STUDY TITLE:

Scheduled Ketorolac administration after cesarean section and its effect on opioid use: a randomized control trial

PRINCIPAL INVESTIGATOR

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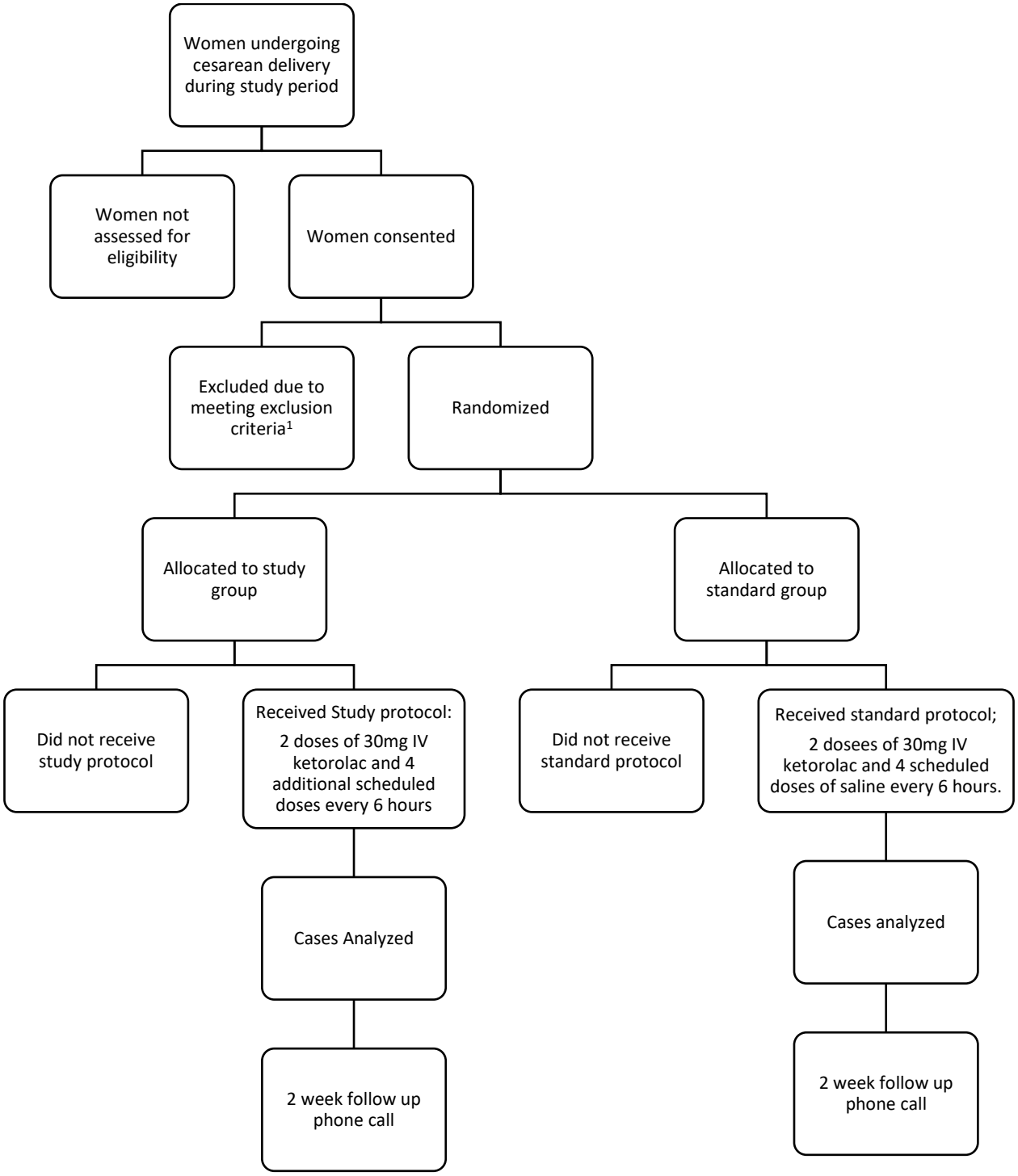
1. Study Schema



1. Exclusion criteria: see section 4.2 for full list of exclusion criteria

2. Introduction

2.1 Background and Rationale

Post-operative pain control is an issue not only in regards to patient satisfaction, but also patient outcomes. Pain in the early postpartum period can interfere with a woman's ability to care for herself and her infant. [1] Over-prescription as well as misuse of narcotic pain medications across the United States has been a popular topic of investigation. Compared to other surgical subspecialties, there is a paucity of literature regarding effective methods to decrease post-operative narcotic use in obstetric units, especially in the immediate postpartum period[2]. Our study evaluates how a protocol of scheduled non-narcotic analgesic used in the immediate post-operative period affects the amount of oral narcotic medication administered and patient pain scale scores.

