PROTOCOL TITLE:

Effect of Acetaminophen on Postpartum Blood Pressure Control in Preeclampsia with Severe Features

PRINCIPAL INVESTIGATOR:

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REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☐	FDA (Food and Drug Administration)
☐	HHS (Department of Health and Human Services)
☐	Other:

Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☒ Yes ☐ No

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

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1. Objectives

1.1. To compare the duration of post-partum severe range hypertension, the proportion of study participants requiring postpartum antihypertensive use, and the length of hospital stay among women diagnosed with severe preeclampsia who are randomized to acetaminophen for postpartum pain, as compared to women randomized to ibuprofen.

1.1.1. Compared with those randomized to receive ibuprofen, we hypothesize that women randomized to receive acetaminophen for post-partum pain will:

- have a shorter duration of severe range hypertension postpartum
- be less likely to require antihypertensive use
- have similar length of postpartum hospitalization

1.2. To compare postpartum pain control among women diagnosed with severe preeclampsia who are randomized to the ibuprofen arm as compared to women randomized to the acetaminophen arm.

1.2.1. We hypothesize that women randomized to the ibuprofen arm will have lower mean pain scores than those randomized to the acetaminophen arm.

2. Background

2.1. Hypertensive disorders are significant contributors to maternal morbidity and mortality , and many women diagnosed with a hypertensive disorder of pregnancy, or preeclampsia, require prolonged postpartum observation or intervention for persistent hypertension.[1,2] In addition, women with hypertensive disorders of pregnancy are at increased risk for cesarean delivery with its attendant need for postoperative pain relief. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly cyclo-oxygenase (COX) inhibitors, is known to increase the risk of development of hypertension in healthy, non-pregnant women as well as antagonize the effects of some antihypertensive drugs in hypertensive patients receiving treatment.[3–10] Various mechanisms of action have been proposed, including the inhibition of prostaglandin E2-mediated sodium excretion, inhibition of prostacyclin-mediated vasodilation, and altered aldosterone metabolism.[11,12] The American College of Obstetrics and Gynecology (ACOG) suggests avoiding the postpartum use of NSAIDs in women diagnosed with preeclampsia, though this recommendation is not formally included in its most recent guidelines, likely due to the paucity of published data on preeclampsia and NSAID use[2]. Animal studies are limited to a single investigation in a rat model of preeclampsia and showed that indomethacin had no effect on blood pressure while rats were still pregnant.[13] In humans, the extremely limited data on the influence of COX inhibitors on postpartum blood pressure among women with preeclampsia is conflicting.[14–16] In fact, no prospective studies have been published which examine the effect of COX inhibitors on postpartum blood pressure control in patients with preeclampsia.

COX inhibitors are ideally suited for postpartum pain control; before issuance of the most recent guidelines, they were widely used for postpartum and post-cesarean section pain management particularly in bridging from opiate to non-opiate pain relievers.[17,18] They are more effective than acetaminophen to alleviate pain from postpartum perineal injury, and have also been shown to decrease opioid use after Cesarean delivery.[15,17–21] Given New Mexico's high rate of opioid addiction and opioid-related deaths, any therapeutic option which may decrease the requirement for opioid use is of high value. Additionally, the analgesic alternatives to COX inhibitors have significant risks. The use of opioids while breastfeeding is associated with neonatal central nervous system (CNS) depression, and acetaminophen use is contraindicated in the setting of severe, acute elevation of liver enzymes, a common occurrence among patients with preeclampsia[22]. Whether the theoretical effect of short-term COX inhibitor use on postpartum blood pressure is clinically significant remains unclear. Systolic blood pressure has been shown to increase by up to 10mm Hg among both healthy and hypertensive COX inhibitor users, with changes in blood pressure appearing with just a few doses per month.[23–25] Another study in men

found that systemic vascular resistance increased by up to 20% immediately following intravenous administration of indomethacin. [12] However, COX inhibitors do not seem to have any effect on blood pressure when a patient is already being treated with a calcium channel blocker, which is the drug class of choice for postpartum hypertension at UNM.[7,8,26]

At UNM and many other institutions, COX inhibitors are routinely used for postpartum pain in women diagnosed with preeclampsia. It is unclear whether or not to continue their routine use in this population as no prospective data exists to guide our practice. The only human study of COX inhibitor use in preeclampsia was a retrospective review and found that postpartum COX inhibitor use was not associated with any difference in outcomes.[16] Overall, the literature is mixed on whether short term COX inhibitor use would be expected to affect blood pressure in the setting of preeclampsia. Thus, our study is necessary to determine whether avoiding postpartum COX inhibitor use is associated with improved outcomes for women diagnosed with preeclampsia.

3. Study Design

3.1. The proposed study is a randomized, controlled double masked trial comparing the effects of acetaminophen versus ibuprofen for mild postpartum pain among women with preeclampsia.

3.2. Study participants, study personnel and providers will be blinded to randomization status of study participants. Blinding will occur through the double masked design. The ibuprofen and acetaminophen will be made to appear identical to each other and will be unmarked through compounding and encapsulation. After delivery, study participants will be randomized by the investigational pharmacy to receive either acetaminophen or ibuprofen, and allocation will only be known by the investigational pharmacy. Block randomization will be used to ensure equal allocation to the two study arms.

