Protocol:
Nifedipine for Acute Tocolysis of Preterm Labor

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1. Introduction and Purpose:

1. *Describe why this research project will be done. Clearly state the overall objectives, specific aims, hypotheses and rationale for performing the study.*

Preterm birth, defined as birth at less than 37 weeks, affects 11 - 13% of all births in the United States and results in significant morbidity and mortality for the approximately 500,000 infants born preterm each year. The leading cause of preterm birth is preterm labor, and obstetrical interventions have included various tocolytic medications. Efficacy studies on these have yielded disappointing results. (Leveno et al, 1986; Leveno et al 1990; Canadian Preterm Labor Investigators Group, 1992; Leveno and Cunningham, 1992, Mercer and Merlino, 2009). There has been recent interest in nifedipine as a tocolytic for preterm labor (Conde-Agudelo et al, 2011). In 2008, a survey of maternal-fetal medicine specialists reported that 32% were using nifedipine as their tocolytic of choice (Fox et al, 2008), despite that there are no placebo-controlled, randomized studies of nifedipine for acute tocolysis preterm labor showing a benefit.

This is a randomized, double-blinded, placebo-controlled trial of nifedipine for acute tocolysis of preterm labor. Our objective is to determine whether nifedipine decreases the rate of preterm birth. Our null hypothesis is that nifedipine does not reduce the rate of preterm birth.

2. *Indicate the Primary and Secondary Study Endpoints. Also indicate the Primary Safety Endpoints (unless the study is a safety study).*

The primary outcome will be prolongation of pregnancy until at least 37 weeks. Secondary outcomes will include 1) number of patients who receive at least 2 doses of betamethasone, 2) delivery within 48 hours of diagnosis of preterm labor and 3) delivery within 7 days.

3. *Explain why the study risks are reasonable in relation to the potential benefits to subjects and society.*

Given the prevalence of this off-label use of nifedipine, it is unlikely that serious adverse events are commonly encountered. The main serious risk associated with nifedipine is pulmonary edema, but in the 17 reported cases, this risk was reported in the context of other specific risk factors, such as use with other tocolytic drugs, use of rapid-acting formulations, prolonged tocolysis, and use when there was evidence of preexisting maternal cardiac disease/dysfunction. Importantly, in 26 published trials involving isolated use of nifedipine for acute tocolysis, there were no cases of pulmonary edema among patients receiving nifedipine (References 8a-aa).

We plan to restrict use to healthy, normotensive women with singleton pregnancies not receiving additional tocolytic agents. We will also **not** use prolonged or sublingual (rapid acting) administration of nifedipine. Therefore, these reported adverse reactions are most unlikely. Milder side effects associated with nifedipine include headache, flushing and low blood pressure, which resolve with discontinuation of the medication. The balance of benefits and risks favors performing this study to quantify benefits, if any, given the potential for nifedipine to stop preterm labor and its high use rate in the community.

2. Background:

1. *State the purpose of the research and describe the related theory/data supporting the intent of the study.*

The purpose of this research is to determine whether nifepidine is effective compared to placebo for delaying delivery sufficient to ensure delivery of corticosteroids and thus reducing preterm birth related morbidity. Nifedipine interferes in calcium transport across cell membranes and is an effective smooth muscle relaxant. We believe that uterine relaxation (tocolysis) from nifedipine may reduce preterm birth.

2. *Describe what is considered standard care (approved and/or customary) for the medical condition being studied, if applicable.*

Although tocolysis is not currently used at Parkland Hospital, it is considered within the standard of care for physicians caring for women in preterm labor.

3. *Explain how the new treatment or procedure may improve standard care, if applicable. Clearly delineate what is considered research study items from the "standard care".*

If nifedipine is identified as an effective tocolytic for reducing preterm birth, it would be included as part of the standard care for women with preterm labor.

4. *Provide a short statement concerning the status of the drug, drug combination, delivery method, device, or other interventions/concepts to be studied.*

Nifedipine is FDA approved for treatment of angina and hypertension, but it is widely used off-label as a tocolytic for preterm labor.

5. *Indicate whether the research is confirming or an extension of previous work, or whether it is pioneering with little prior information. Include an evaluation of existing knowledge and identify the information gaps that the project intends to address.*

No placebo controlled, randomized trials of nifedipine as an intervention for acute tocolysis of preterm labor (defined as cervical dilatation with contractions) have been reported, therefore, this study will be an important contribution to the medical literature.

6. *Describe published research with animals and/or humans that supports the study hypothesis or objectives. If applicable, include information regarding toxicity. Include a bibliography of key references/citations as applicable.*

Ex Vivo Data

In human myometrium collected at the time of cesarean section Nitrendipine, a dihyropyridine calcium channel blocker similar to nifedpine, depressed myometrial contractions. (Maigaard, 1986).

Randomized Trials of Nifedipine

Vis et al (2014) recently reported an unusual study of "randomized women" and "nonrandomized eligible women" with nifedipine tocolysis versus placebo in women between 24 and 34 weeks' gestation with intact membranes, a short cervix by ultrasound, a negative fetal fibronectin (in theory, low risk of preterm birth) and "symptoms of preterm labor" (symptoms were not further defined). This

was a non-inferiority trial and the authors reported that placebo was not inferior to nifedipine tocolysis. The very small sample size and its very unusual design raise questions about its utility.

No placebo-controlled, randomized trials of nifedipine for acute tocolysis of preterm labor (defined as cervical dilatation and contractions) have been reported. Published studies of nifedipine as a treatment for preterm labor are comparisons to other tocolytic agents (References 8a-aa). These other agents include magnesium sulfate, atosiban and beta-agonist drugs such as ritodrine, none of which have been demonstrated to improve birth outcomes.