A retrospective cohort study [3]was conducted to evaluate the difference in oral narcotic requirements postoperatively after implementing a new post-operative pain management protocol. This study included two hundred and eight cesarean sections, 3 of which were excluded for allergies to either hydrocodone/acetaminophen (HA) or NSAIDs. 110 women were in the standard protocol group and 95 were in the Ketorolac protocol group. The subjects in the standard group received up to 2 doses of 30mg of IV Ketorolac in the post operative period. The subjects in the Ketorolac group received 6 scheduled doses of 30mg IV Ketorolac during their post operative course. On average, the standard group received 5.39 doses (±4.682) of hydrocodone10mg/acetaminophen (H10A) and the Ketorolac group received an average of 3.44 doses (±4.544) of H10A. See table below. Assuming equal variance, a t-score of 3.026 (CI 0.680-3.226) was calculated, with a P value of .003 for doses of H10A administered. After a secondary analysis of the data, a significant difference in the amount of hydrocodone5mg/acetaminophen (H5A) required by the Standard protocol and the Ketorolac protocol was identified in patients who underwent a primary cesarean section (3.84 vs. 2.39, respectively. P= 0.031) Those who underwent repeat cesarean section had similar outcomes as the total sample, in that those in the Ketorolac group required less doses of H10A post operatively (5.49 Standard Group, 3.13 in Ketorolac group, P = 0.026). When these doses of H5A and H10A were converted to MME, the study group consumed an average of 69.9MME and the Ketorolac group consumed an average of 47.3 MME. The Ketorolac group consumed approximately 33% less MME than the standard group. This data supports that scheduled Ketorolac in the post cesarean section population, may help to decrease the amount of narcotic required while in house. We hypothesize that subjects who receive scheduled IV Ketorolac during the post-operative period will require less morphine milligram equivalents than those receiving the standard pain control protocol. A randomized controlled trial, would allow us to test this hypothesis. We hypothesize that there will be a difference in the secondary outcomes as well; that both the pain scores and overall patient satisfaction, as evaluated by phone call, will be improved for the study group.

Pain Scores, HA Doses Before and After Implementing Ketorolac Protocol

Variable	Standard Protocol	Ketorolac Protocol	*P*
Pain Score* **			
6 hours	3.20±2.579	2.93±2.505	0.444
12 hours	3.26±2.577	3.35±2.753	0.820
24 hours	4.21±2.709	3.88±2.508	0.368
48 hours	3.45±2.611	3.62±2.667	0.663
Opioid Dose			
H5A*	3.20±3.117	2.60±2.251	0.112
H10A*	5.39±4.682	3.44±4.544	0.003

***Based on a 100mm visual analog pain scale
*In number of doses, hydrocodone5mg/acetaminophen (H5A), hydrocodone10mg/acetaminophen (H10A)
Data are mean±standard deviation
P values are determined using Students *t* test for parametric data and X^2 for categorical variables

Post-operative pain is typically controlled using a stepwise, multimodal approach[4]

. Although this approach was initially developed for the treatment of cancer pain, it can be adapted to postoperative and postpartum pain.[1] A stepwise approach refers to administering medications based on the patient's level of pain. Pain can be assessed with a visual analog scale (VAS)[5]. A multimodal approach refers to using medicines with varying mechanisms of action to control pain. Typically, a combination of nonsteroidal anti-inflammatory drug (NSAID) and an opioid are used during the postpartum period[1].

Given the relatively recent opioid epidemic in the United States, the Substance Abuse and Mental Health Services Administration has identified opioids as the most commonly abused prescription drug in the United States[6]. Additionally, over prescription of narcotic pain medications has been associated with the increase of overdose deaths involving opioids.[6] Efforts to decrease the amount of opioids dispensed in the hospital and prescribed as an outpatient can help decrease the propagation of this epidemic.

NSAIDs like Ketorolac combine analgesic and anti-inflammatory properties. Ketorolac's efficiency which is comparable to morphine, with a longer duration of action and fewer adverse effects.[7] Ketorolac has been shown to have a morphine-sparing effect in orthopedic and gynecologic surgery.[8–10]There is data to support that Ketorolac is a safe and effective analgesic for the postpartum patient.[10–13] However, there is a paucity of literature that evaluates the effect of scheduled intravenous Ketorolac on the amount of oral narcotic administered in the postpartum period.

Is there an active control group?