4. Inclusion and Exclusion Criteria

4.1. All patients admitted to the labor and delivery unit with a diagnosis of a severe hypertensive disorder (preeclampsia with severe features, chronic hypertension with superimposed preeclampsia with severe features, hemolysis, elevated liver function tests and low platelets (HELLP) syndrome, or eclampsia) will be assessed for eligibility.

4.2. Inclusion criteria include age at least 18, ability to give informed consent, pregnant or recently pregnant (< 6 hours postpartum) with a diagnosis of severe hypertensive disorder of pregnancy (as defined in 4.1). We will also approach women diagnosed with preeclampsia without severe features who are being expectantly managed, anticipating that they may eventually develop severe features and be eligible for the study.

4.3. Exclusion criteria include current incarceration, serum creatinine > 1.0mg/dL or suspicion of acute kidney injury, aspartate aminotransferase (AST) > 200 unit/**L** , alanine aminotransferase (ALT) > 200 unit/L, known allergy or sensitivity to NSAIDs or acetaminophen, delivery > 6 hours prior to enrollment, chronic kidney disease, chronic liver disease, prior liver transplant, chronic infectious hepatitis, gastritis, gastro-esophageal reflux disease (GERD), peptic ulcer disease, or bleeding disorder. Additionally, a patient may be excluded from participation if their provider feels that participation is not in the best interest of the patient.

4.4. This study will enroll women at the time of their diagnosis of preeclampsia, at which time they will most likely still be pregnant. Randomization and study intervention will not occur until they are postpartum. Our study will not include minors, prisoners, or adults who are unable to give informed consent.

4.5. The population of interest for this study is post-partum women with preeclampsia, which excludes men, as they do not become pregnant and do not suffer from preeclampsia.

5. Number of Subjects

5.1. Total number of subjects to be accrued is 100.

5.2. Given that we plan to consent patients diagnosed with preeclampsia without severe features in anticipation of a possible future diagnosis of preeclampsia with severe features, we plan to consent a total of 150 potential subjects.

5.3. **Sample size justification:** Based on preliminary data obtained from n=31 patients (as part of HRRC Study ID 16-073), the duration of severe-range hypertension was found to follow an exponential distribution with mean lifetime = 35 hours (var = 1217 hr^2). We performed a sample size estimate based on this data to detect a 24-hour difference between patients receiving acetaminophen and those receiving ibuprofen. Therefore, we hypothesize that the acetaminophen group will have a duration of severe-range hypertension = 35 hours and ibuprofen will have duration = 59 hours. Based on the preliminary data and our hypothesis, using a one-sided F-test, we require a sample size of n=50 patients per group to detect a mean lifetime difference of 24 hours between groups with 83% power at a significance level $\alpha = 0.05$.

6. Study Timelines

6.1. Describe:

- The duration of an individual subject's participation in the research will be from the time she is consented (while admitted to the labor and delivery or OB Special Care units) until her discharge from the hospital after her delivery. This may be only a few days if she is enrolled just prior to or following delivery, but may last as long as several weeks if she is enrolled during a long course of inpatient expectant management prior to delivery.
- We anticipate to enroll all study participants over the course of approximately 24 months.
- We expect the study to conclude and analysis to be complete within 6 months of completing enrollment.

7. Study Endpoints

7.1. The primary endpoint will be duration of severe range hypertension (systolic blood pressure ≥ 160mm Hg, diastolic blood pressure ≥ 110mm Hg) after delivery, measured in hours. Secondary outcomes will include:

- Length of hospitalization
- Mean arterial pressure over the entire postpartum hospitalization
- Mean arterial pressure, stratified by postpartum day 1, 2, 3, etc.
- Mean number of severe range blood pressures
- Proportion with severe-range hypertension in each group
- Maximum blood pressure for entire postpartum hospitalization (in mm Hg)
- The proportion of study participants requiring the use of any scheduled oral antihypertensives at discharge
- Number of scheduled oral antihypertensive agents required at discharge
- Number of doses of antihypertensives (either oral or intravenous) given for acute lowering of blood pressure
- The proportion of study participants requiring the use of intravenous antihypertensives
- Mean daily pain level, as reported by patient on scale from 1-10, stratified by postpartum days 1, 2, 3.
- Use of opioid analgesics, measured in morphine milligram equivalents per day, stratified by postpartum days 1, 2, 3.
- Serum creatinine trend from day of delivery to day of discharge
- Mean drop in hematocrit from pre-delivery to the nadir prior to discharge

7.2. Primary safety endpoint is a composite of adverse events, and includes: seizure, stroke, posterior reversible encephalopathy syndrome (PRES), and repeat course of intravenous magnesium sulfate for seizure prophylaxis. Secondary safety endpoints include: new onset elevation of liver function

tests (AST, ALT) above twice the normal limit, acute kidney injury (new onset doubling of serum creatinine or serum creatinine > 1.1mg/dL), and delayed postpartum hemorrhage of greater than 1000mL.

