PROTOCOL TITLE: A randomized double blind clinical trial comparing oxytocin low-dose and high-dose regimens for labor augmentation

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Table of Contents

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1.0 Objectives

1.1 Objectives:

i. Determine the rate of cesarean delivery in women who receive high-dose oxytocin regimen (HDOR) compared to women who receive low-dose oxytocin regimen (LDOR) for augmentation of labor.

ii. Determine the rates of several measures of maternal morbidity in women who receive HDOR compared to women who receive LDOR. The measures of maternal morbidity that will be examined are labor duration (time interval from admission to labor and delivery to delivery of neonate), postpartum hemorrhage, and intrauterine infection.

iii. Determine the rates of several measures of morbidity in neonates born to women who receive HDOR compared to women who receive LDOR. The measures will be examined as a composite outcome and will include perinatal death, umbilical cord arterial pH less than 7.0 or base excess greater than 12, Apgar scores at five minutes of less than <=3, admission to neonatal intensive care unit (NICU) for greater than 48 hours, severe respiratory distress requiring cardiorespiratory support and/or ventilation (intubation, continuous positive airway pressure, high-flow nasal cannula) for more than 12 hours, major birth injury (brachial plexus injury, bone fractures, other neurologic injury, facial nerve injury), neonatal encephalopathy, neonatal seizure, need for hypothermic treatment (cooling), and neonatal sepsis (positive blood, urine, or cerebrospinal fluid culture; or in the absence of positive culture(s), clinical evidence of cardiovascular collapse or an unequivocal X-ray confirming infection).

1.2 Hypothesis: The use of HDOR for labor augmentation will lower the incidence of dysfunctional labor and the subsequent need for cesarean delivery compared to the use of LDOR. We hypothesize that women who receive HDOR will have shorter labor durations, as well as lower rates of postpartum hemorrhage and intrauterine infection. Furthermore, we hypothesize that there will be no significant difference in morbidity in neonates born to women who receive HDOR compared to women who receive LDOR.

2.0 Background

One in three pregnant women undergo cesarean delivery in the United States.[1] Cesarean deliveries have increased at an alarming rate without a concomitant improvement in maternal and neonatal outcomes. Rather, the increasing rate has become a major health concern, as cesarean deliveries are associated with significant

maternal morbidity, increased costs, and adverse implications for future pregnancies.[2-4] The factor that has contributed the most to the increase in cesarean deliveries is the increased frequency of labor dystocia (i.e. dysfunctional labor due to ineffective uterine contractions).[5,6] In an effort to avoid the need for a cesarean delivery when labor fails to progress, oxytocin is widely used to augment contractions. In fact, in 2003, 645,075 pregnant women (17% of all women in the United States who gave birth and were registered) received oxytocin augmentation. Though this statistic has no longer been reported in the CDC National Vital Statistics Reports since 2003, this percentage has likely further increased. While the total dose amount of oxytocin needed to produce a clinical response (i.e. progressive cervical dilation) may vary from patient to patient, the optimal dosing rate needed to achieve this endpoint has not yet been established.

Oxytocin dose protocols have been categorized into 'high' versus 'low' dose regimens, but these terms are to an extent, misnomers because the difference is typically in the rate of dose increase rather than the total dose used. Both protocols titrate the dose of oxytocin to achieve a frequency of uterine contractions (usually 4 to 5 contractions in a 10-minute interval) that is usually sufficient to result in progressive labor, and thus the target total dose should theoretically be similar. Numerous oxytocin dose protocols that vary in initial dose, incremental dose increase, and the time interval between dose increases have been studied. HDOR have been associated with significantly shorter labor duration and lower cesarean delivery rates, when compared to LDOR,[7-13] without adverse effects on the newborn. It is postulated that by more rapidly progressing to the required therapeutic dose, cervical dilation is achieved more quickly, and the likelihood of a spontaneous vaginal delivery is increased. Furthermore, use of HDOR showed trends toward lower rates of postpartum hemorrhage and intrauterine infection for the mother.

Despite these positive findings, use of LDOR has become the prevailing obstetric practice in the United States.[14] The preference for LDOR stems from unsubstantiated concerns that HDOR are associated with more uterine tachysystole (defined as more than 5 contractions in 10 minutes, averaged over a 30-minute window), which could lead to higher rates of neonatal morbidity.[15-17] Prior studies have refuted this conclusion by showing similar neonatal outcomes when comparing use of HDOR and LDOR. However, the adoption of HDOR has been very uncommon due to persisting safety concerns and criticisms that prior studies had small sample sizes, inappropriate eligibility criteria, and inherent biases in study design.

As the frequency of cesarean deliveries performed for labor dystocia continues to increase, it is timely and critical to address the controversy surrounding the oxytocin dose regimens with an adequately powered prospective randomized trial. It is imperative that the study is double blinded to both care providers and patients to eliminate the subjective and unintentional biases that are likely contributing to the slow adoption of high-dose regimens that are effectively used for labor augmentation in other parts of the world.[18]

PROTOCOL TITLE: A randomized double blind clinical trial comparing oxytocin low-dose and high-dose regimens for labor augmentation

The overarching goal of the proposed study is to conduct a double blind randomized trial to determine whether the use of HDOR is effective in lowering the incidence of cesarean delivery in a manner that is safe for both mother and neonate. Our data will allow us to help establish evidence-based guidelines for the optimal use of oxytocin for labor augmentation. Furthermore, this project will allow us to build a foundation for a program of research to study other approaches to the management of labor dystocia. Our long-term goal is to conduct research that will develop a better knowledge base to guide clinical decisions and encourage policy changes that can lead to safe prevention of cesarean delivery, both at Northwestern Memorial Hospital (NMH) and nationally.