☐ **Yes** ☑ **No**

2.2 Risks to Subjects

Foreseeable risks, discomforts, hazards and/or inconveniences include;

1. Adverse reaction to Ketorolac. The probability of this is low and the magnitude of the reaction is unpredictable. Adverse reactions are typically quickly and effectively reversed when recognized quickly. Side effects of Ketorolac are rare, but can potentially include headache, upset stomach, nausea, vomiting. Other side effects or risks of Ketorolac include gastrointestinal bleeding, ulceration and perforation, kidney failure, hemorrhage, renal papillary necrosis and other renal injury, cardiovascular thrombotic events, myocardial infarction and stroke, hypertension, congestive heart failure and edema, skin reactions, increased liver function tests, anemia and anaphylaxis. Precautions will be in use with patients with a history of asthma.
2. Therapy with other NSAIDs will not be administered to subjects.
3. Discomfort or pain at peripheral IV line. The probability of this is low and the magnitude is small. The discomfort can easily be treated or reversed. An IV will be kept in place for nor longer than the standard time frame. Patients who are tolerating PO can have the IV removed if they wish. Those in the study group, however, need an IV for drug administration. Women who are assigned to the study plan will need to have an intravenous catheter in place for the first 24 *hours after leaving the operating room. Typically, the IV is removed about 12 hours after a patient leaves the operating room.* Loss of privacy of protected health information. The probability of this is low because the study database will be kept on a password protected computer in a locked office.
4. Ketorolac is approved by the American Academy of Pediatrics and considered safe for breastfeeding moms and babies (L2 risk category). Any adverse events experienced by the subject or her newborn during the study will be promptly discussed with the newborn's healthcare provider.

2.3 Potential Benefits to Subjects

There is no direct benefit to the study participants.
Potential benefits may include:

1. Decreased postoperative pain. This benefit could potentially aid in faster recovery

2. Decreased need for opiate medications. This benefit could also lead to enhanced recovery with quicker return of bowel function and decreased drowsiness.
3. Decreased amount of opiate medications

2.4 Alternatives

The alternative is to NOT participate in the research study. Patients who forgo participation in the research study will receive the standard post-operative pain protocol. The standard clinical care includes oral ibuprofen and acetaminophen, as well as intravenous Ketorolac on an as needed basis. Patients who do not participate in the trial may receive Ketorolac if they request pain medications during the first 18 post-operative hours.

3 Objectives

Our study evaluates how a protocol of scheduled non-narcotic anesthetic used in the immediate post-operative period affects morphine milligram equivalents (MME) for oral narcotic medication administered. The objective of the study is to identify a post-operative pain control regimen that can decrease the MME administered in the post-operative period.

The primary outcome will be the amount of morphine milligram equivalents (MME) used in each group. Secondary outcomes will include pain scores, postoperative complete blood count, post operative vaginal bleeding, and post-operative satisfaction with care received during admission.

4 Enrollment and Withdrawal

4.1 Inclusion Criteria

Women presenting for care at Tufts Medical Center as an outpatient in obstetrics clinic or on Labor and Delivery and undergo a cesarean section for any indication at Tufts Medical Center, and who are willing to have a phone call follow up conversation 2 weeks after their surgery. There is no age *eligibility*. All of the subjects will be pregnant women. Some of these subjects may be pregnant minors.

4.2 Exclusion Criteria

1. Subjects under the age of 16 years old.
2. Patients with allergy to Ketorolac, NSAIDS or aspirin
3. Patients with peptic ulcer disease, preexisting kidney or liver disease.
4. Duramorph is not used as the anesthetic for the spinal/epidural during the cesarean section.
5. Patient is hemodynamically unstable due to hemorrhage.
6. Patient requires therapeutic anticoagulation in the post-operative period
7. Patients with peripartum cardiomyopathy, other cardiocascular disease, or history of congestive heart failure or cardiac decompensation.
8. Patients with HEELP, eclampsia, pre-eclampsia or hypertension
9. Patients with coagulation disorders, or bleeding diatheses
10. Patients taking probenecid or pentoxifylline
11. Past history of Stevens-Johnson Syndrome, toxic epidermal necrolysis
12. Recent history of gastrointestinal bleeding, suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis
13. Patients with a history of asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDS
14. Patients who are currently receiving a full dose of aspirin or NSAIDs
15. Patients who have an epidural or intrathecal administration
16. Emergent circumstances where there is not sufficient time to perform informed consent.
17. Provider decision to exclude patient.

18. ***A study subject may participate in any other research study while participating in this research study. Participation in another research study is not an exclusion criteria for this study.

