Prescription After Cesarean Trial (PACT)

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National Clinical Trial (NCT) Identified Number: NCT04296396

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Summary of Changes from Previous Version

Affected Section(s)	Summary of Revisions Made	Rationale
1.1	Recruitment window updated	Delays due to COVID-19 pandemic
1.3, 5.5.2, 7.1.3	Six week post-partum visit changed from an in-person visit to an in-person or telehealth visit.	The 6-week postpartum clinic visit may be performed virtually due to the COVID-19 pandemic.
5.5.2	Deleted sentence pertaining to a small gift for the baby and childcare.	This sentence was inadvertently included.
6.1.1	The calculation of the individualized opioid prescription protocol was changed to exclude the first 12 hours after a cesarean delivery (rather than the first 24 hours).	Women are being discharged earlier in some locations due to the COVID-19 pandemic.
7.1.3	Added the collection of COVID-19 testing and results.	This is a new variable that should be addressed in the analyses.
8.4.7	Added a new planned subgroup analysis to evaluate time from delivery to discharge.	Women are being discharged earlier in some locations due to the COVID-19 pandemic and this may have an affect on pain level and opioid use following discharge.

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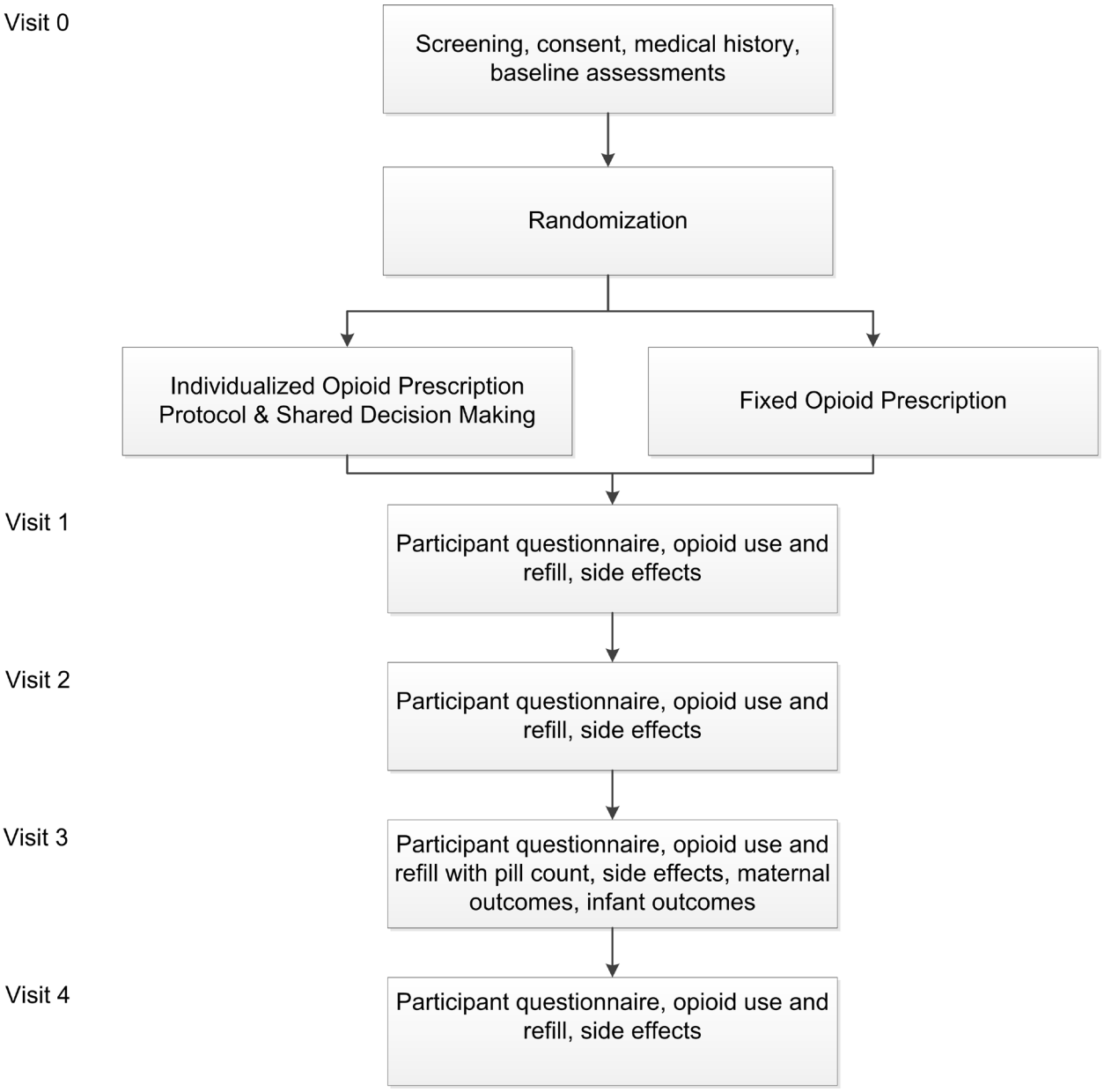
1 Protocol Summary

1.1 Synopsis

Title:	Prescription After Cesarean Trial (PACT)
Study Description:	This is a non-inferiority randomized trial of 5,500 women with a cesarean delivery randomized prior to discharge to either an individualized opioid prescription protocol (IOPP) that includes shared decision making or to a fixed opioid prescription of 20 tablets of oxycodone 5mg.
Objectives:	Primary: To evaluate whether IOPP with shared decision making is not inferior to a fixed opioid prescription of 20 tablets of oxycodone 5mg in pain management defined as the presence/absence of moderate to severe pain at 1 week after discharge. Moderate to severe pain is defined as a value of 4 or higher on the Brief Pain Inventory worst pain scale (0 to 10) in the last 24 hours. Secondary: To evaluate whether IOPP with shared decision making 1) decreases an opioid refill prescription, 2) decreases the total amount of opioid tablets prescribed and the total morphine milligram equivalents used, 3) has equivalent pain intensity and interference, and satisfactions scores, and 4) reduces adverse maternal and infant outcomes.
Endpoints:	Brief Pain Inventory pain severity (worst, least, average, current) in last 24 hours, Brief Pain Inventory pain interference during the past week, number of opioid prescriptions filled beyond that prescribed at discharge, number of opioid tablets prescribed and unused from discharge, total morphine milligram equivalents used, global impression of change in overall pain with treatment, maternal outcomes, and infant outcomes
Study Population:	Women with a cesarean delivery who deliver at one of the NICHD Maternal-Fetal Medicine Units Network hospitals
Description of Sites Enrolling Participants:	The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, currently consisting of twelve clinical centers: University of Pittsburgh, University of Alabama at Birmingham, Ohio State University, University of Utah, Brown University, Columbia University, University of Texas Medical Branch – Galveston, Case Western Reserve University, University of Texas Houston, University of North Carolina Chapel Hill, Northwestern University, and University of Pennsylvania.
Description of Study Intervention:	An individualized opioid prescription protocol that includes shared-decision making.
Study Duration:	Recruitment between June 2020 – August 2021. Follow-up, closeout and data analysis by March 2022.
Participant Duration:	90 days postpartum