3.0 Inclusion and Exclusion Criteria

3.1 Nulliparous women with singleton gestations who require oxytocin for labor augmentation will be recruited for the proposed study. Pregnant women who present to the Northwestern Memorial Hospital Prentice Women's Hospital (NMH-PWH) Obstetric Triage Unit for obstetric evaluation will be screened for eligibility. Subjects meeting eligibility criteria will be approached for potential recruitment, with the assent of their primary obstetric physicians and midwives, once their hospital admission for a trial of labor has been confirmed.

3.2 Criteria

i. Inclusion criteria:

- Able to give informed written consent
- Age ≥18 years
- Nulliparous
- Pregnant with a singleton gestation that is equal to or greater than 36 weeks.
- Diagnosed with at least 6 regular uterine contractions within 60 minutes of observation. In addition, at least one of the following: cervix greater than or equal to 3 cm dilated or 80% effaced OR spontaneous rupture of membranes
- Subject's attending obstetric physician or midwife has determined that the subject needs administration of oxytocin infusion for labor augmentation. Labor augmentation will be defined as stimulation of uterine contractions when spontaneous contractions have failed to result in progressive cervical dilation or descent of fetus.

ii. Exclusion criteria:

- History of prior cesarean section or uterine surgery
- Fetus in non-cephalic presentation

- Subject undergoing labor induction (i.e. receipt of cervical ripening with intracervical foley balloon placement or prostaglandins)
- Non-English speaking

3.3 Special Populations

i. *Adults unable to consent*: Subjects who are unable to consent will not be included in our study.

ii. *Individuals who are not yet adults (infants, children, teenagers)*: Our study will only include subjects who are adults, and are 18 -45 years of age.

iii. *Pregnant women*: This population will be included since our study is focused specifically on the obstetric population.

iv. *Prisoners*: This is not applicable to our study; we will recruit solely from the population of pregnant women who deliver at Northwestern Memorial Hospital – Prentice Women's Hospital.

4.0 Study-Wide Number of Subjects – Not applicable

5.0 Study-Wide Recruitment Methods – Not applicable as this is a single-center clinical trial

6.0 Multi-Site Research - Not applicable as this is a single-center clinical trial

7.0 Study Timelines

7.1 Timelines

i. After informed consent is obtained, subjects will be enrolled in the study if and when their primary obstetric physician or midwife determines that oxytocin needs to be initiated for labor augmentation. The individual subject will be expected to participate in the study from the time of enrollment until time of discharge from the hospital after delivery.

ii. Previous work by the principal investigator (A.M.P.) showed that Active Management of Labor, with HDOR as one of its components, reduced the rate of labor dystocia and thus the rate of cesarean delivery, without increasing maternal or neonatal morbidity.[10] This randomized trial was conducted at NMH and recruited 720 patients (75% of eligible women participated in the study) in a 12-month period. Recent hospital data revealed that 3,466 women in the 12-month period prior to the original study proposal would have meet eligibility criteria. As of July 22, 2019, 839women have been enrolled in this study.

iii. The estimated date for completion of this study including primary analyses of the data is 4 years after the start of the clinical trial. Patient recruitment commenced in September 2015, and we expect to complete primary analyses by November 2019.

8.0 Study Endpoints

8.1 Study Endpoints

i. Primary study endpoint:

- The incidence of cesarean delivery

ii. Secondary study endpoints:

- Measures of maternal morbidity

a. Length of labor duration (defined as the number of hours from admission to labor and delivery to delivery of neonate)

b. Incidence of postpartum hemorrhage (defined as an estimated blood loss greater than 500 mL for vaginal delivery or greater than 1000 mL for cesarean delivery)

c. Incidence of intrapartum chorioamnionitis (defined as fever great than 100.4° Fahrenheit in the intrapartum period with the initiation of a therapeutic antibiotic regimen in the intrapartum period)

d. Incidence of postpartum endometritis (defined as fever greater than 100.4° Fahrenheit in the postpartum period with the initiation of a therapeutic antibiotic regimen in the postpartum period)

8.2 Safety Endpoints

i. Primary safety endpoint:

- Cesarean delivery performed for primary indication of non-reassuring fetal status

ii. Secondary safety endpoints:

- Measures of neonatal morbidity

a. Stillbirth or neonatal death

b. Umbilical cord arterial blood pH less than 7.0 or base deficit greater than 12 mmol/L; or cord venous blood pH less than 7.0 or base deficit greater than 12 mmol/L when umbilical artery values are not available.

c. Neonatal Apgar score at five minutes of life of less than 3

d. Admission to Neonatal Intensive Care Unit (NICU)

i. Length of stay in NICU, if applicable

e. Additional morbidities: severe respiratory distress requiring cardiorespiratory support and/or ventilation (intubation, continuous positive airway pressure, high-flow nasal cannula) for more than 12 hours, major birth injury (brachial plexus injury, bone fractures, other neurologic injury, facial nerve injury), neonatal encephalopathy, neonatal seizure, need for hypothermic treatment (cooling), and neonatal sepsis (positive blood, urine, or cerebrospinal fluid culture; or in the absence of positive culture(s), clinical evidence of cardiovascular collapse or an unequivocal X-ray confirming infection).