Meta-Analyses of Trials Involving Nifedipine

Cochrane Review of Calcium Channel Blockers for Inhibiting Preterm Labor

The authors included published and unpublished data from 12 trials (1029 women) comparing calcium channel blockers to other tocolytic agents. The relative risk for giving birth within 7 days was decreased (RR 0.76, 95% confidence interval, 0.60-0.97) with nifedipine, and the relative risk for maternal side effects was less (RR 0.32 95% CI, 0.24-0.41). There were fewer adverse neonatal outcomes among patients treated with nifedipine, with the relative risks (95% CI) for RDS, necrotizing enterocolitis & intraventricular hemorrhage being 0.63 (0.46-0.88), 0.21 (0.05-0.96), 0.59 (0.36-0.98).

Other Meta-Analyses

Tsatsaris et al (2001) analyzed 9 randomized trials involving 679 patients comparing nifedipine to beta-agonists. The relative risks (95% confidence intervals) for delaying delivery at least 48 hours, side effects, respiratory distress syndrome and neonatal intensive care unit admission compared to other beta-agonists were 1.52 (1.03-2.24), 0.12 (0.05-0.29), 1.51 (0.63-3.65) and 0.65 (0.43-0.97), respectively. Conde-Agudelo et al (2011) reviewed 26 trials with 2179 women. Compared to beta-agonists, nifedipine significantly reduced risk of delivery within 7 days and before 34 weeks, RDS, necrotizing enterocolitis, IVH, neonatal jaundice and ICU admission. Compared to magnesium sulfate, nifedipine showed no significant differences. Maintenance tocolysis is ineffective.

Safety

Reviews of Adverse Outcomes Involving Nifedipine: In a review of the literature on adverse events following the use of calcium channel blockers like nifedipine for tocolysis, Oei (2006) concluded that: 1) calcium channel blockers should not be combined with intravenous beta-adrenergic agonists (such as ritodrine hydrochloride or terbutaline), 2) intravenous nicardipine or high oral doses of nifedipine should not be used in cases of multiple gestation or when the mother is compromised cardiovascularly, and 3) blood pressure should be monitored and cardiotocography should be recorded when immediate release tablets are used.

Importantly, in the proposed study, only healthy women with **singleton** pregnancies will be consented for participation, sub-lingual (rapid-acting) administration will **not** be used and multiple tocolytics will **not** be employed. Compared to the only FDA approved tocolytic (ritodrine), nifedipine has fewer side effects.

Recently, Xiao et al (2014) reported the effect of magnesium sulfate and nifedipine on the risk of developing pulmonary edema in preterm births: “nifedipine did not increase the odds of developing pulmonary edema [adjusted odds ratio (OR)=1.22 (confidence interval (CI) 0.50, 3.01), P=0.67]”

Hemodynamic and Metabolic Effects

Papatsonis et al (2003) compared 95 patients randomized to oral nifedipine to 90 patients randomized to intravenous ritodrine. Compared to nifedipine, patients who received ritodrine had significantly lower mean diastolic blood pressures at 24 and 48 hours (65 +/- 12 versus 70 +/- 8, p=.001, and 65 +/- 12 versus 71 +/-8, p=.004, respectively), and significantly higher mean maternal pulses at 24 and 48 hours (105 +/- 17 versus 86 +/- 13, p<.0001, and 100 +/- 21 versus 85 +/- 12, p<.0001). Gucglu et al (2006) studied maternal hemodynamic parameters as well as Doppler waveforms of various fetal structures in 28 women who received nifedipine for preterm labor. The maternal and fetal heart rates were unaffected despite that maternal mean systolic and diastolic blood pressures were lower at 24 hours. Changes in the umbilical artery Doppler measurements were "minimal and not sustained." Additionally, De Heus et al (2009) reported the effects of the tocolytics atosiban and nifedipine on fetal movements, heart rate and blood flow and concluded: "tocolysis with either atosiban or nifedipine combined with betamethasone administration appears to have no direct fetal adverse effects."

Recently, Ulubasoglu (2014) reported that there were no statistically significant differences between 24-hour values for the umbilical artery pulsatility index, resistance index (RI), systolic-diastolic (S:D) ratio, right uterine artery measures (pulsatility index, RI, S:D ratio) or left uterine artery measures (RI and S:D ratio), and they concluded that "oral nifedipine is a safe tocolytic agent with no long-term effect on fetomaternal circulation in pregnant women at risk of preterm delivery."

3. Concise Summary of Project:

1. *Provide a brief description of the study design. If applicable, describe the treatment arms, use of placebo or comparison drug/device and randomization.*

This will be a randomized, double-blinded, placebo-controlled trial of nifedipine for acute tocolysis (48 hours total duration) of preterm labor in women with singleton gestations between 28-0/7 weeks and 33-6/7 weeks' gestation. After initial monitoring on Labor & Delivery, all women will be admitted to the antepartum ward until approximately 34 weeks' gestation and completion of the full course of corticosteroids, although the provider will determine when it is safe for the patient to be discharged, as is our current routine without tocolysis. Discharge can be affected by whether the patient is considered stable (is she contracting again?), if her cervical exam has changed (if her cervix has increased dilatation, particularly to 4 cm or more, she may not be considered safe for discharge) and if she is receiving any other interventions. We will avoid creating an expectation that by participating in this study, then an exact or particular discharge date is assured.