1.2 Schema


Visit 0
Screening, consent, medical history, baseline assessments
Randomization
Individualized Opioid Prescription Protocol & Shared Decision Making
Fixed Opioid Prescription
Visit 1
Participant questionnaire, opioid use and refill, side effects
Visit 2
Participant questionnaire, opioid use and refill, side effects
Visit 3
Participant questionnaire, opioid use and refill with pill count, side effects, maternal outcomes, infant outcomes
Visit 4
Participant questionnaire, opioid use and refill, side effects

1.3 Schedule of Activities

Measure	Visit 0: Screening & randomization	Visit 1: 1-wk post discharge remote visit	Visit 2: 2-wk post discharge remote visit	Visit 3: 4-8-wk postpartum in-person or virtual visit	Visit 4: 90-day postpartum remote visit
Informed consent	X				
Demographics	X				
Medical history	X				
Substance use (TAPS) *	X				
Opioid Risk Tool	X				
Randomization	X				
BPI pain severity *	X	X	X	X	X
BPI pain interference *	X	X	X	X	X
Pain score assessed by a visual analog scale	X			X	
Pain Catastrophizing Scale *	X			X	
Physical functioning (PROMIS) *	X			X	
Sleep duration and disturbance (PROMIS)*	X			X	
Depression (PHQ-2) *	X			X	
Edinburgh Postnatal Depression Scale	X			X	
Anxiety (GAD-2) *	X			X	
Global impression of change in overall pain with Treatment *		X	X	X	X
Number of opioids prescribed, used (MME) and unused		X	X	X (pill count)	X
Opioid prescription refilled (or initially filled if not prescribed at discharge)		X	X	X	X
Opioid-related side effects		X	X	X	X

Measure	Visit 0: Screening & randomization	Visit 1: 1-wk post discharge remote visit	Visit 2: 2-wk post discharge remote visit	Visit 3: 4-8-wk postpartum in-person or virtual visit	Visit 4: 90-day postpartum remote visit
Current Opioid Misuse Measure				X	X
Other pain medication use	X	X	X	X	X
Breastfeeding	X	X	X	X	X
Maternal & infant outcomes				X	

* Effectiveness Research Network common data element

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 between providers and institutions. Pain thresholds and analgesic requirements vary between patients, and studies suggest that most women are given prescriptions for at least 10 more tablets at discharge than needed.[1,2] The consequence of over-prescribing opioids for 1.2 million cesareans annually is 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. The one-size-fits-all approach to pain management is clearly suboptimal. Some women may not even need opioids: one small study reported that pain scores were higher among women who were prescribed opioids than those who were prescribed ibuprofen and acetaminophen.[3]

While recent studies have evaluated opioid prescribing practices, there are limited data on the effect of using an individualized opioid prescription protocol following a cesarean delivery. It is plausible that modifying the opioid prescription quantity and incorporating a patient driven approach would improve post-cesarean opioid prescribing practices by reducing the number of excess tablets. To test whether this approach can be used without compromising pain management, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal Fetal Medicine Units (MFMU) Network proposes a randomized trial of an individualized opioid prescription protocol (IOPP) at discharge after cesarean delivery versus a prescription for a fixed amount of opioid tablets which approximates current standard of care at the participating institutions.

2.2 Background

The US today faces a major opioid pandemic. Deaths from prescription opioid overdoses quadrupled between 1999 and 2010, with a total of 16,651 deaths in 2010.[4-6] 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%).[7] 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).[8,9] Secondly, surgeons tend to provide more opioids than a patient uses post-operatively, 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.

In 2017, approximately 1 in 3 women (32%) in the US gave birth by cesarean delivery.[11] Almost universally, postoperative pain control regimens constitute non-opioid analgesia (which typically includes a non-steroidal anti-inflammatory drug (NSAID) and acetaminophen), in addition to opioid analgesics. While many hospitals have pre-set pain level dependent postoperative analgesia policies and protocols, there are very sparse data in the literature to guide post-hospital discharge analgesic requirements and appropriate prescription quantities. This is of grave concern when prescribing opioids, as 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.[1,12]

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.[2,13-15] These unused opioids are then available for diversion,

nonmedical use, overdose and development of chronic dependence. There has been a major push for increased use of non-opioid analgesics as the primary mode of postoperative pain control, and an attempt to develop enhanced recovery after surgery (ERAS) protocols in obstetrics.[16-18] Many large hospital systems, including many of the MFMU Network sites, have adopted a version of ERAS protocols for cesarean deliveries. These protocols focus on preoperative education, multimodal analgesia, with emphasis on timed and consistently administered non-opioid analgesics, and medications administered preoperatively, intraoperatively, and immediately after surgery.[19,20] While ERAS protocols have been successful at reducing in-hospital opioid use, many do not address post-discharge opioid consumption, and have had very little impact on discharge opioid prescribing practices.[21,22] The majority of patients are still discharged home with an opioid prescription, including those with a combination of low discharge pain scores, no preoperative opioid use, and low MME consumption before discharge.[23]

Physicians struggle to prescribe and dose post-operative opioids appropriately while tackling the real needs of acute pain after surgery. Without guidance from the literature to direct obstetric providers on the appropriate amount of opioids to prescribe upon discharge, nationwide prescription amounts are prescriber-dependent and vary widely by up to 65 tablets.[14,23-25] The efficacy of the different amounts is unclear. A study that evaluated patient outcomes by number of opioids prescribed at discharge (≤30, 31-40, >40 tablets) reported a difference in pain scores at 1 week post-discharge although the median value for all 3 opioid categories was 4 on a scale from 0-10, and no difference in pain scores were reported at 2 weeks post discharge (median score of 2).[2] A recent randomized trial of 170 women undergoing cesarean reported that women prescribed opioids at discharge had higher mean pain scores 2-4 weeks later than women prescribed ibuprofen and acetaminophen (mean score 15.9 on a scale from 0 to 100 vs 12.4; adjusted mean difference 4.9; 95% CI -2.2 to 12.0) compared with women prescribed ibuprofen and acetaminophen.[3] This raises the question as to whether opioids are even needed to manage pain post-discharge effectively.