7.3. There are no exploratory endpoints.

8. Research Setting

8.1. Research will take place at University of New Mexico Health Sciences Center.

8.2. Potential study participants will be identified and approached for participation while admitted to either the labor and delivery unit or the OB Special Care (antepartum) unit.

8.3. Locations of research "procedures" are as follows:

– screening, recruitment, consenting: Labor and Delivery, OB Special Care (antepartum) unit, outpatient Women's Health Clinic and Women's Imaging ultrasound suite (for women already diagnosed with preeclampsia without severe features and being managed as an outpatient)
– randomization: investigational pharmacy
- administration of study drug: OB Special Care or Mother-Baby units
- study monitoring (vital signs, laboratory): OB Special Care or Mother-Baby units
– data collection: on the UNM campus with an UNM-owned, encrypted computer
– data analysis: UNM HSC CTSC

8.4. A community advisory board will not be necessary for this study.

8.5. No research is planned outside of UNM HSC.

9. Resources Available

9.1. The PI, Dr. Luis Izquierdo, has completed residency training in obstetrics and gynecology as well as a fellowship in Maternal-Fetal Medicine. He is board-certified in both general OB/GYN and Maternal-Fetal Medicine. He has many years' clinical experience, and as an Associate Professor of clinical education, he has the resources necessary to oversee and complete the project. Dr. Ellen Mozurkewich, who oversaw the majority of the study design and continues as a co-investigator, has many years' experience directing clinical research, including acting as PI for a multi-center randomized controlled trial of oral misoprostol versus oxytocin for induction of labor among women with pre-labor rupture of members at term as well as a randomized controlled trial that compared EPA- and DHA-rich fish oil with soy oil placebo for prevention of perinatal depression among women at risk.

9.2. We will be collaborating with the UNM CTSC for statistical support for the study. Our CTSC statistician is Cristina Murray-Crezan.

9.3. The following licensed providers will be primarily responsible for oversight of the medical services to which patients will be admitted:

- Ellen Mozurkewich, MD, MS
- Luis Izquierdo, MD, MBA
- Conrad Chou, MD
- Larry Leeman, MD, MPH
- Sarah Gopman, MD
- Nicole Yonke, MD, MPH
- Mary Beth Sutter, MD

9.4. Describe other resources available to conduct the research:

- Our labor and delivery unit sees an estimate of 3-6 patients with severe preeclampsia per week. In order to recruit the necessary number of study participants, we would need to enroll approximately 1 subject per week over the course of 24 months.

- One of the co-investigators, Nathan Blue, is a fellow in Maternal-Fetal Medicine at UNM and has one full year of dedicated research time over the course of his fellowship (2015-2018), during which the majority of the research work will be completed.
- No special facilities will be required to conduct the research.
- Given that participation in the study involves taking one of two commonly used medicines for mild postpartum pain, either of which may be prescribed to patients not participating in the study, we do not anticipate the need for additional medical or psychological resources as a result of participating in the study.
- Prior to involvement in the study, all persons assisting with the research will be oriented by a co-investigator, at which point they will review the protocol, consent process, and their specific duties in detail.

10. Prior Approvals

10.1. Describe any approvals that will be obtained prior to commencing the research. (e.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

- We have applied for internal funding by the UNM department of Obstetrics and Gynecology. This funding proposal was submitted on April 1, 2016.
- We obtained our preliminary data with approval by the HRRC, as described in the protocol submitted under study number 16-073.

10.2. The signed "Departmental Review Form" in included in Click under "supporting documents."

10.3. If a study includes ionizing radiation, the Radiation Safety Attachment (HUS-FORM_1) must be uploaded (attached) in Click with your submission. The consent should include radiation exposure information in the Risks section.

- N/A – this study does not include any ionizing radiation.

10.4. The signed "Drug Attachment" is included in Click with the submission.

11. Multi-Site Research

11.1. If this is a multi-site study where the UNM HSC PI is the lead investigator, or UNM HSC is the coordinating site, describe the processes to ensure communication among sites, such as:

- N/A – UNM is the only site where the study will take place.

11.2. Describe the method for communicating to engaged participating sites: N/A – see 11.1

11.3. If the UNM HSC investigator is serving as the "sponsor-investigator" of a FDA-regulated trial, describe how sponsor responsibilities will be fulfilled, including, but not limited to: N/A – this study is not an FDA-regulated trial

12. Study Procedures

12.1. Study participants randomized to the ibuprofen arm will receive oral ibuprofen 600 milligrams (mg) every 6 hours starting immediately postpartum and continuing until hospital discharge. Participants randomized to the acetaminophen arm will receive oral acetaminophen 650mg every 6 hours starting immediately postpartum and continuing until hospital discharge. The purpose of the scheduled dosing of either ibuprofen or acetaminophen is to treat mild pain (level 1-3 on Wong-Baker scale). Around-the-clock, scheduled dosing of either ibuprofen or acetaminophen for mild pain is the current practice at UNM. Pain will be assessed and recorded in Cerner PowerChart as per the standard protocol for the OB Special care and Mother-Baby units by inpatient nursing staff using the Wong-Baker scale. If study participants report a pain level of 1-3, no additional medication will be given. If they report a pain level of 4-6, oxycodone 5mg will be given as often as every 4 hours, as needed. For a pain level of 7-10, oxycodone 10mg will be given as often as every 4 hours, as needed.