2. *Include specific details regarding the study drug(s) being used, including the generic/trade name of the study drug. Include details about drug preparation, packaging, shipping, storage, dispensing, return and destruction. Include details of any dose reductions or dose escalations that may occur including the dose change and duration of transition from one dose to another.*

The generic name is nifedipine which is marketed as Adalat or Procardia as trade names. Generic nifedipine in 20 mg doses will be obtained from a distributor in the United States. The Investigational Drug Service at Parkland Hospital has arranged for the placebo and study drug to be encapsulated by Abrams-Royal Pharmacy, 8220 Abrams Road, Dallas, TX 752313550 Parkwood Blvd, Bldg F, Ste #630, Frisco TX 75034. This pharmacy has experience with drug encapsulation for randomized controlled trials. The Investigational Drug Service at Parkland Hospital is aware that Abrams-Royal Pharmacy will be encapsulating the placebo and study drug. Unused or expired study drug will be returned to the investigational drug service (IDS) pharmacy.

Women who consent to participate in the above study will be randomized by the IDS pharmacy to receive either placebo or a loading dose of nifedipine 20 mg oral capsule, which will then be repeated after 90 minutes if there are persistent contractions. Four hours after the first dose, they will begin nifedipine 20 mg oral capsule every 4 hours for a total duration of 48 hours, up to a maximum of 160

mg the first 24 hour period (120 mg the second 24 hour period), unless delivery occurs sooner. We anticipate that women will remain on Labor & Delivery for monitoring for at least 24 hours prior to consideration of transfer to the high-risk antepartum unit.

3. *Include information regarding the study drug(s) classification and the mechanism of action, if known.*

Nifedipine is a dihydropyridine class of calcium channel blocker, and are selective for smooth muscle. The dihydropyridines are thought to inhibit uterine myometrial contractions by causing relaxation of the uterine smooth muscle.

4. *Include a brief description of outcome variables and study endpoints, as appropriate.*

The primary outcome will be delay of delivery until 37 weeks'. Secondary outcomes will include 1) at least 2 doses of betamethasone, 2) delivery within 48 hours' gestation and 3) delivery within 7 days.

5. *Indicate the maximum number of local subjects to be consented on this protocol, including projected screen failures and early withdrawals. Include subjects who will receive interventions as well as controls, if applicable. For multi-center research, indicate the total sample size for the entire project across all sites.*

Assuming a 50% consent rate, we will be approaching approximately 300 women for consent. Sample size calculations indicate we need 75 women per arm or 150 total women to demonstrate a 33% reduction in preterm birth, based upon 2 prior Randomized Placebo Controlled Trials of tocolysis (magnesium sulfate and ritodrine) performed at Parkland Hospital (Leveno et al, 1986; Cox and Leveno, 1990).

6. *If the study involves use of existing charts, records, or specimens, specify the maximum number that will be reviewed to compile the data or the sample population necessary to address the research question.*

This is a prospective trial and existing records will not be reviewed.

7. *Provide the total number of subjects to be studied at this site and approximately how long the study will last.*

It is anticipated that the study will take approximately 4-5 years to consent and study a total of 150 women with preterm labor between 28-0/7 weeks and 33-6/7 weeks.

8. *Include conditions which would result in the subject exiting the study prior to the expected completion date, such as non-compliance, safety reasons, subject withdrawal of consent, disease progression, etc.*

This is an intent to treat study. Withdrawal of consent would be the only indication for early exit.

4. Study Procedures:

1. *Provide a chronological description of all study procedures. If applicable, divide procedures into pilot, screening, and procedures performed at each regular visit. Indicate how many total visits and approximately how long visits will last. For studies that are providing medication(s), give the name(s), dosage, and route of administration. For studies that have more than one arm/part, provide the above information for each.*

Women presenting with symptoms of preterm labor will be assessed using electronic external fetal heart rate and uterine contraction monitoring. Women will receive a baseline and subsequent cervical exams as necessary. If at any time during her evaluation, the woman is dilated to at least 2 cm and has uterine contractions, she will be potentially eligible for study. Women with a singleton gestation between 28-0/7 weeks and 33-6/7 will be approached for consent to participate by Research Nurses employed by the Department of Obstetrics & Gynecology or Dr. Wells if a Research Nurse is unavailable. They will be randomized by the IDS Pharmacy into treatment (study drug, nifedipine) or control (placebo) groups.

Study women will receive nifedipine 20 mg or placebo oral capsule followed by a second dose after 90 minutes if there are persistent contractions. Four hours after the initial dose, they will begin nifedipine 20 mg or placebo oral capsule every 4 hours for a total duration of 48 hours, up to a maximum of 160 mg the first 24 hour period (120 mg the second 24 hour period), unless delivery occurs sooner. We anticipate that women will remain on Labor & Delivery for monitoring for at least 24 hours prior to consideration of transfer to the high-risk antepartum unit.

There will be a "HOLD DOSE" parameter in which a dose will be held if an enrolled patient:

- refuses medication
- has heart rate greater than 120

If a dose is held, the nurse will contact the 4th year resident who will ensure Dr. Wells is notified.

There will be a "STOPPING RULE" for further individual participation in the study for any of the following criteria: withdrawal of consent, diffuse rash or anaphylaxis reaction to medication (requires confirmation by house officer), hypotension requiring delivery or medication such as ephedrine, or development of any obstetrical outcomes that would normally preclude tocolysis (development of ruptured membranes, development of chorioamnionitis, development of preeclampsia/gestational hypertension, development of bleeding suspicious for abruption, cervical dilatation of 6 cm or more or fetal death), or if a decision is made to either deliver the patient or to use regional anesthesia.