9.0 Procedures Involved

9.1 Study Design: We propose a double blind randomized clinical trial:

i. Recruitment*:* Patients meeting eligibility criteria (as listed above) will be approached for potential recruitment, with the assent of their primary obstetric physician or midwife, once their hospital admission for a trial of labor has been confirmed.

ii. Intervention*:* After informed consent is obtained, subjects will be enrolled if and when their primary obstetric physician or midwife determines that oxytocin is to be initiated for labor augmentation. One group, labeled as LDOR, will undergo our primary institutional protocol (Protocol #12.0053) with a starting oxytocin concentration rate of 2mU/min that can be increased at increments of 2mU/min, as per the discretion of each individual's primary obstetric physician or midwife. The other group, labeled as HDOR, will undergo our supplemental institutional protocol for Active Management of Labor (Protocol #12.005m Appendix A) with a starting oxytocin concentration rate of 6mU/min that can be increased at increments of 6mU/min, as per the discretion of each individual's primary obstetric physician or midwife. The solutions used in the two groups will appear identical and volume infusion rates (2mL/hour) will be identical to ensure double blinding. The sole difference between the two groups will be the oxytocin concentration, with 30U oxytocin in 500mL of 0.9% normal saline (NS) in the LDOR group and 90U oxytocin in 500mL of 0.9% NS in the HDOR group. Once a patient is enrolled, randomized, and in receipt of the assigned intervention, further clinical management will be left to the discretion of each patient's primary obstetric physician or midwife. Each subject will have a unique drug code, which will remain with her for the trial duration, and

drug preparations will be labeled with the same unique code by the pharmacy.

iii. Randomization*:* Fixed allocation procedure will assign the interventions to subjects with equal probability using a blocked randomization scheme without stratification. To maintain a double blind design, the NMH Investigational Pharmacy will carry out the randomization and preparation of oxytocin solutions according to the random assignment so that neither the patients and their care providers nor the investigators will know the identity of the intervention assignment.

9.2 Emergency unblinding procedures will be established so that patient safety is not jeopardized. Once a patient is enrolled, randomized, and in receipt of the assigned intervention, further clinical management will be left to the discretion of each subject's primary obstetric physician or midwife.

9.3 Procedures to lessen the probability or magnitude of risks:

i. Continuous external fetal monitoring (EFM) will be required during oxytocin infusion for both treatment groups. As per established institutional clinical protocol (Protocol #12.0053), each subject will be monitored closely during oxytocin infusion. Specifically, in latent labor, the subject's clinical nurse will assess and document contraction intensity, duration and frequency as well as fetal heart rate (FHR) baseline, variability, and any periodic change every 30 minutes and with each oxytocin rate change. In active labor and stage 2 of labor, the subject's clinical nurse will assess and document contraction intensity, duration and frequency as well as FHR baseline, variability, and any periodic change every 15 minutes and with each oxytocin rate change. If a tachysystole contraction pattern (defined as more than 5 contractions in 10 minutes, averaged over a 30-minute window) is identified, the oxytocin infusion will be decreased to the previous milliunit rate setting and reevaluated in 15 minutes. If a tachysystole pattern persists at this first 15 minute-mark, the oxytocin infusion will be decreased by one-half the current rate, and reevaluated again in 15 minutes. If a tachysystole pattern persists at this second 15-minute mark, the oxytocin infusion will be discontinued. The oxytocin infusion may then be restarted if the FHR is normal, and contraction frequency, intensity, and duration are normal at the initial start dose. If a FHR pattern is deemed to be Category 2, the subject's primary obstetric physician or midwife will be required to visualize the EFM recording and will determine further oxytocin titration. For a prolonged deceleration (defined as a decrease in FHR from baseline lasting more than two minutes), the oxytocin infusion will be discontinued. If a FHR pattern is deemed to be Category 3 (absent baseline FHR variability with any of the following: recurrent late decelerations, recurrent variable decelerations, bradycardia, or sinusoidal pattern), the oxytocin infusion will be discontinued, and the primary obstetric physician or

midwife will be notified. If the oxytocin has been discontinued for a Category 2 or 3 pattern, the oxytocin may be restarted per the order of the primary obstetric physician or midwife when the FHR tracing has returned to a Category 1 or reassuring Category 2 tracing at no more than one-half the dose that preceded the discontinuation. Maternal pulse, respirations, and blood pressure will be evaluated and recorded hourly or more frequently if necessary based on patient status. Maternal temperature will be evaluated every 2 hours with intact membranes, and every hour following rupture of membranes.