4.3 Withdrawal of Subjects

Anticipated circumstances under which subjects will be withdrawn from the research without their consent:

1. Adverse reaction to Ketorolac
2. If an above mentioned exclusion criteria develops, the study drug will be stopped.
3. This is an intent to treat study. The patient's will remain in the group that they are randomized too.
4. If a subject requires additional pain medication, the subject will get an opioid medication, as is current practice.
5. A creatinine value will be measured on POD#1 and POD#2. If creatinine is equal to or greater than 1.2mg/dL, then the study drug will be stopped. If the incidence of creatinine values equal to or greater than 1.2mg/dL reaches 5% of the subjects, the study will be stopped for safety.[15]

Information collected on subjects prior to withdrawal from the research study will be included in the final analysis. No additional specific safety precautions are necessary for subjects who withdraw or are withdrawn aside from routine post-operative care.

4.4 Recruitment and Retention

4.4.1 Local Recruitment Methods

Describe the following attributes of the recruitment plan for the local Tufts site:

Subjects will be recruited either in their prenatal visits, when their cesarean section is scheduled, or upon presentation to labor and delivery. They will be interviewed and consented by the principle investigator, co-investigator another member of the research team. If they are consented during their prenatal visit, the subject will have several days to weeks to consider participation. If they subject is consented upon admission to labor and delivery, then they will have hours to consider participation. Patients in emergent circumstances where there is not sufficient time to perform informed consent will not be enrolled or approached for participation in this study.

The first study visit will be consent and enrollment. This visit may occur during a patient's prenatal visit or at the time of admission to labor and delivery. Subjects will be from the maternal fetal medicine and general obstetrics clinics at the main Tufts Medical center, as well as any patents admitted to Tufts Labor and Delivery unit.

Potential subjects will be identified by clinicians in the outpatient clinics and on labor and delivery.

5 Patients may also be consented remotely. This situation may arise when their prenatal care is not at Tufts or if they are having prenatal care over telemedicine. Additionally, patients that present to labor and delivery for planned vaginal delivery may be consented for the study in the event that they have a cesarean section. I have reviewed HRP-092 and will follow this policy. We will follow SOP: remote informed consent process HRP-092 if consent is not obtained in person.

5.4.1 Study-Wide Recruitment Methods

Is this is a multicenter study where subjects will be recruited by methods not under the control of the local Tufts site (e.g., call centers, national advertisements)?

☐ **Yes** ☑ **No**

5.4.2 Payment

Will subjects receive money, gifts, or any other incentive for participating in this study?

☐ **Yes** ☑ **No**

5.4.3 Reimbursement

Will subjects be reimbursed for their expenses, such as travel, parking, meals, or any other study related costs?

☐ **Yes** ☑ **No**

6 Study Design

5.1 Study Timelines

The subject's participation will last a total of 2 weeks. This time will span from immediately after delivery until 2 weeks postpartum.

The enrollment period is anticipated to last 6 months.

The estimated date of completion of this study is May 2022.

The first study visit will be consent and enrollment. This visit may occur during a patient's prenatal visit or at the time of admission to labor and delivery. A phone call conversation at the 2 week postpartum mark will occur. This phone call will include a series of 9 questions and should take about 10 minutes to complete.

5.2 Procedures

- Is there a placebo control arm?

☑ **Yes** ☐ **No**

All patients who are seen at Tufts Medical Center for maternal fetal medicine or general obstetric care in the outpatient setting will be screened. They will be consented and enrolled if eligible at that time. See section 4.4.1. All patients who are not already screened or enrolled will be screened upon admission to Tufts Medical Center Labor and Delivery unit.

A full medical history and physical examination is routinely performed. The H&P will be reviewed prior to consenting the patient to assess for exclusion criteria. Also, permission of the attending surgeon will be solicited prior to consent.

Ketorolac is the drug used in this research. It is already used routinely on Labor and Delivery at Tufts Medical Center, as well as the Mother-Infant Unit.

Subjects who consented to be part of the trial will be randomized at the time of skin closure of their cesarean section to either the standard group or the study group. These groups will be blinded to the subjects and providers. If a serious adverse reaction occurs during the study period, that subject may become unblinded. The investigational drug pharmacy services (IDS) will have the randomization scheme and will assign the subject to either study or standard group. A paper order will be faxed down to the IDS pharmacy one the subject leaves the operating room after her cesarean section. This paper order will be signed by either the PI or a co-investigator of the study. The standard group will receive the standard treatment of 2 doses of 30mg IV