Using information gathered by in-hospital pain scores and opioid use during hospitalization can assist in identifying an individualized quantity of opioids to be prescribed. Individualized Opioid Prescription Protocols (IOPPs) are tailored to a woman's specific pain need and provide specific guidance for gradual reduction. Tapering schedules for postoperative opioid use include daily reduction of 10 to 20 percent which is reported as well tolerated by most people[26], or even up to 50 percent.[27,28] The fact that the IOPP has a taper component is powerful because it provides guidelines for reducing the amount taken gradually and not abrupt cessation when all of the opioids have been consumed. Shared decision-making includes the patient in the decision process, emphasizing patient-driven care, and has been demonstrated to improve outcomes and patient satisfaction in a variety of clinical settings.[21,29-32] A recent study found that incorporation of shared-decision making into opioid prescribing after cesarean delivery was associated with approximately 50% decrease in the amount of opioids prescribed.[21]

2.3 Risk /Benefit Assessment

2.3.1 Known Potential Risks

While opioid pain medication is routinely prescribed after major abdominal surgeries like cesarean, using opioids for pain control (even after surgery) is associated with a small risk of opioid dependence which can lead to overdose and death. This risk is present anytime opioids are prescribed and is not unique to either arm of the study.

Having prescription opioids in the home increases the risk for persistent use, diversion, or the risk that others (friends, family members) will use or abuse the prescription opioids. This risk occurs any time an opioid is prescribed and would be present for patients not participating in this study. The risk may be higher in the control group (due to potentially receiving a prescription for more opioids than the intervention arm).

2.3.2 Known Potential Benefits

Women in both arms of the study will receive study discharge instructions that include educational material on opioids, the use of non-opioid medication to manage pain, and the proper disposal of opioids.

2.3.3 Assessment of Potential Risks and Benefits

A described above, potential risks are not more than encountered in usual care after cesarean delivery. Precautions have been taken within the study to minimize these risks. First, there is a maximum number of opioid tablets that can be prescribed at discharge in either arm of the study (20). Second, all participants will receive discharge instructions on the appropriate storage and disposal of opioids. In addition, the risk of continuing pain after the initial prescription is mitigated because all patients, regardless of arm, may contact the study team or their provider to obtain an opioid refill prescription if they have inadequate pain control after discharge.

3 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
To evaluate whether IOPP with shared decision making is not inferior to a fixed opioid prescription of 20 tablets of oxycodone 5mg in pain management at 1 week post-discharge	Presence or absence of moderate to severe pain at 1 week post-discharge; moderate to severe pain is defined as a value of 4 or higher on the Brief Pain Inventory worst pain in the last 24 hours numeric scale (from 0 to 10; worst pain imaginable)
Secondary	
To evaluate whether IOPP with shared decision making decreases opioid refill prescriptions	Opioid prescription filled (beyond that prescribed at discharge) between one week post discharge and 1) two weeks post-discharge, 2) six weeks postpartum, and 3) ninety days postpartum
	Total number of opioid prescriptions filled by one and two weeks post-discharge, and six weeks and ninety days postpartum
To evaluate whether IOPP with shared decision making decreases the total amount of opioid tablets prescribed and the total morphine milligram equivalents (MME) used	Number of opioid tablets prescribed and unused from discharge to 1 week and 2 weeks post discharge, and 6 weeks and 90 days postpartum
	Total morphine milligram equivalents (MME) used from discharge to 1 week and 2 weeks post-discharge, and 6 weeks and 90 days postpartum
To evaluate whether IOPP with shared decision making has equivalent pain intensity, interference with life, and global impression of change in overall 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 2 weeks post-discharge, and 6 weeks and 90 days postpartum
	Pain interference scores assessed on the Brief Pain Inventory at 1 and 2 weeks post-discharge, and 6 weeks and 90 days postpartum
	Global impression of change in overall pain with treatment at 1 and 2 weeks post-discharge, and 6 weeks and 90 days postpartum
To evaluate whether IOPP with shared decision making reduces adverse maternal and infant outcomes	• Maternal postpartum weight retention at 6 weeks postpartum • Maternal depression score ≥ 13 at 6 weeks postpartum • Infant hospital readmission within 6 weeks postpartum

4 Study Design

4.1 Overall Design

This is a non-inferiority multi-center unblinded randomized trial of 5,500 women undergoing a cesarean delivery who are randomized before discharge to either an individualized opioid prescription protocol (IOPP) that includes shared decision making or to a fixed opioid prescription of 20 tablets of oxycodone 5mg. The primary endpoint is the presence or absence of moderate to severe pain assessed one week post-discharge; moderate to severe pain is defined as a worst pain score at or above 4 in the last 24 hours on a numeric scale from 0 to 10. The primary hypothesis is that the proportion of women experiencing moderate to severe pain will be at most only slightly higher (less than 5 percent) in the IOPP arm than in the control arm (fixed amount of 20 opioid 5mg tablets). Consenting women will be assigned in a 1:1 ratio to one of the two arms using a secure internet based randomization system maintained centrally by the DCC (described in Section 6.2). Randomization will be stratified by site. Women will be followed through 90 days postpartum.

Although the inferiority design is appropriate, it is susceptible to bias especially given the unblinded nature of the study. Methods employed to minimize bias include randomization methodology, blinding of research staff to treatment arm, and conducting assessments in such a way that certain information is completed prior to the assessment of opioid use and side effects. Details are presented in Section 6.2. Both intent to treat and per protocol analyses will be conducted.

4.2 Scientific Rationale for Study Design

A prescription for a fixed amount of opioid tablets was selected as the control group as this currently represents usual care in the majority of the MFMU centers. While not providing an opioid prescription was considered as a comparator, there were significant concerns that it would limit the number of participants that would agree to enroll in the study as well as the number of clinical providers that would be unwilling to forgo giving an opioid prescription.

Under the assumption that current prescribing practices provide sufficient pain relief , a non-inferiority study design was chosen because if the pain management offered through an individualized opioid prescription protocol was acceptable compared with usual care, the IOPP has multiple other advantages. These include decreasing the number of unused tablets, tailoring to individual needs, enhancing awareness of the risks of opioids and empowering the patient in her post-operative care.