ii. Subjects in the LDOR group will receive standard oxytocin infusion according to the established NMH Clinical Protocol for Induction and Augmentation of Labor, Protocol #12.0053 (protocol is attached). In accordance with this protocol, the oxytocin infusion will be started at a rate of 2 mU/min (to maintain blinded design, pump rate will be "set" at 2 mL/hr with a concentration of 30 U oxytocin in 500mL of 0.9% NS) for the subjects in the LDOR group. The rate will be increased by 2 mU/min no more frequently than every 15-30 minutes until a labor pattern with uterine contractions every 2-3 minutes of moderate to strong intensity is established. Subjects in the HDOR group will receive oxytocin infusion according to the established supplemental NMH Clinical Protocol for Induction and Augmentation of Labor, Protocol #12.0053 (Appendix A – Active Management of Labor). In accordance with this supplemental protocol, the oxytocin infusion will be started at 6 mU/min (to maintain blinded design, pump rate will be "set" at 2 mL/hr with oxytocin concentration of 90 U oxytocin in 500mL of 0.9% NS) for the subjects in the HDOR group. The rate will be increased by 6mU/min (to maintain blinded design, pump rate will be "increased" by 2 mL/hr with oxytocin concentration of 90 U oxytocin in 500mL of 0.9% NS) until a labor pattern with uterine contractions every 2-3 minutes of moderate to strong intensity is established.

iii. The medical record of each subject's hospital stay will be reviewed and used to collect data. A data collection form will be utilized by the study investigators to extract data from each subject's medical record ('data collection' form attached)

9.4 Clinical data that are pertinent to the study endpoints during the hospital stay will be collected (see 'data collection form'). There will be no long-term follow-up; the study period begins at randomization and ends with discharge from hospital following delivery. Data will be collected only up until time of each subject's hospital discharge.

9.5 Not applicable

10.0 Data and Specimen Banking

10.1 The principal investigator Dr. Alan Peaceman,co-investigators Dr. Moeun Son and Dr. Bethany Stetson, and research assistant Dr. Archana Roy will serve as custodians of all research data. As stewards of the research data, these individuals will be responsible and accountable for research data as it

is collected, processed, stored, analyzed, and reported. Every effort will be made to maintain high quality data that will remain protected and kept strictly confidential in accordance with local, state, and federal law; as such, institutional resources REDCap (Research Electronic Data Capture) and NITRO Study Tracker will be used for data entry and monitoring. Once all data collection forms and medical charts have been reviewed, all identifiers will be removed and subject data will be stored and archived in a de-identified manner. The identifiable data will be permanently discarded by permanently deleting the password protected encrypted database with patient identifiers at the earliest opportunity.

10.2 Once the data collection forms and medical charts have been reviewed, all identifiers will be removed, and patient data will be stored in a de-identified manner (for the list of data to be stored, please see attached 'stored data' form). Data will be stored in accordance with Northwestern University Information Technology (NUIT) File Sharing Policy using SharePoint and Northwestern file servers, which are available for storing and sharing sensitive research data in order to maintain confidentiality and privacy. Only the study investigators who are on the Authorized Personnel list of the IRB approved protocol will be granted access to the research data.

10.3 De-identified data will be stored in accordance with NUIT File Sharing Policy using SharePoint and Northwestern file servers, which are available for storing and sharing sensitive research data in order to maintain confidentiality and privacy. Only the study investigators who are on the Authorized Personnel list of the IRB approved protocol will be granted access to the research data.

11.0 Data and Specimen Management

11.1 Data Analysis Plan: All outcome data will be collected and entered into the computer database before breaking the code and revealing intervention assignment. All analyses will be performed using the *intention to treat* principle. Descriptive statistics (means, standard deviations, proportions) will be calculated to check for any major differences in the study groups with regard to patient demographics and other baseline characteristics. All univariate comparisons will be unpaired and all tests of significance will be two tailed. For univariate analysis, continuous variables will be compared by Student's t-test. Categorical data will be compared using Chi-square testing or Fisher's Exact Test, depending on sample size. All values will be expressed as the mean $\pm$ standard error (continuous variables) or as a percentage of the group from which they were derived (categorical variables). A p value of less than 0.05 will be considered statistically significant. An interim analysis of the first 100 patients will be performed by an independent expert physician, and the Haybittle-Peto rule will be used as a guide for stopping the trial if the analysis of the primary outcome demonstrates a significant difference between the group using a $p < 0.001$. The overall type I error rate will be preserved at 0.05.

11.2 Power Analysis: We based our power analysis on our previous work, literature review, and a review of recent institutional data. During the 12-month period prior to this proposal, the rate of cesarean delivery at NMH was 22.4% for nulliparous women with term singletons pregnancies who received oxytocin prior to delivery and had fetuses in the vertex presentation. For the purpose of the study design, a slightly lower rate was assumed for a population of women delivering at term that excluded women with history of prior uterine surgery and those undergoing induction of labor. A sample-size calculation suggests that, assuming a cesarean delivery rate of 20% in the traditional management LDOR group, **1002 patients (501 patients per group)** would be required for this sample to provide 80% power to detect a decrease in the rate of cesarean delivery to 13.4% (one-third decrease) in the HDOR group. Chi-squared test comparing two independent proportions at a two-sided significance level of 0.05 is assumed in the power calculation.