- The two agents being compared, ibuprofen and acetaminophen, are both marketed on-label for the treatment of pain.
- Monitoring: During the first 24 hours postpartum, study participants will receive intravenous magnesium sulfate for seizure prophylaxis, which is standard management for preeclampsia with severe features. Again, as routine practice for treatment of preeclampsia at our institution, vital signs are measured hourly. Once off of magnesium sulfate, vital signs will be monitored every 4 hours until discharged from the hospital. Serum studies are routinely sent daily as part of normal clinical practice to assess for sequelae of preeclampsia until any abnormalities resolve and blood pressures are at goal (< 160 mmHg systolic and 110 mmHg diastolic), though they may be checked more often if deemed necessary by her providers. They include complete blood count, lactate dehydrogenase, uric acid, prothrombin time, partial thromboplastin time, serum creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin. As is our current practice, patients remain hospitalized for at least 72 hours postpartum and until they are free of "severe range" blood pressure (systolic ≥ 160mm Hg, diastolic ≥ 110mmg Hg) for at least 24 hours. All of these monitoring practices are part of standard of care for women with severe range blood pressures and preeclampsia.
- Use of antihypertensives: if a study participant had been started or maintained on oral labetalol or nifedipine prior to delivery, it will be continued postpartum at the same dose, as is our current practice. If not on any oral antihypertensives, study participants will be started on either labetalol or extended-release nifedipine, according to their provider's discretion, if they have more than one blood pressure of 150 mmHg systolic or 100 mmHg diastolic, 4-6 hours apart, as recommended by recent ACOG guidelines (ACOG 2013).[2] Antihypertensives will be titrated according to the provider's discretion to achieve a goal blood pressure of less than 160mmHg systolic and 110mmHg diastolic. We chose to use these drugs for postpartum hypertension as they are first line for hypertension during pregnancy, and thus are the most likely agents which enrolled participants will already be on, and they are the first line treatment for postpartum hypertension at our institution due to their relative safety while breastfeeding.
- Demographic data will be collected from study participants at the time of enrollment. Outcomes data to be analyzed will be collected from the patient's electronic medical record in PowerChart.
- All procedures which are part of the study (including the use of either acetaminophen or ibuprofen for mild postpartum pain and serial laboratory studies) would be done if the patients were not enrolled in the study, because they are the current standard of care at UNM.
- The following will be hospital discharge criteria for study participants:
  1.1..1. No blood pressures > 160/110 mm Hg within the last 24 hours prior to discharge
  1.1..2. At least 72 hours of inpatient observation after delivery
  1.1..3. Serum creatinine that is at the patient's baseline, or trending toward normal
  1.1..4. Serum AST < 250 and ALT < 250 and trending toward normal
  1.1..5. All other postpartum or postoperative discharge criteria (tolerating regular diet, ambulating, voiding, etc.) met per the discretion of the provider

13. Data Analysis

13.1. Summary statistics will be calculated to describe the patient characteristics. Means and standard deviations or medians and quartiles will be reported for continuous data, as appropriate (exponential means for times to events or durations of events); frequencies and percentages will be reported for categorical data. For all analyses, the intention-to-treat population will be used. For the primary analysis, the exponential mean lifetimes (means) and variance will be calculated for each group and will be compared via the F test for the ratio of the lifetimes. We will report 95% confidence intervals for the times and the p-value for the test will be compared to a type I error rate of 0.05. All of the secondary outcome measures will be summarized with descriptive statistics as reported above and 95% confidence intervals will be calculated for each endpoint by group. Graphical tools may be used for visual comparison of the group effect. Exploratory

analysis may include linear modeling of the exponential mean duration of severe-range hypertension to adjust for potential covariates such as chronic hypertension, chronic pain, chronic opioid use, and mode of delivery.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

14.1. A Data Safety Monitoring Board (DSMB) will perform safety monitoring. It will be comprised of physicians with a background in obstetrics and gynecology but who will not be enrolling patients or supervising the care of potential study participants. The members of the board are affiliated with UNM and the department of Obstetrics and Gynecology, and include:

- *Valerie Rappapport, MD*
- *Yuko Komesu, MD*
- *Sharon Phelan, MD*

Due to the relatively small number of subjects, there will not be interim analysis. The DSMB will convene in the event of one of the following sentinel events occurs to determine whether the event was attributable to the patient's randomized intervention:

- stroke
- seizure / eclampsia
- posterior reversible encephalopathy syndrome
- death

14.2. If a sentinel event occurs, it will be reported to the DSMB within 24 hours, and the DSMB will convene within another 48 hours to review the case in detail and determine whether the event is attributable to the patient's study participation. The DSMB will then render advice regarding trial continuation on a case-by-case basis.