4.3 Justification for Dose

Individualized post-discharge opioid prescribing guided by in-patient opioid use has been shown to decrease the amount of prescribed opioids by half compared with a standard prescription, without compromising adequate pain control.[33] Patients' in-hospital morphine milligram equivalents requirements serve as a valuable way to determine the optimal patient -specific amount of opioids for discharge, tailoring to a specific individual's pain needs.[34]

After surgery, acute postoperative pain is expected to improve and instructions for reductions in opioid use post-discharge are limited and highly variable. A 10-20% daily reduction in opioid dose is well tolerated by most people and withdrawal symptoms are usually avoided when a dose reduction is 25% or less than the previous daily dose.[24,25]

Therefore, using an individualized opioid prescription protocol that incorporates the patient's in-hospital opioid requirements and provides specific guidance for gradual reduction, rather than standard "one-size-fits-all" approach for opioid prescriptions at discharge, will lead to a decrease in over- and under-prescribing of opioids.

The fixed amount of 20 tablets was chosen as it 1) represented the currently prescribed amount at the majority of MFMU sites, and 2) was the median amount of opioid tablets requested by participants in the study by Prabhu and colleagues.

4.4 End of Study Definition

A participant is considered to have completed the study if she has completed her last (remote) study visit scheduled for 90 days postpartum. If the visit is missed, attempts will be made to contact the participant through 180 days postpartum.

5 Study Population

5.1 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, twin or triplet gestation

5.2 Exclusion Criteria

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

- An opioid prescription filled during the current pregnancy
- Known history of opioid use disorder, by medical record review
- Contraindication to opioids
- Contraindications to both acetaminophen and ibuprofen
- Significant surgical procedures (e.g., hysterectomy) prior to randomization as pain trajectory will be completely different
- Fetal or neonatal death prior to randomization
- Inability to randomize within 1 day before planned discharge from the hospital
- Inability to participate in shared decision making as assessed by research staff
- Language barrier (non-English or Spanish speaking)
- Participation in this trial in a previous pregnancy
- Participation in another intervention study that influences the primary outcome in this trial

5.3 Lifestyle Considerations

There are no lifestyle considerations specific for this study. General post cesarean discharge instructions will be given to participant at discharge.

5.4 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.

5.5 Strategies for Recruitment and Retention

5.5.1 Recruitment Plan

Good recruitment will depend on access, promotion, education and clinical staff buy-in. A pamphlet with general information about the study will be created to give to participants during a prenatal visit or upon admission to the hospital. 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 on post-operative days 1, 2 or 3 to inform them about the study. Randomization should occur within 1 day of planned discharge, but not earlier.

Care providers will be educated about the study via Grand Rounds and other 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 research staff will also visit private doctors' offices to share information about the study. Educational brochures will be provided. In addition, the study will be advertised through printed flyers, posters, and electronic media in clinic waiting areas.

The MFMU Network has 37 separate hospitals, encompassing both academic medical centers and community-based hospitals, and over 165,000 deliveries per year. Assuming a 30% rate of cesarean deliveries this is approximately 50,000 cesarean deliveries per year. Not all sites have 24/7 coverage; therefore it is conservatively assumed that approximately 36,000 women annually 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 11,000 women could be enrolled annually.

The MFMU Network is currently conducting a randomized trial in women undergoing cesarean delivery. The aim of the trial is to determine whether prophylactic tranexamic acid (TXA) reduces the need for transfusion. Women are randomized upon arrival to the operating room and study drug is administered immediately after cord-clamping. The group has determined that there is no barrier to co-enrollment between the TXA trial and this study. TXA trial recruitment is restricted by the fact that research staff have to be present in the delivery room and by a requirement for scheduled deliveries – which are easier to recruit – to be balanced in number with unscheduled deliveries which are easier to miss. Even with these major barriers to recruitment, sites have been able to recruit approximately 400 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 400 participants per month.

5.5.2 Retention Plan

At the time of enrollment, comprehensive patient contact information is obtained including e-mail, cell phone and social media, along with significant other and family member contact information to ensure that contact with the patient at 1 week post-discharge, 2 weeks post-discharge, 6 weeks and 90 days postpartum will be successful. Research staff also ensure that the potential participant understands what level of commitment is necessary to be involved in the research study in addition to the key elements of informed consent.

Best practices identified in previous MFMU studies include 1) providing consistent and informative visit reminders in the form of letters, phone calls, texts and emails to participants, 2) allowing flexibility in study visits to accommodate the busy schedules of participants, and 3) providing participant compensation for participation as well as for parking and other travel-related expenses. Study staff are always trained on the importance of minimizing lost to follow-up.[35] If the 1 and 2 week contacts are unsuccessful, special efforts will be taken to ensure that the woman does attend her 6 week postpartum visit, including texting/emailing reminders. All women are expected to have a 6 week postpartum visit, either in person or as a telehealth (phone or video) visit, and research staff will attempt to find information about her appointment if other methods have been unsuccessful.

6 Study Intervention

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

Women will be randomized within 1 day before planned discharge to either Individualized Opioid Prescription Protocol (IOPP) with shared decision making or to a fixed amount of opioids (20 tablets of oxycodone 5mg). Randomization should occur as close to discharge as possible.

6.1.1.1 IOPP

IOPP will be based on inpatient oral opioid intake during the 24 hour period prior to randomization and should not include the 12 hours immediately after the cesarean. If discharge is delayed after randomization, the number of tablets dispensed should be re-calculated.

Opioid use will be converted to equianalgesic doses of morphine sulfate (morphine milligram equivalents [MMEs]) using standard ratios. A standardized formula for a taper of 20% reduction of MME per day post-discharge will then be calculated[36] up to a maximum of 20 tablets. Table 1 demonstrates some sample individualized opioid prescription protocols based on inpatient MME and standardized taper.

Table 1. Sample IOPP Protocols

Opioid (mg/day)	Conversion factor	MME in last 24hr	# oxycodone 5mg tablets at discharge
hydrocodone 5mg	1	5	2
hydrocodone 20mg	1	20	12
oxycodone 5mg	1.5	7.5	4
oxycodone 20mg	1.5	30	19

The algorithm for calculating the amount of the IOPP takes the MME in the prior 24 hours as the starting MME and then calculates a 20% reduction in MME per day until MME for half a tablet of oxycodone is achieved (3.75 MME). For example, if MME in last 24 hours is 7.5, then day 1=7.5 MME (1 tablet), day 2=6 MME (1 tablet), day 3=4.8 MME (1 tablet), day 4=3.8 MME (1 tablet), and day 5=3.1 MME (0 tablets) for a total prescription of four tablets of oxycodone 5mg.