11.3 Data Security: A Data Security Plan will be developed to ensure that protected health information and personally identifiable information will be entered, stored, transmitted, analyzed, and reported in a manner that maintains confidentiality. All the members of the study investigative team will be included on the Authorized Personnel list of the IRB approved protocol; only these individuals who are authorized will be granted access to the research data. All members of the study investigative team will be trained and certified by the Collaborative Institutional Training Initiative (CITI) Program. Data integrity and confidentiality will be maintained in several ways. Sources of data include patient records (electronic and paper), patient care providers, and subjects. All data will be collected using standardized data collection forms. Once all data collection forms and medical charts have been reviewed, all data obtained will be entered in a HIPAA compliant into an electronically (passwords and encryption) protected and secure server maintained by NUIT. All identifiers will be removed and patient data will be stored and archived in a de-identified manner. The identifiable data will be permanently discarded by permanently deleting the password protected encrypted database with patient identifiers at the earliest opportunity. Data will be stored in accordance with NUIT File Sharing Policy using SharePoint and Northwestern file servers, which are available for storing and sharing sensitive research data in order to maintain confidentiality and privacy. The data collected and transmitted to the central server is designed to strengthen de-identification and prevent any possibility of linking data to specific subjects. Specifically, subject name, initials, date of birth, date of admission, date of delivery, date of enrollment will be removed from the database at the earliest opportunity. We will organize dataset entries by unique subject study numbers (coinciding with drug treatment code number) in an anonymous manner. No patient specimens will be collected. Only the principal investigator (A.M.P), co-investigators Dr. Moeun Son and Dr.

Bethany Stetson, andresearch assistant Dr. Archana Roy (A.R) will have access to data in an identifiable manner before final de-identification.

11.4 Quality Control of Collected Data: Data collection forms will be developed, pretested, and used by the investigators and trained clinical staff to gather baseline and outcome data. Investigator meetings will be held on a quarterly basis, including just prior to the initiation of patient enrollment. After initiation of patient enrollment, investigator meetings will be held monthly for the first three months to discuss any questions regarding the protocol, and also as needed thereafter. Data will be extracted from the electronic medical record system, and investigators and clinical staff will remain blinded to group assignment during the data collection process. Every effort will be made to maintain high quality data; as such, institutional resources REDCap and NITRO Study Tracker will be used for data entry and monitoring.

11.5 Describe how data and specimens will be handled study-wide:

i. Clinical data that is pertinent to the study endpoints will be extracted from the medical record of each subject (see 'data collection' form) and will be recorded on a standard data collection form. Once all data collection forms and medical charts have been reviewed, all identifiers and protected health information will be removed and research data will be stored and archived in a de-identified manner. The identifiable data will be permanently discarded by permanently deleting the password protected encrypted database with patient identifiers at the earliest opportunity.

ii. Data will be stored in accordance with Northwestern University Information Technology (NUIT) File Sharing Policy using SharePoint and Northwestern file servers, which are available for storing and sharing sensitive research data in order to maintain confidentiality and privacy. Only the study investigators who are on the Authorized Personnel list of the IRB approved protocol will be granted access to the research data.

iii. Research data will be retained and stored for a minimum of three years after the conclusion of the study as per the Northwestern University Policy. However, research data will be kept for as long as deemed necessary to protect any intellectual property resulting from the work. The research data will be stored and archived in a de-identified manner in accordance with NUIT File Sharing Policy.

iv. Only the study investigators who are on the Authorized Personnel list of the IRB approved protocol will be granted access to the research data.

v. The principal investigator (A.M.P.),the co-investigators Dr. Moeun Son and Dr. Bethany Stetson, and research assistant (A.R.) will serve as custodians of the research data, and will be responsible and accountable for research data as it is collected, processed, stored, analyzed, and reported.

vi. Data will be stored in accordance with NUIT File Sharing Policy using SharePoint and Northwestern file servers, which are available for storing and sharing sensitive research data in order to maintain confidentiality and privacy.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

12.1 Describe:

i. The scope of risk to the patient falls under two broad categories: 1) risk of breaking confidentiality, and 2) risk for a significantly worse outcome in one study arm or the other. Confidentiality of data will be preserved in multiple ways, as discussed earlier. With regard to intervention safety, both study arms utilize FDA-approved oxytocin at two different dosing rates that are both institutionally approved by protocol for the augmentation of labor. Therefore, adverse events related directly to the drug agent oxytocin are expected to be uncommon. Furthermore, emergency unblinding procedures will be established to prepare for the event of an adverse event. This study compares two institutionally approved clinical oxytocin dosing protocols, and thus the need for an ongoing data safety and monitoring and board (DSMB) was deemed unnecessary. An independent review board has been established in the event the need for review of unexpected serious adverse event arises. An interim analysis was planned to be performed by an independent expert physician after the first 100 patients are enrolled to assess any safety or efficacy concerns since adjustments in the concentrations of the oxytocin formulations have been made in order to allow blinding of intervention. With regard to adverse events, the principal investigator (A.M.P.), co-investigators Dr. Moeun Son and Dr. Bethany Stetson, and research assistant (A.R.) will be empowered to modify or suspend the trial if they are concerned that significant harm has occurred due to the study protocol. Serious adverse events (events felt by the investigators to be related to the dosing of oxytocin infusion and are life-threatening, associated with death, or specifically leads to increased invasive interventions) will be reported to the IRB.

ii. Statistical tests will be used to analyze the safety data to determine whether harm is occurring. All univariate comparisons will be unpaired and all tests of significance will be two tailed. For univariate analysis, continuous variables will be compared by Student's t-test. Categorical data will be compared using Chi-square testing or Fisher's Exact Test, depending on sample size. All values will be expressed as the mean $\pm$ standard error (continuous variables) or as a percentage of the group from which they were derived (categorical variables). A p value of less than 0.05 will be considered statistically significant. The p value will not be adjusted for the interim analysis given its early timing.

