a free text module in REDCap to allow the participant to specify the dates and location of her hospitalization, and to include a description of the complication. An automated email notification will be sent from REDCap to the investigator in real time when a participant reports a complication requiring hospitalization.

9.4 Frequency of data collection

One week and two weeks post-discharge (via the weekly surveys).

9.5 Individuals reviewing the data

The investigators (PI, Co-PI) will review reported SAEs on a case-by-case basis.

9.6 Frequency of review of cumulative data

Not applicable (SAEs will be reviewed on a case-by-case basis).

9.7 Statistical tests

Not applicable

9.8 Suspension of research

There are no criteria for the immediate suspension of research since all study medication have been FDA approved for the treatment of pain in doses and schedules being prescribed.

10.0 Risks

Loss of confidentiality is the most significant risk associated with this study. There is also the risk of patient complaint of suboptimal pain control in the group that's not receiving acetaminophen. You will not be able to select which group you're placed in; this assignment will be made at random by a computer program. You have a 50% chance of being placed in the group that will receive acetaminophen with scheduled ibuprofen. While acetaminophen is generally considered safe and can be purchased over-the-counter, it is metabolized by the liver and too much may lead to liver injury. This could be made worse if you have chronic liver disease or liver injury, which you may not be aware of. If you have a known history of chronic liver disease or other known reason why you should not take acetaminophen, you should not participate in this study. To minimize the risk, acetaminophen dosages have been calculated to be below the daily recommended total dosage.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

None

11.2 Potential Benefits to Others

Will be the first study of its kind to offer high quality evidence examining the effect of a multimodal pain regimen on pain control and narcotic prescription in this population of women after an uncomplicated Cesarean section. Could also be included in body of literature hoping to minimize opiate prescription.

12.0 Sharing Results with Subjects

Not applicable

13.0 Subject Payment and/or Travel Reimbursements

Patients will receive compensation for their completion of surveys. A Clincard will be issued to participants. The amount loaded on the card will be based on the total number of surveys they complete. The participants will receive $10 if they complete the one week post-discharge opiate consumption/pain control survey. The participant will be eligible to receive another $10 if they complete the two week post-discharge opiate consumption/pain control survey. They will also be eligible to receive $20 if they complete the WHOQOL-BREF survey, also two weeks after discharge. Total possible compensation will be $40.

14.0 Economic Burden to Subjects

14.1 Costs

The subjects will not be responsible for any additional costs due to participation in the study.

14.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Penn State Health Hershey Medical Center, 3rd floor labor and delivery and postpartum unit. Post-operative surveys to be completed online at the patient's personal residence.

15.2 Feasibility of recruiting the required number of subjects

On average, we perform 1-3 Cesarean sections five days per week on labor and delivery. Assuming an average of 2 C-section per day, we could theoretically enroll 10 patients per week and 40 patients per month. Assuming half of the patients agree to participate, we could enroll 20 patients per month and reach our target sample size of 144 subjects in 7-8 months.

15.3 PI Time devoted to conducting the research

The Co PI is an MFM fellow in the OB/GYN department with ample block research time to conduct and complete this project. He is entering his second of three years in his fellowship training. The bulk of patient enrollment could be completed during his third year of training, as he will be predominantly assigned to research (for at least 9 months). We will also enlist the help of a medical student and research coordinator to assist in patient enrollment. Assistance from other project members, including the PI, Program Director, Dr. Serdar Ural, will be provided.

15.4 Availability of medical or psychological resources

Resources are available 24/7 at the Penn State Hershey Medical Center if needed.

15.5 Process for informing Study Team

All members of the research team will have access to the IRB approved protocol and supporting documents. Additionally, the MFM division has research meetings during which all projects are discussed. During these meetings, the progress of this study will be reviewed and research members can clarify duties and expectations to ensure timely completion of the study.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Not applicable

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

Not applicable

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility*. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18.2 Recording of Adverse Events

Subjects will be routinely questioned about AEs while participating in this study.
An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms

• The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

• The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

• The test finding is considered an adverse event by the investigator.

18.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

Not applicable

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

The investigators will permit study-related monitoring, audits and inspections by the Penn State Quality Assurance Office, IRB and government regulatory bodies of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.) The investigators will ensure that capability for inspections of applicable study related facilities.

19.1.2 Safety Monitoring

Adverse events will be identified by the clinician providing care for the patient's intra-operatively and post-operatively. They will be educated to report any symptoms concerning for an AE to the PI and or Co-I. The investigator will confirm that all AEs are correctly entered into the AE case report forms and will notify the IRB. AEs will also be monitored via the REDCap "Termination Form" module so that we can monitor how many patients drop out due to AEs.

20.0 Future Undetermined Research: Data and Specimen Banking

Not applicable

21.0 References

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6. Viteri OA, England JA, Alrais MA, Lash KA, Villegas MI, Ashimi Balogun OA, et al. Association of Nonsteroidal Antiinflammatory Drugs and Postpartum Hypertension in Women With Preeclampsia With Severe Features: Obstet Gynecol. 2017 Oct;130(4):830–5.

7. Workman P, Spinosa D, Su H-C, Roeder H. Association of NSAIDs with Postpartum Blood Pressure in Women With Hypertensive Diseases in Pregnancy [26L]: Obstet Gynecol. 2017 May;129:S128.

8. Chang AK, Bijur PE, Esses D, Barnaby DP, Baer J. Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. JAMA. 2017 Nov 7;318(17):1661.

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10. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A Report from the WHOQOL Group. Qual Life Res. 2004 Mar;13(2):299–310.