Prior to discharge, participants will receive 5-10 minutes of scripted counseling by the study coordinator or trained research nurse that will include general education on post-cesarean pain and opioid use and to discuss the number of tablets (if any) requested in the prescription. The general information will be provided to participants as either a video or pamphlet (trained nurse will use a script if a pamphlet is used). The calculated IOPP will be incorporated in the discussion. At the conclusion of the session, participants will choose the number of tablets they will be prescribed at discharge, from zero up to the fixed amount (20 tablets).

6.1.1.2 Fixed Amount (20 tablets)

Those randomized to a fixed amount of 20 tablets will receive general education provided in the post-discharge instructions at the institution. Participants will be provided discharge instructions that include medication instructions including scheduled use of acetaminophen and ibuprofen, proper disposal of unused opioid medication (after the 6 week postpartum visit study pill count), and who to contact if a refill opioid prescription is required.

6.1.2 Dosing and Administration

Study coordinators or research nurses will complete the participant's discharge MME prescription based on the randomized assignment and the clinical provider will sign or e-scribe the prescription. It is possible that participants in the intervention group will not be given a prescription if zero tablets are calculated for the IOPP and/or the participant elected not to have a prescription during the shared decision making process.

The prescription will be given to the participant or sent directly to the pharmacy. Participants will be provided the same discharge instructions as the fixed amount group that include medication instructions including scheduled use of acetaminophen and ibuprofen, proper disposal of unused opioid medication (after the 6 week postpartum visit study pill count), and who to contact if a refill opioid prescription is required.

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 especially for an unblinded study. Eligible and consenting women will be randomized by certified research staff using a secure internet based randomization system maintained by the Data Coordinating Center. 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 IOPP with shared decision making or the fixed opioid prescription will be in a 1:1 ratio according to a randomization sequence prepared and maintained centrally by the MFMU Network Data Coordinating Center. 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] Randomization will be stratified by clinical site to assure balance between the two treatment groups with respect to anticipated differences among the clinic population and possible differences in patient management.

Research staff responsible for randomization, providing the study intervention educational session and administering opioid prescription refills will be identified at the study onset as these individuals will be unblinded. Individuals responsible for administering opioid prescription refills must be unblinded as the amount that may be described is dependent on the amount prescribed previously. Unblinded research staff should not perform the follow-up assessments to minimize any potential bias. Three of the four follow-up visits will be performed remotely, with all data being collected directly from the participant. In addition, study visit assessments will be ordered in such a way that questionnaires related to pain assessment are completed prior to the assessment of opioid use and side effects.

6.3 Study Intervention Compliance

Participants will be provided with a pain medication diary to document opioid use through 90 days postpartum. In addition, a pill count will be performed at the in-person or virtual study visit performed at 6 weeks postpartum.

Opioid prescriptions refilled or initially filled if not prescribed at discharge will be assessed by 3 methods: participant report, review of electronic medical records, and review of the Prescription Drug Monitoring Program (PDMP) database.

6.4 Concomitant Therapy

Medication instructions that incorporate the scheduled use of acetaminophen and/or ibuprofen will be included in the discharge instructions provided to participants in both arms of the study. The medication

diary will be used to document acetaminophen, ibuprofen, and other pain medications used through 6 weeks postpartum.

6.4.1 Rescue Medicine

Following hospital discharge, participants in either arm may contact study staff or their clinical care provider to request an additional opioid prescription refill. The study contact information will be included in the study discharge instructions. Additional prescriptions will be quantified from participant report, review of the electronic medical record, and the Prescription Drug Monitoring Program database.

6.5 Discontinuation of Study Intervention

Since the intervention is a prescription, participants may choose to not fill the prescription or to take less of the tablets than administered by the pharmacy. In addition, women may request an initial or refill prescription if deemed necessary for pain control. This is expected and a secondary outcome of this trial.

Women will be followed through 90 days postpartum regardless of their treatment assignment or how many opioid tablets have been consumed.

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 should occur close to discharge (preferably within 24 hours of planned discharge) 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. Women that elect not to participate will be asked to sign a brief consent to allow collection of the Opioid Risk Tool score to evaluate whether participants enrolled into the trial are representative of the general population in relation to opioid risk level.

7.1.2 Baseline Procedures

If the patient is eligible and signs the consent form, participants will complete the following questionnaires prior to randomization:

- Brief Pain Inventory (BPI) pain severity and interference *
- Pain score on a visual analog scale from 0 to 100mm
- Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) tool * to assess history of substance use
- Opioid Risk Tool[38] to assess family and personal history of substance abuse, history of pre-adolescent sexual abuse, and psychological disease
- Pain Catastrophizing Scale[39] - Short Form 6 to assess thoughts and feelings associated with pain *
- PROMIS Physical Functioning - Short Form 6b to assess physical functioning *
- Patient Health Questionnaire (PHQ-2) * and the Edinburgh Postnatal Depression Scale[40] to assess depression and postpartum depression.
- Generalized Anxiety Disorder (GAD-2) to assess anxiety *
- PROMIS Sleep Disturbance – Short Form 6a to assess sleep quality, and sleep duration*

Questionnaires marked with an asterisk are common data elements that are required to be collected across all trials participating in the HEAL Initiative Effectiveness Research Network. These questionnaires will also be assessed at the 6 week postpartum visit. The participant and the clinical provider will be notified if a safety alert occurs on the Edinburgh (Section 7.2).

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

Following completion of the participant questionnaires, study-certified research staff will obtain the next treatment assignment through an online randomization system created by the MFMU Network Data Coordinating Center. The participant will be informed of her treatment assignment. Section 6.1 contains information on the administration of the study intervention.

7.1.3 Follow-up

Participants will be followed through 90 days postpartum with remote study visits occurring at 1 week and 2 weeks post-discharge and 90 days postpartum, and an in-person or virtual visit occurring at 6 weeks postpartum. Table 1 in Section 1.3 summarizes the study procedures.

One and Two-Week Remote Visits

Study certified research staff will contact participants 7 days (5-9 day window) and 14 days (12-16 day window) from the date they were discharged from the hospital with a minimum 5 days in between the two visits.

The participant will be instructed to complete the online questionnaire that includes:

- BPI pain severity and interference
- Breastfeeding status
- Global impression of change in overall pain with treatment
- Number of opioid tablets used and unused
- Opioid prescription refilled or initially filled if not prescribed at discharge
- Non-opioid pain medication use (e.g., acetaminophen, ibuprofen)
- Opioid-related side effects

Research staff should review the questionnaire upon completion and confirm any missing data with the participant. These questions may also be assessed by research staff via phone or videoconference, if the participant prefers this method of collection. Research staff reviewing or collecting these data should be blinded to treatment arm.