14.3. Material Safety Data Sheets (MSDS) will be available for both ibuprofen and acetaminophen, in addition to the most recently published guidelines for management of hypertensive disorders of pregnancy for review by the DSMB.

14.4. If the DSMB determines that the sentinel event is attributable to study participation and that further enrollment poses undo risk to potential participants, the DSMB will have the power to halt the study.

14.5. When the DSMB convenes following a sentinel event, the conclusion of the board and its recommendation to continue or discontinue the study will be distributed to the investigators, the sponsor and HRRC in writing within 48 hours of the DSMB convening.

15. Withdrawal of Subjects

15.1. Study participants will be withdrawn from treatment allocation and patient and provider masking (but not data collection) who experience the following after enrollment: new onset seizure activity; stroke; focal neurologic findings necessitating neuroimaging; patient request; serum Cr > 1.1 mg/dL; new onset elevation in AST > 250 mg/dL or ALT >250 mg/dL.

15.1.1. Outlined here is our systematic tracking plan to ensure timely recognition of withdrawal criteria and withdrawal from the study. When a patient is recruited for study participation, the on-call team will be notified of her study participation status, and the following information will be added to the electronic sign-out and census: the patient's study participation status, the withdrawal criteria, and the designated Research Phone number.

15.1.2. At the time of delivery, the on-call team refers to the Postpartum Orders Checklist when writing postpartum orders. The orders will include daily lab studies, including serum creatinine and LFTs, to be drawn the following morning at the latest, and earlier if clinically indicated. The Postpartum Orders Checklist will also include information to be placed in the electronic sign-out and census, as described in 15.1.1.

15.1.3. The next morning (postpartum day #1), Dr. Blue (or Dr. Katukuri or Dr. Holbrook, in Dr. Blue's absence) will review the labs with the on-call attending, and will complete a checklist documenting the review of lab studies, as outlined above in section 3.2.5 (see appendix 1 for daily lab review checklist). On weekends and holidays, this will be done by the MFM fellow assigned to rounds (either Dr. Blue, Katukuri, or Holbrook), and reviewed with the attending. The on-call attending will decide whether further lab studies are indicated the following day. This review and documentation will be completed daily for the duration of study participation (until discharge).

15.1.4. If, at the time of daily lab review, the patient meets criteria for withdrawal, the Daily Lab Review Checklist will direct the reviewing fellow and attending to the Study Withdrawal Checklist, which outlines and documents the steps needed to withdraw the study subject.

15.2. As there is no risk related to immediate withdrawal from the study, a patient may be immediately withdrawn without special procedures given that all procedures which are part of the study would continue (with exception of masking to medication use) because these are the routine medications given for postpartum pain at UNM.

15.3. If a study participant requests withdrawal due to reluctance to continue with the randomization allocation or masking procedure but still allows for her data to be collected and analyzed, she will then no longer receive the blinding procedure, but will continue to receive ibuprofen or acetaminophen for mild postpartum pain, at her provider's discretion and if the patient is amenable.

16. Data Management/Confidentiality

16.1. IRB-approved co-investigators will review the study participant's electronic medical records on a daily basis during study participation, and will complete data collection as soon as participation in the study is complete in order to collect outcomes data. Demographics data will be collected at enrollment or prior to completion of study participation. When accessing patients' charts, research team members will open the chart under the "researcher" designation when accessing the chart for this purpose.

16.2. The data collection does require the maintenance of patient identifiers (name, date of birth, medical record number) in order to access the electronic chart to collect the data.

16.3. The data collection does require the accessing and storage of Protected Health Information, including medical comorbidities, elements of medical history, as well as empiric data such as vital signs and laboratory study results.

16.4. The data collection will included substance abuse information, and thus may be considered sensitive.

16.5. A Certificate of Confidentiality will not be used to protect data from forced release (e.g., subpoena) and will be applied for once IRB approval is in place.

16.6. Patient identifiers and collected data will eventually be separated. At the time of enrollment, the data collection sheet with patient identifiers will be stored in a locked cabinet until the data are collected. No patient identifiers will be on the data collection sheets, and the data will be labeled with a case number. In case of need for further review, a file will be maintained linking patient identifiers to the case number. This file will be held in a password-protected, encrypted, and UNM HSC owned computer under the personal control of one of the coinvestigators. The patient identifier file will not be kept on the same computer which will maintain the collected data. Only the PI and the coinvestigator to whom the coding file is assigned will be allowed to access it.

16.7. Data collected will be stored in both paper and electronic formats in order to provide backup should the electronic form be corrupted or destroyed.

16.8. If data will be transferred or transmitted to outside locations or entities, describe: N/A – all data collection and analysis will take place at UNM.

16.9. The de-identified/coded data will be transmitted via email only after being encrypted, but not stored on the internet. The coding file, which will be maintained on a separate computer, will not be transmitted via email or the internet. It will remain on the computer to which it is assigned.