Ketorolac and the remaining 4 doses of placebo (normal saline). The study group will receive 6 doses of 30mg IV Ketorolac scheduled every 6 hours. Ketorolac is FDA approved for safety at this dosage. The subject will receive her first dose in the operating room. A dose of Ketorolac will be administered in the OR to all subjects. This will be administered by anesthesia. Of note, any intrathecal or epidural catheters will be removed prior to administration of Ketorolac. The Ob/Gyn residents will be responsible for placing the orders in Soarian and to fill out the IDS paper order form. These duties are within the scope of their regular job duties as resident physicians. Please see below for sample order set. Pain scores will be evaluated using a visual analog pain scale every 6 hours throughout hospitalization and recorded in the electronic medical record per standard of care. The amount of oral opiate medications administered for subjects in each group will be recorded in the electronic medical record as well. Pre operative and Post operative day #1 hematocrit values will be recorded. This is a routinely performed test, but will be providing data for the research. The number of peripads used will be collected and weighed as a means to estimate post partum vaginal bleeding for the first 24 hours post partum. Post operative day #1 and #2 serum creatinine measurements will also be obtained. The first will be obtained at the same blood draw as the hematocrit measurement. The POD#2 measurement will be an additional blood draw.

An intent-to-treat analysis will be used and a per-protocol analysis will be conducted among those who complied with the protocol.

Data will be collected in the electronic medical record system while the subject is admitted to Tufts Medical Center. A phone survey will be conducted 2 weeks from the delivery date. Survey is attached as separate document. If the participant does not answer, the caller will leave a voicemail. The voicemail transcript is attached. One additional attempt will be made to call the patient within 24 hours of the first call. The phone survey 2 weeks later is the only visit that is solely for research purposes.

Sample Soarian Order Set:

Post-Operative Pain Control Study Order Set

- Ketorolac (Toradol) 30mg IV x 2 doses Q6hrs starting in OR
- = then Post-Operative Pain Control Study IV injection, q6hrs x 4 doses
- 18 hours after intrathecal/epidural morphine, if patient tolerating fluids by mouth, patient may have oral acetaminophen or Percocet
  - Acetaminophen 650mg 1 TAB Q6PRN pain 1-3
  - Oxycodone5 1 TAB Q4HPRN pain 4-6
  - Oxycodone 5 2 TAB Q4HPRN pain 7-10
- If patient has pain prior to 18 hours after intrathecal/epidural morphine that is not controlled, the RN is to page OB resident to evaluate patient and place an order for pain medication.

Schedule of Events

Recruitment	At prenatal visit or admission to labor and delivery at Tufts Medical Center
Randomization	At time of skin closure in operating room

Study Group □ Ketorolac 30mg IV q6hours x 2 doses □ then Ketorolac 30mg IV q6hrs x 4 doses	First dose in the operating room. The remaining doses will be administered on L&D or mother-infant unit.
Standard Group □ Ketorolac 30mg IV q6hrs x 2 doses □ then 4 doses of placebo, q6 hours	First dose in the operating room. The remaining doses will be administered on L&D or mother-infant unit.
Morphine Milligram equivalents (MME) measured using a MME conversion calculator[14] • Example: Oxycodone is 1.5 MME	The MME's used by each subject will be measured from the time the patient arrives to the recovery room until post operative hour 72 (approximately post operative day #3, as this is the standard amount of time patients stay in the hospital after a cesarean section.)
Cases will be analyzed	Upon patient discharge
Phone call	2 weeks after discharge
Data Analysis	

5.3 Evaluations

Will you perform any laboratory tests for this study?

☑ **Yes** ☐ **No**

A complete blood count will be collected and values recorded. This laboratory test is standard of care and not solely for the purpose of this study.

5.4 Collection and Storage of Human Biological Specimens (Tissue Banking)

Will biological specimens be stored for **future, unspecified**, research?

☐ **Yes** ☑ **No**

6 Ethics and Protection of Human Subjects

6.1 Informed Consent Process

Will subjects be required to provide informed consent?

☑ **Yes** ☐ **No**

Informed consent will be obtained after either (1) admission to labor and delivery, (2) during an office visit to the obstetrics and gynecology department at Tufts Medical Center for regular prenatal care at a date prior to their planned hospital admission, or (3) remotely (in accordance with SOP: remote informed consent process HRP-092) if consent is not obtained in person by a qualified member of the research team. For in person consent, the consent interview will take place in the subject's private room at Tufts MC after the patient has been seen by the necessary medical teams. For in person consent or remote consent, when the patient is initially approached to participate in the

study, the study will be explained and they will have the opportunity to ask any questions. We will explain that their participation in the study does not mean they will have a cesarean section, and that study participation will not change their medical care during their hospitalization. We will discuss that even if the patient does not participate in the study, she may receive either of the two pain management protocols, depending on the preference of the medical team. We will discuss that their medical history, demographic information, and outcomes will be kept confidential on a locked computer. Subjects will be asked if they understand the study and that it is voluntary. Subjects will not be pressured to make a decision to participate, and while they will have the option of signing consent at the time of the initial interview, or if they would like more time, then a member of the research team will check in with the subject the next day. The subject can decide not to participate in the study at any time. The persons obtaining informed consent are all medical doctors or research staff from the department of obstetrics and gynecology on the study team; however this person may also be the medical doctor in charge of the patient's care as well as a research team member.