Six-week In-person or Telehealth Visit

The participant will return for an in-person study visit 6 weeks postpartum (4-8 week window). Research staff will attempt to schedule the study visit at the same time as the clinic appointment and remind participants to bring their opioid prescription bottle(s) and medication diary. If the 6 week postpartum clinic visit is performed as a telehealth (phone or video) visit, the research visit may be scheduled as a telehealth visit as well. Optimally this will be done with videoconferencing to verify the pill count and review the diary. Participants have the option to complete the questionnaire online, over the phone or through video conferencing with research staff.

The participant will be instructed to complete the questionnaire that includes:

- BPI pain severity and interference /
- Pain score on a visual analog scale from 0 to 100mm
- Breastfeeding status
- Maternal and infant hospitalizations since discharge
- Pain Catastrophizing Scale
- Physical Functioning
- Patient Health Questionnaire (PHQ-2) and the Edinburgh Postnatal Depression Scale
- Generalized Anxiety Disorder (GAD-2)
- Sleep disturbance and sleep duration
- Global impression of change in overall pain with treatment
- Opioid prescription refilled or initially filled if not prescribed at discharge
- Non-opioid pain medication use (e.g., acetaminophen, ibuprofen)
- Opioid-related side effects
- Current Opioid Misuse Measure

Research staff should review the questionnaire upon completion and confirm any missing data with the participant. The participant and the clinical provider will be notified if a safety alert occurs on the Edinburgh (Section 7.2). If the opioid prescription bottles were returned, research staff should perform a pill count including number of opioid tablets prescribed, used and unused. The medication diary will also be reviewed and information pertaining to opioid and non-opioid pain medication use will be collected.

Medical records should be reviewed for maternal and neonatal complications since discharge. If the mother reports a re-hospitalization for either the mother or baby, medical records will be obtained and the reason recorded.

In addition, the mother's weight will be recorded at the six week visit.

<u>90 Days Postpartum Visit</u>

Study certified research staff will contact participants 90 days postpartum (84-112 day window). The participant will be instructed to complete the online questionnaire that includes:

- BPI pain severity and interference
- Breastfeeding status
- Pain Catastrophizing Scale
- Global impression of change in overall pain with treatment
- Number of opioid tablets prescribed, used and unused
- Opioid prescription refilled or initially filled if not prescribed at discharge
- Non-opioid pain medication use (e.g., acetaminophen, ibuprofen)
- Opioid-related side effects
- Current Opioid Misuse Measure

Research staff should review the questionnaire upon completion and confirm any missing data with the participant. In addition, research staff will ask the participant if she has had COVID-19 testing prior to her visit and the results. These questions may also be assessed over the phone or through video conferencing by research staff if the participant prefers this method of collection. Research staff collecting these data should be blinded to treatment arm.

Following the appointment, research staff will review the electronic medical records and the Prescription Drug Monitoring Program (PDMP) database and record information on opioid prescriptions filled since discharge from the hospital. The PDMP will be the gold standard for capturing prescriptions and the amount of opioid tablets received.

7.2 Safety Alerts

Safety alerts will be identified for the Edinburgh Postnatal Depression Scale. 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 Adverse Events and Serious Adverse Events

7.3.1 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.

7.3.2 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

7.3.3 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, Alternate-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.

7.3.4 Time Period and Frequency for Event Assessment and Follow-up

Adverse events will be recorded from randomization through 90 days 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.

7.3.5 Adverse Event Reporting

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 an independent medical monitor and the Data and Safety Monitoring Committee chair. Cumulative adverse events are reported to the Data and Safety Monitoring Committee at each meeting.

7.3.6 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 at a MFMU hospital 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 an independent medical monitor and the Data Safety Monitoring Committee (DSMC) chair. Cumulative adverse events are reported to the DSMC at each meeting.

7.3.7 Reporting Events to Participants

Participants will not be informed about adverse events, serious adverse events, or study-related results unless the Data and Safety Monitoring Committee 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.

7.4 Unanticipated Problems

7.4.1 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.

7.4.2 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 MFMU Network AE 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 Center PI to the Data Coordinating Center 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 the Data and Safety Monitoring Committee to determine whether changes to the protocol or consent form should be considered. If the DSMC agrees that the event constitutes a UAP and the NICHD concurs with their recommendation, the event will be reported by the DCC to the single IRB. UAP reports should be submitted through the online IRB system no later than 2 weeks (10 business days) from the notification.

7.4.3 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 DSMC will recommend the course of action (for example, a letter to participants) which will be submitted to the single IRB.

7.5 Participant Discontinuation/Withdrawal from the Study

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

7.6 Lost to Follow-Up

A participant will be considered lost to follow-up if she fails to complete at least one study visit after discharge and is unable to be contacted by the study site staff.

8 Statistical Considerations

8.1 Statistical Hypotheses

The primary endpoint is the 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). The null hypothesis is that IOPP is inferior or worse than the fixed opioid group by a margin more than -5%. The alternative hypothesis is that IOPP is inferior or worse than the fixed opioid group by a margin less than -5%.

Key secondary endpoints include:

- Worst pain score assessed at 2 weeks post-discharge
- Total morphine milligram equivalents used from discharge to 2 weeks post-discharge
- Opioid prescription beyond that prescribed at discharge through 90 days postpartum
- Number of opioid tablets unused at 6 weeks postpartum

A superiority test will be used 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

The primary endpoint is pain score at or above 4 assessed on a numeric scale from 0 to 10 at 1 week post-discharge. The observational study by Bateman et al., which used a numeric scale of 0 to 10 as proposed here, reported a median pain score of 4 at one week post discharge. For this trial, it is assumed that 50% of the women in the fixed opioid arm and the IOPP arm will have a pain score of 4 or higher at 1 week post discharge. For this trial, a non-inferiority design is assumed with a noninferiority margin of 5%. It is axiomatic that opioids provide superior pain relief. Selection of a non-inferiority margin could not be based on the effect size on a standard opioid prescription at discharge after cesarean because the data do not exist. Therefore a conservative margin was chosen of 5% which would represent only a 10% relative increase in the proportion of women with moderate or worse pain. For 90% power and 0.025 significance level 1-sided, a total sample size of 4,300 women is required to state that the IOPP is not inferior to the fixed amount of 20 tablets. Given the short window to assess pain at 1 week post-discharge, a 20% missing rate is incorporated which gives a final sample size of 5,500 (2,250 per group).