16.10. Data will not be collected by audio or video recording.

16.11. Data will not include photographs.

17. Data and Specimen Banking

17.1. De-identified study data will be stored for 5 years after study completion, and then destroyed.]

17.2. No data or specimens will be banked or archived elsewhere.

18. Risks to Subjects

18.1. COX inhibitors are known to contribute to acute kidney injury. Even though suspicion for acute kidney injury is one of the exclusion criteria, a patient may have sub-clinical or evolving acute kidney injury at the time of enrollment, which may become apparent only after randomization. The same possibility exists for randomization to the acetaminophen arm and the possibility of evolving subclinical liver injury not identified until after randomization. Should acute kidney or liver injury occur, it will be identified on the serial laboratory studies which are part of the study procedure, the providers will be unmasked to the patient's allocation (per criteria for withdrawal, as described above), and therefor able to withdraw the study medication if needed. Acute kidney injury and acute liver injury are both virtually always temporary in association with preeclampsia, and can both occur in the absence of the use of COX inhibitors. The risk of one of these occurrences is unlikely to be increased by participation in the study because our standard practice is currently to use either ibuprofen or acetaminophen (or sometimes both) for mild postpartum pain in the setting of preeclampsia. Risks could include worse control of hypertension if assigned to the COX inhibitor arm, but this is theoretical in this population and this question is the purpose of the experiment. COX inhibitor use is also known to exacerbate or contribute to GERD.

There is also a risk of accidental breach of confidentiality by inappropriate transmission of identifying information or protected health information

18.2. There is a possibility unforeseen risks/adverse events to patients as a result of participation in this study.

18.3. The only part of the process which will take place during pregnancy is the consent and collection of demographics information. Once she has delivered, she will be randomized and the remaining study procedures will begin.

18.4. There are no risks to others who are not subjects

18.5. Describe the steps being taken to minimize the probability or magnitude of risks.

- Risk of acute kidney injury in those randomized to ibuprofen: only subjects with normal renal function will be enrolled. Daily serum BUN and creatinine will be collected (in addition to other preeclampsia labs) and study participants will be withdrawn and providers un-masked to their randomization status if evidence of acute kidney injury develops.
- Risk of GERD in those randomized to ibuprofen: only subjects without gastritis will be enrolled.
- Risk of acute liver injury in those randomized to acetaminophen: only subjects with normal liver function will be enrolled. Daily serum AST and ALT will be collected (in addition to other preeclampsia labs) and study participants will be withdrawn and providers un-blinded to their randomization status if evidence of acute liver injury develops.

19. Potential Benefits to Subjects

19.1. Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

- If randomized to the ibuprofen arm, study participants may have better pain control. If randomized to the acetaminophen arm, study participants may have better blood pressure control. Again, this is the principle question of the study. Otherwise, there is no direct benefit to study participants.

20. Recruitment Methods

20.1. Potential study participants will be identified by labor and delivery providers while admitted to the labor and delivery unit. Charts may also be reviewed by study personnel to identify potentially eligible subjects. They will be approached by study personnel while admitted to labor and delivery, either during a period of initial observation following the diagnosis, during labor, or within the first 6 hours postpartum. Potential study participants may also be approached for recruitment after transfer from labor and delivery to our antepartum inpatient unit if the plan is for expectant management until delivery at a later time.

20.2. Potential study participants will be identified by their providers, who will notify study personnel. The study personnel will then determine whether the patient is a study candidate.

20.3. To assist in recruitment of potential study participants, we will make use of a study fact sheet which will review the basic information in plain language, in a bullet point fashion. .

21. Provisions to Protect the Privacy Interests of Subjects

21.1. The only settings in which potential study participants will be approached for participation are private: either their labor and delivery room, their private room while undergoing expectant management on the antepartum service, or in an outpatient clinic exam room. Additionally, all research procedures will occur in the privacy of a participant's hospital room.

21.2. Encounters with patients during study recruitment, consent and participation all will occur in a private setting of a patient's hospital room and will be executed by either qualified study personnel or providers who would otherwise already be involved in their care. Documentation of consent will be stored initially in the provider workroom on the labor and delivery unit and will be collected at periodically, usually every 2-3 days, for storage in a locked cabinet accessible only to study personnel. Issues related to data are addressed in the Data Management/Confidentiality Section.

22. Economic Burden to Subjects

22.1. Study participants will not be responsible for any additional cost because of participation in the study.

22.2. The patients' insurers will be responsible for paying for adverse events. If the patient is uninsured, or "self-pay", then the study participants will be financially responsible. Because the medications being studied are both already the standard of care for mild postpartum pain, an adverse even likely would have occurred whether or not a patient is a participant of the study.

23. Compensation

23.1. Upon completion of the study (at the time of hospital discharge) research participants will be compensated with a $15 gift card to a local retailer, such as Target™. This dollar amount was chosen because it is enough to serve as an incentive to complete the trial, but is not so large as to compel potential participants who are economically disadvantaged to participate due to financial need.

24. Compensation for Research-Related Injury

24.1. Study participants will be responsible for their own medical care following a research-related injury, and no compensation plan will be in place.