PROTOCOL TITLE: A randomized double blind clinical trial comparing oxytocin low-dose and high-dose regimens for labor augmentation

13.0 Withdrawal of Subjects*

13.1 Subjects will be informed that they may withdraw from the study at any time for any reason, without prejudice to their medical care. The investigators also have the right to withdraw subjects from the study for the following reasons: non-adherence to the protocol requirements by the subject or the subject's primary obstetric physician or midwife, or the subject no longer meets the protocol eligibility criteria (see Section 3.1 and 3.2). Additionally, the study may be prematurely terminated, if in the opinion of the study co-Principal Investigators and/o, there is sufficient reasonable cause. Circumstances that may warrant termination include, but are not limited to: failure to enroll subjects at an acceptable rate; insufficient adherence to protocol requirements; insufficient complete and/or evaluable data; serious adverse events (events felt by the investigators to be related to the dosing of oxytocin infusion and are life-threatening, associated with death, or specifically leads to increased invasive interventions).

13.2 If a subject withdraws from the study, the primary reason for a subject's withdrawal will be recorded in the data collection. Subject who withdraw or are withdrawn from the study will not be replaced. If immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the investigators will contact the IRB, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented. Unplanned protocol deviations will be reported to the IRB per institutional requirements. If the opinion of the study co-Principal Investigators is that there is sufficient reasonable cause for premature study termination, written notification documenting the reason(s) for study termination will be provided to the both parties, and to the IRB.

13.3 If a subject withdraws from the study, the data collected on the subject to the point of withdrawal will remain part of the study database and will not be removed. Removal of already collected data would undermine the scientific, and therefore the ethical, integrity of the research. Incomplete data could potentially put enrolled study subjects, future study subjects, and users of oxytocin at unreasonable risk as a result of inaccurate data/conclusions.

14.0 Risks to Subjects*

14.1 Currently, both dosing regimens compared in this study (LDOR and HDOR) are approved by established protocols for clinical practice for labor augmentation at NMH. However, reasonably foreseeable risks include increased rates of tachysystole and cesarean deliveries performed for fetal heart rate tracing indications in the HDOR group, increased rates of maternal postpartum hemorrhage and intrauterine infections as well as increased cesarean deliveries performed for labor dystocia in the LDOR. Reasonably foreseeable inconveniences to the subjects include longer labor durations in the LDOR group and increased labor pain in the HDOR group. The protocol has been designed to minimize risks to the subjects and their neonates, regardless of whether they are randomized to LDOR or HDOR

groups. All subjects will sign a form indicating her free and informed consent to participate in the study prior to randomization. Given randomization of dosing regimens that already have well-established safety profiles, we expect a low likelihood of adverse outcomes.

14.2 Investigators will be required to report any suspected or actual Unexpected Adverse Events (UAE) that may occur during study participation. UAEs will be defined as any event that meets the following conditions: the event is **not** a known or reasonably foreseeable risk associated with the study procedures (e.g. risks related to administration of oxytocin and confidential information specified in the informed consent), and the event, in the investigators' opinion, is or could be directly related to the subject's participation in this research protocol. Events that are the result of a natural progression of an underlying disease, disorder, condition, or a predisposing risk factor profile for the subject do not qualify as UAEs. The investigators will be responsible for complying with IRB requirements for reporting of UAEs. However, since both dosing regimens compared in this study (LDOR and HDOR) have already been in clinical use for labor augmentation at NMH, we anticipate a low likelihood of UAE.

14.3 The study will only include pregnant women (see Section 16), and thus potential risks to their fetuses will be considered. Several measures of neonatal morbidity have been predefined as safety endpoints in the study. However, based on prior work[10] showing no increase in neonatal morbidity in women assigned to active management of labor using HDOR compared to traditional management, we anticipate no increased risks to fetuses in the proposed study.

14.4 Based on the randomized nature of the study, we expect that the risk of discrimination based on demographic factors will be minimal. Subjects will only participate in the study during their hospital stay for labor and delivery, and thus we do not anticipate risks to others who are not subjects.

15.0 Potential Benefits to Subjects

15.1 There are potential direct medical benefits to individuals participating in the study if HDOR does in fact decrease primary cesarean delivery rates as we hypothesize. This would not only prevent a surgical intervention for individual patients but may have positive implications for their future reproductive health. Furthermore, use of HDOR could potentially decrease rates of postpartum hemorrhage and intrauterine infection, as well as length of labor for individual patients. Shortened labor durations may also have indirect benefits on medical care costs.

15.2 Not applicable.

16.0 Vulnerable Populations

16.1 This research involves pregnant women, and Checklist HRP-412 has been reviewed. As previously discussed, scientifically appropriate clinical studies

have tested the use of different oxytocin dosing regimens, including the specific dosing used in the LDOR and HDOR in the proposed study. The risk to the fetus is caused solely by the treatment interventions that hold out the prospect of direct benefit for the women, and any risk is the least possible for obtaining the research objectives. Furthermore, only subjects carrying fetuses of at least 36 weeks gestation will be eligible to participate, which eliminates the concerns of a decision to terminate a pregnancy or periviability.

17.0 Community-Based Participatory Research - Not applicable to our study

18.0 Sharing of Results with Subjects

18.1 Given the double blind nature of the study design, individual subject treatment assignments will remain blinded during the study, and individual results will not be shared with the subjects or their primary care providers.