Women without further cervical change after monitoring on Labor and Delivery will be admitted to the antepartum unit for surveillance until approximately 34 weeks' gestation and completion of the full course of corticosteroids, although the provider will determine when it is safe for the patient to be discharged. This is our current practice in such women and is not a study procedure. Discharge can be affected by whether the patient is considered stable (is she contracting again?), if her cervical exam has changed (if her cervix has increased dilatation, particularly to 4 cm or more, she may not be considered safe for discharge) and if she is receiving any other interventions. We will avoid creating an expectation that by participating in this study, then an exact or particular discharge date is assured. Some patients choose to leave earlier (usually due to family obligations) despite the recommendation to stay until 34 weeks' gestation. Women who are discharged from the antepartum unit will be followed-up in the OB Complications Clinic of Parkland Hospital weekly until delivery. This method of outpatient follow-up for patients after discharge from the antepartum unit is also our routine and is not a study specific procedure.

2. *You may include tables, figures and/or flow diagrams if necessary to clarify highly complex studies.*

N/A

3. *Indicate the timing of all study procedures and the anticipated duration of the subject's involvement.*

Study participants involvement in study related procedures will last 48 hours.

4. *As applicable, include the amount and blood to be drawn, tissue samples to be collected, radiation exposure, questionnaires, or other interventions.*

No additional blood, tissue, imaging studies, questionnaires or other interventions are planned.

5. *Note if the subject will be responsible for any research-related costs and estimate the amount of these costs, if applicable.*

This study will be locally funded by the Department of Obstetrics & Gynecology and participants will not be responsible for any research-related costs. Study drug is the only research related cost. All other procedures such as inpatient hospitalization are part of routine care for women with preterm labor and a cervix of 2 cm or more.

6. *If applicable, describe end-of-study procedures, including transition of the subject to alternative care.*

N/A

5. Sub-Study Procedures:

1. *For any sub-studies that may be a part of the research, please provide a subsection title and include information about the procedures that will be performed and whether subjects have the option to participate or not (e.g., pharmacokinetics, biomarkers).*

N/A

2. *For studies that collect blood and/or tissue for DNA analysis where the genetic portion is described in the Master Protocol provide a genetic subsection to include information about the procedures that will be performed and whether subjects have the option to participate in the sub-study.*

N/A

6. Criteria for Inclusion of Subjects:

1. *Describe the characteristics of the subject population. For example, list any characteristics required for eligibility, such as diagnosis, prior therapy, age, or gender.*

Inclusion criteria include:

- Mothers between 16 and 44 years of age inclusive.
- Singleton pregnancy
- Intact membranes
- Between 28-0/7 weeks and 33-6/7 weeks' gestation inclusive
- Reported or documented uterine activity
- Cervical dilation between 2 cm and 4 cm inclusive

2. *Explain the rationale for the use of special classes of subjects who are more likely to be vulnerable, such as pregnant women, children, cognitively impaired people or prisoners.*

Pregnant women are included as this study is for an intervention for preterm labor.

7. Criteria for Exclusion of Subjects:

1. *Describe the exclusion criteria. For example, list any characteristics that would preclude participation, such as prior therapy, concomitant treatments and co-morbid conditions. If exclusion is based on age, gender, language barriers or social/ethnic group, describe the need*

for the exclusion in terms of scientific validity. Do not justify exclusion in terms of convenience or other non-scientific issues, such as lack of funding.

Exclusion criteria:

Oppose inclusion criteria:

- Multifetal gestation
- Less than 28 weeks' gestation
- 34 or more weeks' gestation
- Ruptured membranes

Tocolysis contraindicated:

- Low amniotic fluid (oligohydramnios)
- Fetal growth restriction
- Chorioamnionitis or temperature of at least 38.0 degrees Celsius
- Fetal death
- Preeclampsia
- Suspected placental abruption or placenta previa
- Lethal fetal malformation or amniotic fluid index at least 35
- More than 4 cm dilated

Corticosteroids contraindicated:

- Previously received a course of corticosteroids for fetal lung maturation

Nifedipine contraindicated:

- Systolic BP < 90 mmHg or diastolic BP < 50 mmHg
- Baseline tachycardia (pulse >120 after 2 consecutive measurements 30 minutes apart)
- Chronic hypertension treated with antihypertensives in pregnancy
- Seizure disorder or HIV*
- Women who have received progesterone therapy in the 2nd or 3rd trimester
- Maternal allergy to nifedipine
- Known maternal cardiac disease

* See July 2013 FDA warning regarding nifedipine and phenytoin, also several protease inhibitors are strong inhibitors of metabolizing enzyme CYP3A4

2. *Include situations or conditions, unknown at the time of enrollment that might cause a screening failure.*

No situations known.

8. Sources of Research Material:

1. *Identify the source(s) of materials/data to be used in the research, such as information or specimens from medical records, databases, repositories or other sources. If a combination of these sources are used, and/or new clinical data generated, describe how the research material is acquired.*

Data on obstetrical and neonatal outcomes for all women delivered at Parkland Hospital are routinely entered into Dr. Leveno's obstetrical operations database. Outcomes recorded for study women and their offspring will be linked by Don McIntire, PhD, who is the only person who has access to this password protected and encrypted dataset.

2. *State whether the material or data will be obtained specifically for research purposes, or whether existing records, specimens or other data will be used. If existing records or specimens are being used, please indicate the dates from which data or samples will be extracted (start and stop dates).*

This will be a prospective, double-blind, placebo controlled trial and therefore existing records or specimens will not be used.

9. Recruitment Methods and Consenting Process:

1. *Indicate if the potential subjects will be patients of the investigators.*

All investigators are faculty members and oversee obstetrical care at Parkland Hospital.

2. *Describe and provide details of the recruitment process. Include when, where, by whom and how potential subjects will be approached. Indicate if non-English speaking subjects are being consented and if so, indicate how informed consent process will be conducted.*

Research nurses employed by the Department of Obstetrics & Gynecology, and who are on-call and monitoring Labor & Delivery, will identify, approach and provide informed consent to all potential participants (these tasks will be performed by Dr. Wells if a research nurse is unavailable when a patient presents with preterm labor). If potential participants are non-English speaking, a language-appropriate translator will be obtained as per current Department of Obstetrics & Gynecology research protocols.