We do anticipate enrolling non-English speaking patients, if they fit our inclusion and exclusion criteria. For these patients, the Tufts Medical Center Short Form will be used *per the Tufts IRB policy.*

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8 The research will follow SOP: Written Documentation of Consent (HRP-091) and SOP: remote informed consent process HRP-092 if consent is not obtained in person.

8.1 Waiver or Alteration of Consent Process

- Is a waiver or alteration of the consent process being requested for this study?
  ☐ **Yes** ☑ **No**
- *Is a waiver of the consent process being requested for parents for research involving children?*
  ☐ **Yes** ☑ **No**
- Is a waiver of the consent process for planned emergency research being requested?
  ☐ **Yes** ☑ **No**

8.2 International Research – N/A

8.3 Confidentiality

The data will be stored in a file on a secured computer in the office of Maternal Fetal Medicine Fellows at Tufts Medical Center. The original ICF's will also be stored in the office of Maternal Fetal Medicine Fellows in a secure storage bin. There will be no specimens stored for the research. The data will be stored for seven years after study closure. The PI and other members of the research team will have access to the data. The data will be coded using two spreadsheets. One spreadsheet will have patient identifying information, as well as a code. The second spreadsheet will have the coded information, along with the data retrieved from the study. Again, both spreadsheets will be stored on a password protected computer in a locked office.

8.4 Provisions to Protect the Privacy Interests of Subjects

The patients PHI will be kept in a password protected computer in a locked office.

The patient will be consented in a private room. The patient's family may be present. If the patient is consented on L&D, the patient's nurse may be present as well.

8.5 Provisions to Monitor the Study to Ensure the Safety of Subjects

A Data Safety and Monitoring Board is not necessary for this study. If SAEs occur, the evaluation will be investigator initiated, and events will be reported to the IRB per the IRB's Reportable New Information policy. The investigator and members of the research team will monitor the study through monthly review to ensure the proper reporting of SAE's to the IRB.

Reporting timeframe for SAEs and AEs: SAEs and AEs will be reported to the Tufts MC/TUHS IRB per the IRB's Reportable New Information Policy.

Accountability procedures as they relate to drugs, devices, and data: Every effort will be made to keep a subject's data confidential. Data collected will be maintained on a password protected database in a locked office at Tufts MC. Study data will be kept in a locked electronic database for 7 years after the completion of the study and the study is closed with the IRB.

8.6 Compensation for Research-Related Injury

Does the research involve greater than minimal risk to subjects?

☐ **Yes** ☑ **No**

8.7 Economic Burden to Subjects

Does the research involve any costs to subjects?

☐ **Yes** ☑ **No**

6.10 Vulnerable Populations.

Will pregnant women be enrolled?

☑ **Yes** ☐ **No**

Pregnant women will be enrolled in the study, as the premise of this study is to evaluate postpartum pain control. The study will not alter the course of the subjects' prenatal care or mode of delivery. If a woman decides to participate in the study, any study interventions will not occur until after delivery. This population was chosen for research due to the increased risk of opioid misuse among women of childbearing age. The hope is to decrease the amount of opioids required while inpatient, and outpatient. Any risk of this research is the least possible for achieving the objectives of this study.

There will be no risk to the fetus, or neonate as the medication will not be administered to the subject until after delivery.

Will the research involve neonates of uncertain viability or non-viable neonates?

☐ **Yes** ☑ **No**

Will subjects who are not yet adults (neonates, children, teenagers) be enrolled?

☐ **Yes** ☑ **No**

Will minors who are:

i) married, widowed, divorced; or
ii) the parent of a child; or
iii) a member of any of the armed forces; or
iv) pregnant or believes herself to be pregnant; or
v) living separate and apart from his/her parent or legal guardian, and is managing his/her own financial affairs be approached for study participation for either themselves or their child?