19.0 Setting

19.1

i. Women who present to the NMH-PWH Obstetric Triage Unit for a chief complaint of “labor” or “spontaneous rupture of membranes” will be screened for study eligibility by a trained member of the investigative team when it has been determined by the primary care team that the patient will be admitted to the labor and delivery unit for labor management. Patients meeting eligibility criteria will be approached for potential recruitment, with the assent of their primary obstetric physician or midwife, once their hospital admission for a trial of labor has been confirmed. The study will be explained in detail and all questions will be answered prior to signing written informed consent to participate in the study.

ii. Once informed consent is obtained, subjects will be enrolled into the study if and when their primary obstetric physicians or midwives have determined that oxytocin infusion is to be initiated for labor augmentation on the labor and delivery unit. It is at this point that subjects will be randomized into one of two intervention groups, as allocated by the NMH Investigational Pharmacy.

iii. Not applicable

iv. Not applicable

20.0 Resources Available

20.1 The principal investigator (A.M.P) is a Professor of Obstetrics and Gynecology and the Division Chief of Maternal Fetal Medicine at NU, and Chief of Obstetrics at PWH. He is a leading expert in the antepartum and intrapartum management of pregnancies, particularly in the area of high-risk pregnancies. He has been a PI for the Maternal-Fetal Medicine Units (MFMU) Network, which is funded by the National Institute of Child Health and Human Development (NICHD) to conduct collaborative multi-center

clinical trials. He has extensive experience in developing and conducting large-scale clinical trials in single-center and multi-center settings. He was also one of the principal investigators for previous work[10] at NMH using HDOR. The co-investigator Dr. Moeun Son is an Assistant Professor of Obstetrics and Gynecology at NU. She was previously the P.I. but will be transitioning to another institution. She will remain an Adjunct Assistant Professor of Obstetrics and Gynecology at NU. The co-investigator Dr. Bethany Stetson is an Assistant Professor of Obstetrics and Gynecology at NU. The research assistant (A.R) completed her residency in Emergency Medicine from Manipal University, India. She is currently completing a Master Degree in Public Health at Northwestern University, and she will use part of this study for her thesis. She is a clinical researcher at Northwestern University and has served as a clinical research assistant in eight multicenter MFMU clinical trials. She will be applying for residency in Obstetrics and Gynecology next year.

20.2 Resources

i. We are in a unique position to perform this clinical trial at NMH as both LDOR and HDOR protocols have been developed and validated for use on our Labor and Delivery Unit based on our previous work.[10] Furthermore, NMH-PWH is one of the nation's busiest labor units with over 12,500 deliveries per year, which will make it feasible to achieve our target sample size.

ii. The principal investigator (A.M.P.) will be responsible for the overall direction and scientific conduct of this proposed study. He will provide clinically relevant translation and execution of all aspects of the research design, patient recruitment, implementation, data analysis, and dissemination of findings.

iii. The study will be conducted in the NMH-PWH Labor and Delivery Unit with the cooperation of the physicians, nurses, and other care providers who have privileges to practice obstetrics at NMH. The randomization of subjects and distribution of study medications will be managed by designated NMH Investigational Pharmacy staff.

iv. Once a patient is enrolled, randomized, and in receipt of the assigned intervention, further clinical management will be left to the discretion of each patient's care team. However, it is important to note that NMH-PWH has a comprehensive Labor and Delivery Unit in the case of an adverse event. There is availability of a clinical obstetric staff including an Attending Obstetric physician as well as clinical Anesthesia staff including an Attending Anesthesia physician in house 24 hours a day, seven days a week. There is also the availability of a highly equipped surgical staff, blood bank capabilities, and a pharmacy at all times.

v. All persons assisting with the research will undergo training in order to be adequately informed about the protocol prior to the start of subject recruitment. All IRB-approved members of the investigative team will be responsible for assisting with recruitment efforts including participation in quarterly investigator team meetings, being advocates

for the study locally, and attending scientific meetings to present the study results when appropriate.

21.0 Prior Approvals

21.1 Approval for collaboration with the NMH Investigational Pharmacy has been established (see attached 'Pharmacy letter'). NMH has a dedicated Investigational Pharmacy that is a separate division of the NMH pharmacy department. The Investigational Pharmacy employs two research pharmacists and three research pharmacy technicians who are responsible for all research drugs for studies conducted at NMH. The Pharmacy agrees to randomize and dispense study medication in a blinded manner to study subjects. Appropriate Pharmacy staff will be trained on the details and requirements of the protocol.

22.0 Recruitment Methods

22.1 The clinical trial will be registered in a publicly accessible database (www.clinicaltrials.gov) before recruitment of the first subject. Potential subjects will be screened for study eligibility by a member of the investigative team using a screening script. Patients who meet eligibility criteria will be provided further explanation of the study. For patients who agree to participate, a member of the investigative team will fully explain the study to the subject and obtain written informed consent according to our institutional IRB requirements.

22.2 All women who present to the NMH-PWH Obstetric Triage Unit and are admitted to the Labor and Delivery Unit for delivery will be screened for eligibility.

22.3 Potential subjects will be identified through the electronic patient board in the NMH-PWH Obstetric Triage Unit. Potential subjects will be screened for study eligibility by a member of the investigative team.