3. *Explain measures that will be taken to respect the privacy of the potential subjects.*

Patients will generally be consented in one of the private rooms on Labor & Delivery.

4. *Explain what precautions will be taken to minimize the potential for undue influence or coercion.*

Professional research nurses already on staff with the Department of Obstetrics & Gynecology, and who do not have an interest in a particular study outcome, will be providing the informed consent during weekdays and most weeknights. If a patient presents with active preterm labor when a research nurse is unavailable, Dr. Wells will obtain informed consent. Dr. Wells has observed several of these nurses obtain informed consent in a dispassionate and thorough manner, which emphasizes to the patient that the usual care that we provide will not be affected by her decision to participate or not.

5. *If you are requesting a waiver of informed consent, explain how the criteria for waiver are met.*

N/A

6. *If vulnerable populations will be included, describe the additional protections that will be provided, such as methods to obtain surrogate consent (cognitively impaired subjects), and plans for obtaining assent and/or the permission of one or both parents (minors).*

N/A

10. Potential Risks:

1. *Describe the known risks and/or potential discomforts associated with each intervention or research procedure. Risks may be physical, psychological, social or economic.*

Mild side effects associated with nifedipine include headache, flushing and low blood pressure, which generally resolve with discontinuation of the medication and without further intervention. In a systematic review, Khan et al (2010) reported that the use of calcium channel blockers for tocolysis or for hypertension in pregnancy was associated with a 3-fold increased risk of tachycardia and an 8 to 9-fold increased risk of hypotension when the dose exceeded 60 mg per day. However, this analysis included all pregnant women receiving all different types of calcium channel blockers (including severely hypertensive women, particularly women with preeclampsia and severe gestational hypertension, a very different population that we propose to study), and thus was not limited to

women with preterm labor, the sub-population than we propose to study. Regarding the possibility of hypotension, Luewan et al (2010) studied blood pressure in normotensive pregnant women treated with nifedipine 10 mg every 15 minutes up to 40 mg, followed by 60 mg controlled release tablet in 4 to 6 hours. The authors defined hypotension as a decrease in diastolic blood pressure of at least 15 mmHg from baseline, and reported up to 17% of patients met these criteria. They concluded that "hypotension secondary to nifedipine was not associated with significant clinical symptoms, suggesting that nifedipine is relatively safe in terms of hypotensive effect."

Houtzager et al (2006) performed long-term follow-up of children exposed in utero to nifedipine or ritodrine for preterm labor and reported: "The results do not support any differential postnatal effect of the tocolytic agents ritodrine or nifedipine on the child's long-term psychosocial and motor functioning. The slightly better outcome of children randomised in the nifedipine group is most likely due to more favourable perinatal outcomes in this group."

More serious side effects are rare when the widespread use of nifedipine in the community is considered. In the English-language medical literature, there are 22 reported cases of pulmonary edema, 1 stillbirth and 2 cases of myocardial infarction associated with nifedipine tocolysis, but these risks were reported in association with other particular risk factors such as use with other tocolytic drugs, use of rapid-acting formulations, prolonged tocolysis and use when there was evidence of preexisting maternal cardiac disease/dysfunction (Bal et al, 2004; Vaast et al, 2004; Abbas et al, 2006; Van Geijn et al, 2005; Nassar et al, 2007; Gatault et al, 2008; ; Kutuk et al, 2013; Serena et al, 2014; Van Veen et al, 2005; Oei et al, 1999; Verhaert and Acker, 2004). The single report of stillbirth was disputed and provoked a series of follow-up letters in response to the controversy (Johnson, 2005; Kandysamy, 2005; Papatsonis et al, 2005). Importantly, in 26 published trials involving isolated use of nifedipine for acute tocolysis, there were no cases of pulmonary edema or more serious side effects among patients receiving nifedipine (References 8a-aa). More recently, Kutuk (2013) reported a case of pulmonary edema with nifedipine use in a woman with ruptured membranes at 33 weeks. The authors note that the pulmonary edema occurred on the 4th day of her admission in association with prolonged tocolysis. In this case report of a single patient, there was prolonged use of nifedipine in a woman with ruptured membranes, which was arguably not acute tocolysis at all since the event occurred during a period typically associated with maintenance tocolysis. Our study restricts use to acute tocolysis with only 48 hours' duration, and in women with intact membranes. Four other cases of pulmonary edema were reported by Serena et al (2014), but these were all in women with prolonged intravenous use of nicardipine, and intravenous tocolysis is a recognized risk factor for pulmonary edema (Oei, 2006). We are not using intravenous formulations nor will we be using nifedipine for prolonged periods (maximum 48 hours of acute tocolysis).

Recently, Xiao et al (2014) reported the effect of magnesium sulfate and nifedipine on the risk of developing pulmonary edema in preterm births: "nifedipine did not increase the odds of developing pulmonary edema [adjusted odds ratio (OR)=1.22 (confidence interval (CI) 0.50, 2.01), P=0.67]". Of note, Sciscione et al (2003) reviewed 62,917 consecutive pregnancies delivered between 1989 and 1999 and reported that acute pulmonary edema due to tocolytics was exclusively in women who received multiple simultaneous tocolytic agents "the most common combination was intravenous magnesium sulfate and subcutaneous terbutaline." In the current study, we are not using multiple tocolytics, and women in this study will not be receiving magnesium sulfate, so this risk is felt to be very low.