24.2. Study participants will be informed of their responsibility for seeking their own care for research-related injury at the time obtaining consent. Available care options include care options available under an existing insurance plan or any other options which the participant desires to pursue at their own cost.

25.Consent Process

25.1. Prior to study participation, consent will be obtained from each participant.

25.1.1. Coinvestigators or study personnel will be responsible for obtaining consent. Their minimum qualifications include completion of the following online training modules:

- Collaborative Institutional Training Initiative (CITI) Program: Biomedical Responsible Conduct of Research
- CITI Program: Human Research
- UNM Conflict of Interest training

25.1.2. The consent process will take place in the patient's hospital room or outpatient exam room. Other patients, or persons unknown to the patient will not be present for the consent process.

25.1.3. In order to minimize coercion or undue influence, potential study participants will be given the option of reviewing study contents alone or with the provider or study personnel.

25.1.4. After being approached, potential study participants will have the option for a waiting period of at least 30 minutes for review of consent materials prior to the obtaining of consent.

25.1.5. In order to ensure ongoing consent throughout the study, study participants will be asked by care providers administering the medication whether they continue to give consent for participation, or whether they have any reservations or questions about study participation. If patients express concerns or have questions, study personnel will be contacted immediately to address the questions or concerns.

25.1.6. In order to ensure that the consent is understood by the potential study participant, the provider or study personnel will ask that the patient repeat back the general nature of the study and the potential treatments to which she may be randomized. Consent will not be complete until this step is accomplished.

Subjects not fluent in English

25.1.7. Study participants speaking primarily Spanish may also be recruited and enrolled.

25.1.8. For patients who speak primarily Spanish and have a poor understanding of English language communication, oral consent will either be obtained in Spanish by study personnel who speak Spanish fluently, or through the use of interpreters. Spanish language translations of consent documents will also be used and provided to the patients for review.

25.1.9. Patients not understanding either English or Spanish will not be recruited for participation, thus short-form consent documents will not be used.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

25.1.10. Patients with limited decisional capacity (either due to long-term cognitive impairment or short-term medical etiology) will not be approached for study participation.

25.1.11. Potential study participants will only be approached for participation in the study if the assessment of the providers administering their care is that their decisional capacity is intact. Documentation of a potential study participant's decisional capacity will be included on the consent form.

25.1.12. Prior to approaching a potential study participant for recruitment, study personnel will review with the patient's providers whether she has demonstrated intact decisional capacity during her hospital admission so far. If not, the potential participant will not be approached for recruitment. If the patient has demonstrated intact decisional capacity and meets other inclusion criteria, she will be approached. The study personnel reviewing the consent with the potential participant will assess her decisional capacity by requiring her to repeat not only the general nature of the study (as noted in section 25.1.6 above), but also the potential risk and benefit of each randomization arm (randomization to acetaminophen may have risk of worse pain control, whereas randomization to ibuprofen may have risk of higher blood pressure). If the potential participant is unable to articulate this, then she will not be enrolled for participation. Intact decisional capacity will be documented with a checkbox on the consent form.

25.1.13. Decisional capacity will be evaluated on a daily basis by the providers administering medical care. If a participant's decisional capacity becomes affected and she is unable to provide ongoing consent, she will be withdrawn from the study. Given the short duration of the study, participants regaining decisional capacity will not be re-consented for continued participation.

25.1.14. Potential participants unable or unauthorized to give their own consent (as determined either by age or lack of decisional capacity) will not be enrolled in the study.

25.1.15. Given that only potential participants who are able to provider their own consent will be enrolled, obtaining assent is not applicable.

Subjects who are not yet adults (infants, children, teenagers): All study subjects will be a minimum age of 18.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered): N/A

26. Documentation of Consent

26.1. Full written informed consent will be documented on all participants.

26.2. Consent will be obtained verbally with the use of both a script and an information sheet. An information sheet summarizing the salient points of the consent will be provided for use by the consenting provider or study personnel and for review by the potential study participant.

27.Study Test Results/Incidental Findings

27.1. **Individual Results:** Individual test results obtained as part of the study protocol (i.e. daily preeclampsia labs) will be shared with the study participant by her team of medical providers as part of her ongoing medical care (as would normally be the routine).

27.2. **Incidental Findings:** No experimental tests will be used as part of the study protocol. All tests that will be performed as part of the study protocol are relevant to the care of the study participant and would be performed anyway as part of her care and will be reviewed by her team of medical providers. Thus, any incidental findings will be communicated to the study participant by her medical provider(s).

28. Sharing Study Progress or Results with Subjects

28.1. As the study data will not be analyzed until the completion of enrollment and because duration of participation is relatively short, study progress will not be reviewed with study participants while the study is underway.

28.2. We do not intend to provide subjects with a summary of the study results after the study is complete.

29. Inclusion of Vulnerable Populations

29.1. The study will not exclude economically disadvantaged persons from participation, as there is no anticipated economic burden associated with participation. As the compensation for participation is of small value, they are not vulnerable to economic coercion.

29.2. The study will not exclude educationally disadvantaged persons from participation. If a potential participant's educational disadvantage is significant enough that they are unable to understand and articulate back the general nature of the study and the risks associated with randomization to each arm, they will not be enrolled in the study.