22.4 Not applicable

22.5 Not applicable

23.0 Local Number of Subjects

We based our power analysis on our previous work, literature review, and our recent institutional data. During the 12-month period prior to this proposal, the rate of cesarean delivery at NMH was 22.4% for nulliparous women with term singletons pregnancies who received oxytocin prior to delivery and had fetuses in the vertex presentation. For the purpose of the study design, a slightly lower rate was assumed for a population of women delivering at term that excluded women with history of prior uterine surgery and those undergoing induction of labor. A sample-size calculation suggests that, assuming a cesarean delivery rate of 20% in the traditional management LDOR group, **1002 patients (501 patients per group)** would be required for this sample to provide 80% power to detect a decrease in the rate of cesarean delivery to 13.4% (one-third decrease) in the

HDOR group. Chi-squared test comparing two independent proportions at a two-sided significance level of 0.05 is assumed in the power calculation.

24.0 Confidentiality

24.1 Not applicable

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Every precaution will be taken to protect the privacy of research subjects and the confidentiality of their personal information to minimize the impact of the study on their physical, emotional, and social integrity. Confidentiality of data will be preserved in multiple ways, as discussed earlier.

25.2 The informed consent process will involve an extensive discussion about the study protocol and we will ensure that patients will feel comfortable about asking questions to the investigators. We will make it clear that subjects will maintain the option to withdraw from the study at any time. We also hope to make the subjects feel at ease with the research situation that both the HDOR and LDOR protocols used in our study have been developed and validated for use on our Labor and Delivery Unit based on our previous work.[10]

25.3 With their informed consent, we will obtain the subjects' permission to access their electronic medical records during their hospital stay. Data collection forms will be developed, pretested, and used by the investigators and trained clinical staff to gather baseline and outcome data. Data will be extracted from the electronic medical record system, and investigators and clinical staff will remain blinded to group assignment during the data collection process. Every effort will be made to maintain high quality data; as such, institutional resources REDCap and NITRO Study Tracker will be used for data entry and monitoring.

26.0 Compensation for Research-Related Injury

26.1 In the event of research-related injury, the subject will need to seek medical treatment through her primary obstetric physician or midwife or a treatment center of her choice. If she seeks treatment from someone other than the investigators, she will need to promptly tell the investigators about any related injury or illness. Generally, this care will be billed to the subject, her insurance, or other third party. NMH will not pay for medical care required due to a research-related injury. However, this will not prohibit subjects from seeking compensation for the care required due to a research-related injury.

26.2 Not applicable

27.0 Economic Burden to Subjects

27.1 There will be no additional costs that the subjects will be responsible for because of their participation in the research. The study has been selected for funding from the fiscal year 2016 Friends of Prentice Grants Initiative, for a total amount of $49,934 that is expected to be available by September

2015. This will be primarily used to cover the costs of medications and supplies for the subjects. As calculated by the Pharmacy Department, the total cost of oxytocin IV infusion will be $46,032 for 1002 subjects x $45, 1 vial at $0.47 x 501, 3 vials at $0.47 x 501. The projected costs include a $45 intravenous drug dispensing fee per subject, and a drug cost of $0.47 per vial of oxytocin 10U. For our sample size of 1002 subjects, 501 subjects will receive 1 vial of oxytocin and 501 subjects will receive 3 vials of oxytocin. The anticipated cost for IV tubing and drug labels is about $902 for 1002 subjects at about $0.90 per subject.

28.0 Consent Process

28.1 Participation by competent individuals as subjects in the study must be voluntary. Subjects who are interested will first be screened by an intake to verify that they meet the eligibility criteria. Subjects who are deemed eligible for study inclusion will be given a copy of the informed consent document. The study will be explained in detail by one of the members of the investigative team, and all questions will be answered prior to signing written informed consent to participate in the study. Also, the patients will be told that they can, at any time, decline continued participation in the trial. Full disclosure of the nature and potential risks of participating in the trial will be made.

i. The consent process will take place in either the NMH-PWH Obstetric Triage Unit or the Labor and Delivery Unit.

ii. While there will not be a pre-specified waiting time period, we will ensure that the prospective subject has adequate time to read over the informed consent document, ask any further questions, and discuss with family members or friends or their primary obstetric physician or midwife prior to signing written consent to participate.

iii. We will ensure that the subjects understand their option to withdraw from the study at any time.

iv. We will be following “SOP: Informed Consent Process for Research (HRP-090).”

Non-English Speaking Subjects

Not applicable

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

Not applicable

Subjects who are not yet adults (infants, children, teenagers)- Not applicable

Cognitively Impaired Adults

Not applicable

PROTOCOL TITLE: A randomized double blind clinical trial comparing oxytocin low-dose and high-dose regimens for labor augmentation

Adults Unable to Consent

Not applicable

Adults Unable to Consent

Not applicable

29.0 Process to Document Consent in Writing

29.1 We will be following "SOP: Written Documentation of Consent (HRP-091." Please see attached 'consent document.'

30.0 Drugs or Devices

30.1 Through our collaboration with the NMH Investigational Pharmacy (see above), the oxytocin used for our study will be stored, handled, and administered by authorized members of the Investigational Pharmacy staff who have been trained on the details and requirements of the study protocol. Investigators and care teams will remain blinded to treatment allocation to maintain double blind study design.

30.2 Not applicable

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