A single case report of severe resistant maternal hypotension following tocolysis with nifedipine was published in December 2014 (Khoo and Mathur, 2014). There are several aspects of patient management within this case report that raise concern, and which are distinct from protocols in our present study. First, the patient in the case report presented with hypotension (87/51 mmHg) and ruptured membranes. In our present study, we exclude women with low blood pressure (systolic value less than 90 mmHg and/or a diastolic value less than 50 mmHg), as well as women with ruptured

membranes. Second, more aggressive dosing of nifedipine was used in the case report (nifedipine 10 mg every 15 minutes for 4 doses). This more aggressive dosing amounted to 40 mg in the first hour, compared to the protocol in our present study, which calls for 20 mg, with an additional 20 mg after 90 minutes if there are persistent contractions and hold-dosing parameters are not met. Third, the nifedipine was continued despite tachycardia (135 beats per minute) and persistent hypotension (88/43 mmHg). In the case report, despite the patient feeling weak and having persistent hypotension and tachycardia (83/43 mmHg and 121 beats per minute) 5 hours after the first dose of medication, the medication was continued. In our study, there is a hold dose parameter for heart rates of 120 beats per minute or more. In the case report, the blood pressure dropped further to 76/42 with persistent tachycardia at 7 hours after the first dose of nifedipine, and the blood pressure at delivery was 56/43. The authors could not be sure of the hypotension being attributable to the nifedipine and the authors considered sepsis in the differential diagnosis, and her intravenous antibiotics were noted to be "oralised" on the third postoperative day. Again, this single case report was notable for more aggressive nifedipine dosing in a woman with baseline hypotension and ruptured membranes at the outset, and the nifedipine was continued despite worsening clinical status and persistent tachycardia. We exclude women with ruptured membranes and baseline hypotension, and our hold-dose parameters offer further protection; therefore, the outcome reported in this single case report is most unlikely to occur given the protections set up in the present study.

Two recent reviews of the literature recommend nifedipine as the first choice tocolytic for its possible beneficial effect and favorable side effect profile:

1) Van Vliet et al (2014) wrote: "for the initial tocolysis, the use of atosiban or nifedipine for 48 h is recommended based on the largest effectiveness and most favorable side effect profile."
2) Haram et al (2014) wrote: "nifedipine may be a reasonable first choice because it is easy to administer and also of limited side effects relative to Beta2-mimetics."

We plan to restrict use to healthy, normotensive women with singleton pregnancies not receiving additional tocolytic agents. We will also not use sublingual administration of nifedipine. Therefore, these reported adverse reactions are most unlikely.

2. *Estimate the probability (chance or likelihood of occurrence) that a given harm may occur and its severity (mild, moderate or severe) and define risks by percentages, when available, or by categorizing with the terms rare, unlikely, likely.*

Mild Events:

Mild headache or flushing: **Likely;** *Moderate headache, Dizziness or Nausea:* **Unlikely**

A review (Chan et al, 2008) of nifedipine for first-line tocolysis of 212 episodes of preterm labor in 203 women reported that moderate headache was the most common side effect (9 of the 203 women, 4.4%). Other side effects included flushing (9 of the 203 women, 4.4%), dizziness (4 of the 203 women, 2%), nausea (3 of the 203 women, 1.5%), shortness of breath (1 of the 203 women, 0.5%). A study by Guclu (2006) found that up to 71% of patients had flushing and 25% had headache. A review (Marin et al, 2007) of nifedipine tocolysis in 24 patients reported that 11 (45.8%) had mild headache.

Moderate Events:

Hypotension or Tachycardia: **Unlikely**

A review (Chan et al, 2008) of 203 women for whom nifedipine was prescribed as the first-line tocolytic in 212 episodes of preterm labor reported that nifedipine was discontinued for hypotension less than 90/60 in 3 women (1.5%). One woman (0.5%) developed tachycardia of at least 140 BPM.

Pulmonary Edema: **Rare**

There are 8 case reports/case series (Bal et al, 2004; Vaast et al, 2004; Abbas et al, 2006; Van Geijn et al, 2005; Nassar et al, 2007; Gatault et al, 2008; Kutuk et al, 2013; Serena et al, 2014) including a total of 22 patients with pulmonary edema in the English-language medical literature. Risk factors appear to be multiple gestation, sublingual (rapid-acting) or intravenous dosing of nifedipine or

nicardipine, use of multiple tocolytics, prolonged use of tocolysis and maternal cardiac disease or dysfunction. These risk factors will be avoided due to our very specific inclusion and exclusion criteria and the non-sub-lingual formulation of nifedipine used. In an expert review of the literature, Oei (2006) recommends that intravenous nicardipine or high doses of nifedipine should not be used in cases of multiple gestation or when the mother is compromised cardiovascularly. Intravenous formulations will not be used in this study, and multiple gestations will be excluded. Importantly, in 26 published trials involving nifedipine for acute tocolysis, there were no cases of pulmonary edema among patients receiving nifedipine .

Severe Events:
Stillbirth or myocardial infarction: **Extremely rare**
Van Veen et al (2005) reported the only identified case of stillbirth in the English language literature after use of nifedipine. Importantly, this patient received multiple tocolytics (atosiban, indomethacin, nifedipine) which will not be the case in our study. Only 2 case reports were found of myocardial infarction associated with nifedipine tocolysis in the literature (Oei et al, 1999; Verhaert and Acker, 2004). In both cases healthy babies were ultimately delivered and there were no abnormalities on maternal follow-up testing. Importantly, in these cases nifedipine was used with another tocolytic (ritodrine), and in one case there were ruptured membranes. We will not be using nifedipine in conjunction with another tocolytic (in this case ritodrine), nor will we be using nifedipine in patients with ruptured membranes (at higher risk for infection). Of note, there have been 3 placebo-controlled trials of nifedipine for maintenance tocolysis over prolonged periods (Lyell et al, 2008; Parry et al, 2012; Roos et al, 2013). Importantly, none of these reported severe adverse events for nifedipine during the long periods that maintenance tocolysis was employed.