The study is also powered to assess whether an opioid prescription was filled (beyond that prescribed at discharge) by 6 weeks postpartum which is the best surrogate for long-term opioid addiction. Bateman et al[2] reported opioid refill rates by 2 weeks postpartum of 5.9% for those initially prescribed 30 or fewer tablets, 5.0% for women prescribed 31-40 tablets, and 5.8% for women prescribed more than 40 tablets. A poll of the individual MFMU sites noted that currently most prescribe a standard amount of 20 tablets, with a small percentage prescribing a smaller range of tablets. Prabhu et al[21] reported a 50% decrease in the number of opioids prescribed post cesarean using a shared decision-making approach compared the standard prescription at the time of 40 tablets. The number of women requiring an opioid refill was 8%. Assuming an outcome rate of 5% in the fixed opioid group, a sample size of 5,500 will have 85% power to detect a 1/3 reduction in the intervention group (3.3%) with an alpha of 0.05 two-sided. Minimal lost to follow-up is anticipated since this outcome is attainable through the national drug database.

The study is also powered for other key secondary outcomes including amount of opioids used (MME) from discharge. A sample size of 5,500 has >90% power to detect a mean difference of 7.5 MME, the equivalent of 1 tablet.

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.

Only the primary endpoint will be tested for non-inferiority. A superiority test will be used for the secondary endpoints. For key secondary outcomes (4 specified above), adjustment for multiple comparisons using a false discovery rate of 5% will be made to determine statistically significant two-sided p-values. Other secondary outcomes will use a p-value < 0.05 two sided to indicate statistical significance.

8.4.2 Analysis of the Primary Endpoint

The primary analysis will be conducted under the Intention-to-Treat principle using a complete case analysis.

The primary outcome is binary and defined as a pain score at or above 4 on a numeric scale from 0 to 10 assessed at one week post-discharge. Analyses of the primary outcome will consist of summarizing the proportions of trial participants with the primary endpoint for each group and calculating the corresponding between-group risk difference (control minus IOPP) with 95% confidence intervals. IOPP will be determined as non-inferior if the lower 95% confidence limit for the risk difference is -5 percentage points or greater (i.e., closer to zero). If the treatment groups are found to differ on a pre-treatment factor known to be a risk factor for the outcome, the statistical analysis will adjust for these differences and an adjusted risk difference will be reported. If IOPP is determined to be non-inferior to the fixed amount of opioids, a superiority test will be conducted without adjusting the Type I error. IOPP will be determined as superior if the lower 95% confidence limit for the risk difference is greater than 0.

An analysis adjusting by center will be performed to ensure that center differences do not change the conclusions.

While missing data in superiority clinical trials are known to potentially yield lower statistical power and biased results for comparing treatments, missing data in non-inferiority trials (NIT) may present additional challenges, such as the assumptions of assay sensitivity and constancy. Therefore, additional sensitivity analyses will investigate the robustness of the observed differences between the two groups with respect to the missing data. First, an inverse probability weighting (IPW) analysis will be conducted with each case weighted by the inverse probability of being a complete case. Under a missing at random mechanism, the IPW approach would result in an unbiased estimate of the difference between groups assuming a correctly specified model for the missing data. Second, a tipping-point analysis will describe the additional number of events in the control group versus the IOPP group among the participants with missing data that would change the conclusion of non-inferiority.

In addition, per-protocol analyses will be performed using both the complete cases only, and then accounting for the missing data as described above. The per-protocol population is defined as participants that only received the assigned intervention through one week post-discharge.

8.4.3 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.

8.4.4 Safety Analyses

Side effects, adverse events and serious adverse events will be reported by treatment group to the DSMC. The total number of events as well as the number of participants that report at least one event will be reported. In addition the DSMC will review maternal and neonatal outcomes by treatment group.

8.4.5 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.

8.4.6 Planned Interim Analyses

No interim analyses are planned given the short duration of enrollment and follow-up. Given the sample size estimate is based on the assumption of a primary endpoint rate of 50% in the fixed opioid arm, this proportion will be evaluated after 1,100 women (20% of the sample size) complete the 1 week visit. The DSMC would be charged with making a recommendation regarding potential revision of the sample size.

In addition, the DSMC will review recruitment, protocol adherence, and safety data as noted in sections 7.3.5 (Adverse Event Reporting), 7.3.6 (Serious Adverse Event Reporting) and 9.1.6 (Safety Oversight).

8.4.7 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
    - Transversus abdominis plane (TAP) block
- Incisional type (Pfanensteil vs vertical midline)
- Primary vs repeat cesarean
- Opioid risk score (≤ 3 vs >3)

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

8.4.8 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.

Within 24 hours of planned discharge, 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 who elect not to participant in the study will be asked to sign a brief consent that allows for collection of the Opioid Risk Tool score. Women that elect to participate in the full study will sign the full 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: recruitment materials, brief consent and assent for non-randomized participants, full study consent and assent, study intervention, participant completed questionnaires, pain medication diary, and discharge instructions. All participant materials will be IRB approved and translated into Spanish. Both verbal and written informed consent and authorization will be obtained in the participant's fluent language. Participants not fluent in English or Spanish will be excluded.

9.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause noted by the sponsor (NIH) or the single IRB. Circumstances that may warrant termination or suspension include but are not limited to: determination of unexpected, significant, or unacceptable risk to participants. If the study is prematurely terminated or suspended, the Principal Investigators will be informed who will then promptly inform study participants. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. The study may resume once concerns about safety are addressed.

9.1.3 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 Institutional Review Board (IRB), which is a group of people who are responsible for making sure the rights of participants in research are respected.
- The Office for Human Research Protections (OHRP) and or Department of Health and Human Services (DHHS)
- The National Institutes of Health (NIH) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, the George Washington University Biostatistics Center.

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.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the MFMU Network Data Coordinating Center at George Washington University. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by MFMU Network Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and submitted to the appropriate NIH data repositories.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure.

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

9.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be stored at the MFMU Network Data Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the NIH data repository (e.g., NICHD Data and Specimen Hub), for use by other researchers including those outside of the study. Permission to transmit data to the NIH data repository will be included in the informed consent.

No biological samples will be collected in this study.

9.1.5 Key Roles and Study Governance

The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, consisting of twelve clinical centers, the Data Coordinating Center (DCC) and the NICHD. The study is also part of the larger HEAL Initiative Effectiveness Research Network.

The MFMU Network is governed by a Steering Committee which includes the Principal Investigator from each of the twelve clinical centers, the DCC and the NICHD MFMU Network Project Scientist. The Chair, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for designing and conducting study protocols and monitoring study implementation, recruitment and protocol adherence.