☑ **Yes** ☐ **No**

Pregnant subjects who are under the age of 18, are considered emancipated minors, persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities. They will be deemed capable of executing informed consent for this study. Subjects who are under the age of 18 and are pregnant will be evaluated, as for all other potential subjects, for their ability to appreciate the risks, benefits, and alternatives for indicated care. Informed consent will be executed in the same way as for other subjects; in a manner that allows for privacy and independent decision making.

Will wards of the state and/or children at risk of becoming wards of the state be enrolled (this includes foster children or any child that is in state custody)?

☐ **Yes** ☑ **No**

Will cognitively impaired adults (adults with impaired-decision making capacity) or adults who may lose the capacity to consent be enrolled?

☐ **Yes** ☑ **No**

Will prisoners be enrolled?

☐ **Yes** ☑ **No**

Will students and/or employees be enrolled in this research?

☐ **Yes** ☑ **No**

9 Adverse Event Monitoring

9.1 Definitions

Definition of Serious Adverse Event (SAE) and Adverse Event (AE) for this study: A SAE would be one of the following:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. requires inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

An AE would be any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research..

9.2 Reporting Procedures

A Data Safety and Monitoring Board is not necessary. If SAEs occur, the evaluation will be investigator initiated, and events will be reported to the IRB per the IRB's Reportable New Information policy.

Reporting timeframe for SAEs and AEs: SAEs and AEs will be reported to the Tufts MC/TUHS IRB per the IRB's Reportable New Information Policy. For those SAE's and AE's not reported to the IRB, these will be identified and managed internally by the research team. SAE and AE's will be recorded in a database on a password protected computer in a locked office. The subject will be treated accordingly and will be counseled regarding the events.

Accountability procedures as they relate to drugs, devices, and data: Every effort will be made to keep a subject's data confidential. Data collected will be maintained on a password protected database in a locked office at Tufts MC. Study data will be kept in a locked electronic database for 7 years after the completion of the study and the study is closed with the IRB.

9.3 Reportable New Information

Reportable new information will be reported to the IRB per the Tufts Health Sciences IRB's Reportable New Information policy.

10 Statistical Considerations

10.1 Study Endpoints

We expect to see a statistically significant difference in amount of MME's administered between the standard and study protocol arms. The endpoint wil*l be when* 71 subjects *are randomized to e*ach study arm. The study results will be reported in a peer reviewed journal after study completion.

10.2 Statistical Analysis

Demographic and clinical variables will be compared between the two groups to check for balance. If it found that confounders are imbalanced between groups, a multivariable linear regression model will be performed to adjust for those variables. In addition, if subjects do not receive the treatment they were randomized to, a secondary analysis will be performed analyzing patients as they were treated.

All attempts will be made to minimize loss-to-follow-up, and reasons for any missing data will be tabulated. Procedures to prevent missing data are described in detail below.
In addition to evaluating the primary outcome of amount of MME administered, secondary analyses will be performed. For secondary analyses, each outcome will be analyzed independently, including subject reported pain scores and satisfaction with post-operative experience (from phone call survey), estimated blood loss of the surgery and change in pre-operative to post-operative hematocrit.
The average morphine milligram equivalents (MME) administered to patients during the post-operative period after a cesarean section using the current (standard) protocol is 112.4 MME, with a standard deviation of 68.7. The effect size is determined to be a 30% reduction in MME in the Ketorolac group, which would be an average of 80 MME. In order to detect at 30% reduction, with an alpha of 0.05 and a power of 80%, 71 subjects will need to be in each group.

Patient noncompliance from the protocol was not anticipated at the time of study initiation. Review of blinded interim data showed patient noncompliance with the protocol. This interim information was obtained without knowing the allocation of these participants or outcome data. With this information, the sample size was adjusted to account for 4% noncompliance.

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(68.7^2 + 68.7^2/1)(1.96 + 0.84)^2}{32.4^2}$$

$$n_1 = 71$$

$$n_2 = K * n_1 = 71$$

$\Delta=(\mu_2-\mu_1)$ = absolute difference between two means

$\sigma 1,\sigma_2$ = variance of mean #1 and #2

n_1 = sample size for group #1

n_2 = sample size for group #2

α = probability of a type I error (0.05)

β = probability of a type II error (usually 0.2)

z = critical Z value for a given α or β

k = ratio of sample size for group #2 to group #1

Inflated Sample Size = Required Sample Size/(1 - noncompliance percent) = 142/(1-0.04) = 142/(0.96) = 147.9.7 = 148 patients.

10.3 Number of Subjects

All of the subjects of this study will be enrolled at Tufts Medical Center. Per the power calculation as above, 71 subjects will be enrolled in each arm. Anticipating patient noncompliance or withdrawal from the protocol, 74 patients will be enrolled in each arm. Up to 500 subjects will be enrolled in order to have 148 subjects complete the study.