3. *Compare the risks of the research to standard of care. If placebo controls are used, justify their use over active or other kinds of controls.*

At Parkland Hospital, patients receive corticosteroids for fetal lung maturity, ampicillin as prophylaxis for Group B streptococcus, sedation and hydration. Tocolytic drugs are not used for preterm labor. However, use of tocolytic agents is within the standard of care for women with preterm labor. Given that it is uncertain whether nifedipine for acute tocolysis results in a benefit by delaying preterm birth and its associated risks, or only carries risks of side effects without benefits, it is ethical to compare nifedipine to placebo.

11. Subject Safety and Data Monitoring:

1. *Describe what measures have been taken and/or will be taken to prevent and minimize any risks or discomforts.*

Only singleton pregnancies in women with preterm labor and unruptured membranes will receive either placebo or nifedipine. Multiple tocolytics will not be used. Additionally, intravenous or sublingual (rapid-acting) forms of nifedipine will not be used. Only women with preterm labor at 28-0/7 weeks to 33-6/7 weeks will be included, as women with preterm labor between 24-0/7 weeks and 27-6/7 weeks receive magnesium sulfate for neuroprophylaxis and magnesium sulfate can synergize with nifedipine to block calcium movement through calcium channels. Women with hypotension, tachycardia or significant maternal cardiac disease or hypertension treated with antihypertensives will be excluded at the outset. Women with potential indications for delivery will be excluded. Hold dose parameters and stopping rule for further participation are detailed in Section 4(1) above.

2. *If applicable, discuss provisions for insuring necessary medical or professional intervention in the event of adverse events.*

All study participants will undergo regular vital sign monitoring while on Labor & Delivery and on the antepartum unit. Patients on Labor and Delivery will have continuous electronic fetal monitoring and tocometer evaluation, and patients on the antepartum unit will have daily fetal heart testing. If a maternal or fetal complication is identified, physicians will be immediately available to intervene on behalf of the mother and fetus.

3. *Describe the plan for monitoring study data collected to protect subject safety and data integrity. Please review Guidance on Data and Safety Monitoring Plans for instructions on what information should be provided. If desired, the DSMP Template may be used and included in your application packet.*

See DSMP

4. *Note: investigator-initiated studies involving administration of an experimental (i.e. not FDA approved for the indication/population under study) drug, device or intervention **must** submit a Data Safety Monitoring Plan (DSMP Template) and may be required by the IRB to establish a Data Safety monitoring Board (DSMB).*

See DSMP

Summary of Sections 66.0 and 67.0 of the Smart Form for the Data Safety Monitoring Plan and Committee

Who comprises the Data Safety Monitoring Committee (DSMC)?

The DSMC is composed of Dr. Don McIntire, PhD, Professor and Statistician within the Department of Obstetrics and Gynecology, as well as two faculty physicians from the Department of Obstetrics and Gynecology not participating in the study (Dr. Scott Roberts and Dr. Oscar Andujo).

When will the DSMC meet:

The DSMC will meet at least annually during the projected 4 year duration of the study. Additionally, after accrual of 75 patients (half of the planned 150 patients for recruitment), an interim analysis will be performed.

What will be analyzed by the DSMC?

The DSMC will monitor study accrual rate, study attrition including participant withdrawals/dropouts, patterns of AEs and/or unanticipated events, patterns of protocol deviations and/or violations and changes in risk/benefit. Efficacy (positive and negative) as well as possible futility of further study will be examined at the interim analysis. Significance levels for the interim analysis will be altered by the method of Lan-DeMets. Safety will be evaluated at each meeting of the Data Safety and Monitoring Board.

How will safety be evaluated and what study-specific stopping rules will be used by the DSMC?

Safety will be evaluated by analyzing situations in which administration of the study drug is stopped according to the “STOPPING RULE” below.

The study would be stopped if nifedipine is found to significantly delay preterm birth, or if a significantly greater number of stillbirths or emergency deliveries due to nonreassuring fetal heart tracing attributable to study drug during the 48 hour period during which the study drug will be administered for acute tocolysis of preterm labor.

What safety mechanisms are built into the Nifedipine study protocol?

Apart from the strict inclusion and exclusion criteria and the plan to continue maternal and fetal monitoring for at least 24 hours after beginning the study, the following safety parameters are part of the study protocol:

There will be a “HOLD DOSE” parameter in which a dose will be held if an enrolled patient either refuses medication or has a heart rate greater than 120. If a dose is held, the nurse will contact the 4th year resident who will ensure Dr. Wells is notified.

There will be a “STOPPING RULE” for further individual participation in the study for any of the following criteria: withdrawal of consent, diffuse rash or anaphylaxis reaction to medication (requires confirmation by house officer), hypotension requiring delivery or medication such as ephedrine, or development of any obstetrical outcomes that would normally preclude tocolysis

(development of ruptured membranes, development of chorioamnionitis, development of preeclampsia/gestational hypertension, development of bleeding suspicious for abruption, cervical dilatation of 6 cm or more or fetal death), or if a decision is made to either deliver the patient or to give regional anesthesia.

12. Procedures to Maintain Confidentiality:

1. *Describe how data/specimens will be collected and stored and the security methods in place. Note: the more sensitive the study data, the more sophisticated the methods should be to maintain confidentiality.*

Data on all obstetrical and neonatal outcomes are routinely entered into Dr. Leveno's obstetrical operations database (a secure, password-protected database at UT Southwestern).