29.3. All study participants will be recently pregnant.

30. Community-Based Participatory Research

30.1. N/A

31. Research Involving American Indian/Native Populations

31.1. American Indian/Native populations are not the focus of this study, so no additional tribal approval or review will be pursued. Potential study participants of American Indian or Native background who are eligible for the study will be approached for participation in the same manner as all non-Native potential participants.

32. Transnational Research

32.1. N/A

33. Drugs or Devices

33.1. The ibuprofen and acetaminophen administered as part of the study protocol will be stored and distributed by the research pharmacy and administered by the nurse caring for the participant. Both medications are already FDA approved for use to control pain, thus an IND is not necessary.

33.2. Update to study drug preparation process: at the time the study was initiated the investigational pharmacy was unable to source both acetaminophen and ibuprofen in powdered form. As an alternative and to ensure uniformity between the two types of capsules, commercially prepared tablets were obtained for use in preparing blinded capsules. These tablets were broken into pieces which were placed inside a size "00" capsule shell in the required quantity. Subjects numbered 1 through 50 were enrolled in the study between September 29, 2016 and March 10, 2017. In late February 2017, IDS was able to procure both acetaminophen and ibuprofen in powdered form. For the second half of the study, IDS proposes switching from the use of tablet fragments to an equivalent dosage of a powdered formulation when preparing blinded capsules. The reformulated capsules will be smaller and less odorous, resulting in a formulation more agreeable to study subjects receiving the medication. The amount of active ingredient in each capsule will remain the same with a calculated minimum amount of inert filler (microcrystalline cellulose) added to ensure uniform distribution of active ingredients among capsules.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):

   Labor and Delivery workroom monitor and electronic medical records.

2. Describe the purpose for the review (e.g., screening):

   Screening for eligibility.

3. Describe who will conducting the reviews (e.g., investigators, research staff):

   Medical providers, investigators.

4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   ☒ Yes

   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

      ☒ True

      ☐ Other justification:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

      ☒ True

☐ Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☒ True

☐ Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

☒ True

☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☐ Yes. Describe:

   ☒ No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☒ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for <u>one</u> of the following:

   a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

   b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

   ☐ Yes. Please attach a copy to your submission in Click.

   ☐ No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

<u>Note: FDA-regulated research is not eligible for an alteration of consent.</u>

1. Which element(s) of consent do you wish to eliminate <u>and</u> why?

2. Which element(s) of consent do you wish to alter and why?

3. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?
   ☐ All
   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

1. Are you requesting a waiver for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

2. Describe how capacity to consent will be evaluated.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

B. Children

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

   ☐ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

☐ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

Besides obtaining consent and obtaining demographic information, no study procedures will take place while the patient is still pregnant. Randomization, administration of study medication, and monitoring will only begin after delivery.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

Numerous studies have been carried out on non-pregnant (mostly non-reproductive age) humans, and at least one study in pregnant rats assessing the effect of NSAIDs on blood pressure, with varying results. Our goal is not to assess the effect of NSAIDs on blood pressure during pregnancy but rather in the postpartum period. Thus, patients will no longer be pregnant while participating in the study protocol. They will, however, be consented while pregnant.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

   Given that randomization and the study interventions occur after delivery, there is no risk to the fetus. Additionally, both study medications are first line agents for postpartum pain control in the setting of breastfeeding and are considered safe for mothers and neonates who are breastfeeding.

3. Any risk is the least possible for achieving the objectives of the research.

   The interventions in each randomization arm are both first line treatments for mild postpartum pain and are used ubiquitously in postpartum patients, including those with preeclampsia. Besides being randomized to either ibuprofen or acetaminophen, all study procedures effectively mirror the standard of care that would be delivered even if patients were not participating in the study. Additionally, because study participation only occurs while admitted to the hospital, participants undergo very close observation and monitoring in the form of lab tests, symptom checks and vital signs measurements as part of routine care.

D. Neonates of Uncertain Viability or Nonviable Neonates
Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates

Complete this checklist if the subject population will include nonviable neonates.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained

   ☐ True

   ☐ False

6. The research will not terminate the heartbeat or respiration of the neonate

   ☐ True

   ☐ False

7. There will be no added risk to the neonate resulting from the research

   ☐ True

   ☐ False

F. Biomedical and Behavioral Research Involving Prisoners
Complete this checklist if the subject population will include prisoners.

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

☐ Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

   a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her

ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

b) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers

c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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III. Medical Devices

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name:

B. Manufacturer:

C. Does the research involve a Significant Risk Device under an IDE?

☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number*

and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted

☐ No

D. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☐ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

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Appendix

Listed in the Appendix are the supporting documents, including data collection tools and recruitment materials, which are uploaded into Click:

1. Data Collection Postpartum Day #1
2. Data Collection Postpartum Day #2
3. Data Collection Postpartum Day #3
4. Data Collection Postpartum Day #4 and beyond
5. Eligibility log sheet
6. Enrollment Data Collection
7. 6 week post-study questionnaire
8. Patient Fact Sheet