10.4 Data Management

Data with patient demographic and operative information will be recorded on a paper form during the cesarean delivery, and placed in a locked box at the end of the case. Forms will be collected and inputted into a password protected data set which will be on a Tufts Medical Center computer in a locked office and the forms will be stored in a locked office. Clinical data from the hospital admission and phone calls will be recorded in the electronic medical record, which requires a username and password to access. Data will be abstracted from the electronic medical record and inputted into the locked spreadsheet.

The data will be collected from the electronic medical records system and from the phone call 2 weeks postpartum. The data collected will include the number of doses of opiate medications administered during the postpartum period, as well as the pain scores. The phone call will consist of a series of multiple choice questions. All data will be recorded and entered into a secured, de-identified Excel spreadsheet, which is kept on a password protected computer in a locked office. The data will be stored for 7 years after the completion of the study.

Certificate of Confidentiality: Not applicable

Parties who will have access to the data, including the key to the identity code:
Michael House MD, Jean Hostage MD, Members of the investigational drug pharmacy at Tufts Medical Center.

Parties who will have access to research records:
Michael House MD, Jean Hostage MD, Members of the investigational drug pharmacy at Tufts Medical Center

10.5 Randomization

Will subjects be randomized?

☑ **Yes** ☐ **No**

At the time of skin closure, participants will be randomized to receive either the standard or study protocol using a digital randomization sequence generator based on randomly permuted blocks of 4. Based on this sequence, the IDS pharmacy will assign the subject to either the study or standard group. The subjects, care providers and investigators will be blinded to the group assignment.

11 Drugs or Devices

Will the research involve drugs?

☑ **Yes** ☐ **No**

Will the research involve devices?

☐ **Yes** ☑ **No**

If **Yes** to either, describe the following:

This research involves Ketorolac, which is a drug that is already commonly used on the Labor and Delivery and Mother-Infant unit of Tufts Medical Center. The investigational drug pharmacy will be accountable for the drugs.

A computerized order set (see example in section 5.2), will be used for this research. The Ob/Gyn residents, fellows and attendings will use this order set after randomization of subjects to each group. A paper order form created by the IDS pharmacy will also be completed and sent to the IDS pharmacy in order to prepare the standard or study syringes. The anesthesiologists will administer the first dose of Ketorolac in the operating room. Nurses on Labor and Delivery and the Mother-Infant Unit will administer subsequent doses of Ketorolac or placebo, as well as any other medications ordered by the physician teams. This is within the scope of the nurses' typical job duties.

12 Study Administration

12.1 Setting

The study will be conducted at Tufts Medical Center, 800 Washington Street, Boston MA 02111. Records will be kept on a locked spreadsheet on a computer in a locked office at Tufts Medical Center. The record operating room information will be used to input data

into the spreadsheet and then stored in a locked office. Study participation will not require an increase in the length of hospital stay.

12.2 Registration

Patients will be designated a study participant when they sign the informed consent document. Subjects will be randomized to either study arm at the time of skin closure when they undergo cesarean delivery. Not all patients will be randomized or included in the analysis as not all patients who sign an informed consent will have a cesarean delivery.

12.3 Resources Available

The primary investigator and Co-Investigators will be responsible for conducting the study. The PI and other members of the research team will be responsible for consenting patients, organizing and analyzing data and for communicating with study participants. Study personnel will not always be present during randomization and medication administration.

All members of the study team are physicians and have completed CITI training.

Any subject safety issues that occur while the PI is away or unavailable can be addressed by the on call supervising physician.

Our research team will be able to feasibly recruit the required number of suitable subjects within the proposed recruitment period. We will have access to at least 100 potential subjects per month (as estimated by the average number of deliveries at Tufts Medical Center each month), with about 40 of these subjects undergoing cesarean section (as estimated by the 40% cesarean section rate at Tufts Medical Center).

12.4 IRB Review

An appropriate IRB registered with the OHRP, will review and approve this study. Any amendments to the protocol or informed consent documents will be reviewed and approved by the IRB prior to use, unless required to eliminate an apparent immediate hazard to subjects.

12.5 Multi-Site Research

Is this a multi-site study where Tufts is the sponsor, primary grant recipient, or coordinating site?:

☐ **Yes** ☑ **No**

12.6 Community-Based Participatory Research

Will this study involve community-based participatory research?

☐ **Yes** ☑ **No**

12.7 Sharing Results with Subjects

Will results (overall study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) be shared with subjects or others (e.g., the subject's primary care physician or the subject's treating physician)?

☐ **Yes** ☑ **No**

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