2. *If data/specimens will be disclosed to outside persons or entities, list the entities and the method used to code or de-identify the data/specimens.*

No data or specimens are anticipated to be disclosed to any outside persons or entities.

3. *State if you intend to apply for a Certificate of Confidentiality from the NIH.*

N/A

13. Potential Benefits:

1. *Describe the potential benefits of the research to the subjects, to others with similar problems, and to society. If there is no prospect of direct benefit to the subjects, state how the knowledge to be gained will benefit society enough to justify any risks to subjects.*

Potential direct benefits to the study participant are prolongation of pregnancy and avoidance of preterm birth. Potential benefits to society include a better understanding of whether nifedipine is an effective intervention for tocolysis of preterm labor.

14. Biostatistics: (omit this section for peer-reviewed research such as cooperative group, or NIH-sponsored studies, and for industry-sponsored research which has been submitted to FDA)

1. *Describe the statistical methods to be used to answer the study question(s). Pilot studies also require a method of analysis, but the justification of the target sample size is not required.*

T-tests (two-sided) will be used for continuous variables and Chi-squared tests for categorical variables. Power will be 80% and an alpha of 0.05 will be used.

2. *Explain how the target sample size was determined.*

Previous studies done on preterm patients at Parkland Hospital include Leveno et al (1986), Cox and Leveno (1990) and Chao et al (2011). In Chao et al (2011), there were 153 patients in 12 months. Over 4 years, we would anticipate four-times that (153 x 4 = 612). In Chao et al (2011, The Diagnosis and Natural History of False Preterm Labor, Obstet Gynecol), 27% of the patients diagnosed with contractions and with cervical dilation of less than 2 cm delivered prior to 37 weeks' gestation. However, this study by Chao et al was not a prospective study. Additionally, it focused on women with cervical dilatation less than 2 cm, whereas the current study includes women with cervical dilation of 2 to 4 cm dilated. Importantly, women with more cervical dilation are more likely to deliver early, and it is appropriate to revise the target enrollment.

Fortunately, 2 prior Randomized, (placebo) Controlled Trials (RCT) of tocolysis (magnesium and ritodrine) from Parkland Hospital have been published. For the RCT by Leveno et al of ritodrine versus placebo ("Single-Centre Randomised Trial of Ritodrine Hydrochloride for Preterm Labour", Lancet, 1986) in which women with singleton pregnancies and preterm labor with cervical dilation up to 4 cm, 39 of 52 (75%) patients randomized to the control group delivered between 27 and 35 completed weeks. Similarly, for the RCT of magnesium sulfate versus placebo by Cox and Leveno ("Randomized investigation of magnesium sulfate for prevention of preterm birth" Am J Obstet Gynecol 1990) in which women with singleton pregnancies and preterm labor with cervical dilation less than 5 cm, 55 of 80 (68.8%) of patients randomized to the control group delivered between 27 and 35 completed weeks' gestation. These are important data derived from randomized, placebo-controlled, prospective trials done here at Parkland Hospital and we feel that our sample size should incorporate this prospectively obtained data. An average of the above preterm birth rates for these two RCTs at Parkland Hospital is 71.2% (39+55 / 52+80). In slight distinction to the above studies, for the current study, we are including women beginning at 28 weeks' gestation, and we will be assessing preterm birth as delivery at less than 37 weeks. In theory, the preterm labor rate for delivery at less than 37 weeks (the primary outcome of the current trial) would be higher than this average preterm birth rate for women prior to 35 completed weeks' gestation. However, using these prospectively obtained numbers from past studies of preterm labor at Parkland hospital, we would need approximately 150 women (75 women in each of the 2 arms) in order to detect a 1/3 reduction (from 71.2% to 47.5%) in the rate of preterm birth with 80% power and an alpha of 5%.

Analysis of internal obstetrics operations data indicates that for the month of March 2015, there were 10 women between 28-0/7 weeks and 33-6/7 weeks with preterm labor and a cervix of 2 to 4 cm dilation. Of these 10 women, 6 were ineligible for participation in the study (2 had diabetes in pregnancy, 1 women had a twin gestation, 1 women was only 15 years of age and 1 woman had bleeding concerning for abruption). Of the 4 eligible women in March of 2015, 2 elected to participate in the study, consistent with our ongoing consent rate of approximately 50%.

Effective September 17, 2015, there has been a protocol change at the level of the Division of Maternal-Fetal Medicine at Parkland Hospital. This protocol change will be to give corticosteroids for fetal lung maturity to women with diabetes and to all women with hypertension who are at risk of preterm birth. This MFM Division level protocol change will affect this study of women at risk of preterm birth.

Given that 2 of the formerly ineligible women (due to diabetes) who presented in March 2015 would now be eligible due to the above protocol change, we estimate that up to 24 additional women (2 x 12 = 24) would be screened per year, and up to 12 additional women (50% of the 24 additional screened) would participate. Given that there were 29 women recruited over the intitial13 months (which equates to approximately 27 over 12 months), under the new practice in which corticosteroids will be given more broadly (and women with diabetes and mild hypertension not treated with medications are eligible for participation), we estimate that up to 78-90 women would now be screened, and of these, we estimate that 39-40 women would participate per year.

Therefore, over ~4-5 years, we would expect 300 patients screened and 150 patients consented. In order to detect a 33% reduction in the rate of preterm birth less than 37 weeks' gestation, assuming 80% power and a 2-sided alpha of 5%, a sample size of 75 patients per arm (two arms, study drug and placebo), 150 patients total, will need to be recruited. So far in the current study, we have had about a 50% consent rate. Assuming a 50% recruiting rate (50% x 300 = 150), it is estimated that this study will take 4 to 5 years to complete.

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