The Protocol Subcommittee includes investigators from one or more clinical centers, nurse coordinators, outside consultants (if appropriate), the DCC and the NICHD Project Scientist. The Protocol Subcommittee is responsible for the preparation and conduct of the study, and reporting the progress of the study to the Steering Committee.

The Publications Committee is responsible for proposing changes to the existing MFMU Network Publication policy and reviewing all manuscripts and abstracts prior to submission.

9.1.6 Safety Oversight

The Data and Safety and Monitoring Committee (DSMC) for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network is an independent group appointed by the NICHD to oversee MFMU Network trials. The primary objective of the DSMC is to ensure the safety of study subjects and to provide NICHD with advice on the ethical and safe progression of the trial. The DSMC also advises the NICHD on research design issues, data quality and analysis, as well as ethical and human subject aspects of studies. Recommendations will be made to the NICHD and disseminated to the Steering Committee.

The DSMC is composed of individuals with the appropriate expertise, including maternal-fetal medicine or obstetrics, neonatology, ethics, biostatistics/epidemiology, and clinical trials methods. One of the members with expertise in obstetrics or maternal-fetal medicine is appointed as Chairperson. In addition, a layperson or member of the public is appointed as a patient advocate.

The responsibilities of the DSMC members are as follows:

- Before the start of the trial:
    - To review the research protocol and informed consent documents with respect to ethical and safety standards. The study design should be evaluated to determine whether it is adequate to answer the research questions.
- While the trial is ongoing:
    - To evaluate whether the study design assumptions are valid and the impact of the assumptions on how well the research question(s) will be answered.
    - To monitor the safety of the participants including review of serious adverse events as they arise.
    - To monitor recruitment, losses to follow-up, compliance with the protocol by investigators and participants, and data quality.
    - To monitor the evidence for treatment harm or benefit and to evaluate evidence for treatment differences in the main efficacy outcome measures.
    - To assess the impact and relevance of external evidence on the advisability of trial continuation as well as on the need for design modification including the necessity for modification of the informed consent material.
    - To make recommendations for changes to the study design, if necessary, to ensure that the research question(s) will be answered.
    - To recommend continuation or termination of a trial for all participants, certain treatment groups, or certain participant subgroups.

For this study the DSMC will meet annually. The committee may meet more often as needed.

In addition to the DSMC, an independent medical monitor will review all adverse and serious adverse events in real-time. The medical monitor assesses if it is a serious and/or unexpected adverse event, relationship to study drug and specifies the organ system classification.

9.1.7 Clinical Monitoring

Clinical monitoring is performed by the MFMU Network DCC. The DCC will conduct ad hoc site visits to a limited number of centers each year at which they will review organizational and study procedures, the integrity of the randomization logs, regulatory documents including individual participant consent forms, study visit observation, in addition to completing a set of case report forms from the medical charts and comparing these with the data entered on the database as well as the completed case report forms at the centers. The DCC will prepare a status report before each visit, in addition to a report of the findings afterwards.

9.1.8 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database weekly. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Double data entry may be used to enter all study data, to force double entry of selected forms or critical fields or as an option to allow clinical center coordinators to monitor the performance of data entry personnel at regular intervals. Reports of key stroke errors or discrepancies during these sessions are available to the center staff and are also transmitted to the DCC for monitoring purposes. While double

entry of all data would be preferable, the decision on whether to require it is made by clinical center coordinators based on performance of keyers during monitored sessions.

The DCC will present regular reports to the Protocol Subcommittee, the Steering Committee, and the Data and Safety Monitoring Committee. A recruitment report by center and site is sent weekly and monthly. Full Steering Committee reports will be prepared quarterly to coincide with the meetings. These contain recruitment information, baseline data by center, some compliance and protocol adherence information, a graph of actual recruitment versus goal, and bar charts showing recruitment rank for the past three months and rank for loss to follow-up and overdue outcome rates. Any protocol violation, such as randomization of an ineligible patient is listed by center. Data quality tables are also presented by center, showing the frequency of data queries, the timeliness of data entry, and the number of overdue and late forms, overall and by center. A center performance report created by the DCC is also generated and distributed at these meetings and in advance of a site visit.

9.1.9 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 site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

For this protocol, web data entry screens corresponding to the data forms will be developed and maintained by the staff of the DCC. Clinical center staff will enter data into the MySQL database located at the DCC through a web data management system (MIDAS). The data are edited on-line for missing, out of range and inconsistent values. A Users' Manual documenting this system is provided to the centers by the DCC.

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is generated in MIDAS for initial review by DCC staff who then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each patient, is maintained so that the succession of corrections can be monitored.

Retention of study documents is detailed in a separate MFMU Network Record Retention policy. In general, essential study documentation must be kept for the longest period that follows:

- at least two years after publication of the primary manuscript, or
- until the trial/study is deposited in the NICHD Data and Specimen Hub (DASH), or
- as long as required by the grantee institution based on its own internal policies, or
- at least three years after submission of the final report of the grantee institution to the funding agency (federal regulations).

Non-essential study documentation may be discarded upon publication of the primary manuscript.

9.1.10 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.

9.1.11 Publication and Data sharing Policy

All abstracts, presentations and manuscripts will adhere to the MFMU Network Publication Policy. The Publications Committee is responsible for developing publication policies and reviewing all manuscripts and abstracts prior to submission.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. All published manuscripts will be archived to PubMed Central.

After the study is completed, the de-identified, archived data will be transmitted to and stored at the NIH data repository (e.g., NICHD Data and Specimen Hub), for use by other researchers including those outside of the study.

9.1.12 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.

Members of the DSMC may not be affiliated with any of the clinical centers or the DCC and must be financially and intellectually independent of the trial investigators. As part of their service on the DSMC, members must sign an annual conflict of interest and confidentiality declaration. If a new conflict arises for a member, it must be disclosed in a timely manner (within 30 days) to the NICHD. The NICHD will determine whether the conflict limits the ability of the DSMC member to participate in the committee.

9.2 Abbreviations

AE	Adverse event
DCC	Data Coordinating Center
DSMC	Data Safety Monitoring Committee
IRB	Institutional Review Board
IOPP	Individualized opioid prescription protocol
MFMU	Maternal Fetal Medicine Units
MME	Morphine Milligram Equivalents
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
PDMP	Prescription Drug Monitoring Program
PI	Principal Investigator
SAE	Serious adverse event
UAP	Unanticipated problem

9.3 Protocol Amendment History (Cumulative)

Version	Date	Description of Change	Brief Rationale

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