Randomized control trial of nitroglycerin during cesarean delivery in the second stage of labor

NCT02265965

Document Date: 10/19/2017

Study Application (Version 1.11)

1.0 General Information

*Enter the full title of your study:		
Randomized control trial of nitroglycerin during cesarean delivery in the second stage of labor		
***Enter the study number or study alias**		
RCT of NTG for CD in labor * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

2.0 Add Department(s)

2.1 List the departments associated with this study. The Principal Investigator's department should be Primary.:

Primary Dept?	Department Name
◉	**UCSF** - *127037* - M_Anesthesia
○	**UCSF** - *123024* - M_ObGyn-MFM-Core-MFM

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Lucero, Jennifer M. MD, MD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Britton, Atisa B
Other Investigator
Farajian, Viken
Other Investigator
Henry, Dana E
Other Investigator
Lim, Stephanie

Other Investigator
Page, Shannon M
Other Investigator
Thiet-Akram, Mari-Paule
Co-Principal Investigator
Yeh, Peter
Other Investigator

B) Research Support Staff

Balan, Samantha A
Study Recruiter
Gertridge, Lisa C
Research Assistant
Leong, Stephanie A
Research Assistant
O'Leary, Allison S
Research Assistant
Thao, Kao N
Research Assistant
Valdez Lopez, Priscila A
Research Assistant
Wilson, Lisa
Research Assistant

3.3 *Please add a Study Contact:

Henry, Dana E
Lucero, Jennifer M. MD, MD

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Qualifications of Key Study Personnel

4.1 November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in**

which KSP are being added. More information on the CITI training requirement can be found on our website.

List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button. This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
Henry, Dana E	Data Collection	Maternal Fetal Medicine Fellow
Thiet-Akram, Mari-Paule	Co-PI	Director of MFM division and currently PI in multi center RCT drug trial
Dr. Lucero, Jennifer M. MD, MD	PI	Director of Ob-Anesthesia research and a translational researcher and completed am NIH research fellowship
Leong, Stephanie A	Research Recruiter	Recruits for studies on labor and delivery with over a year of experience
Lim, Stephanie	Data Collection and Recruitment	Obstetric Anesthesia Fellow
Gertridge, Lisa C	Research Recruiter	Recruits for studies on labor and delivery with over a year of experience
O'Leary, Allison S	Research Recruiter	Recruits for studies on labor and delivery with over a year of experience
Wilson, Lisa	Research Recruiter	Recruits for studies on labor and delivery with over a year of experience
Britton, Atisa B	Data Collection and Recruitment	Obstetric Anesthesia Fellow
Page, Shannon M	Data Collection and Recruitment	Obstetric Anesthesia Fellow
Thao, Kao N	Research Recruiter	Recruits for studies on labor and delivery with over a year of experience
Valdez Lopez, Priscila A	Research Recruiter	Recruits for studies on labor and delivery with over a year of experience
Farajian, Viken	Data Collection and Recruitment	Obstetric Anesthesia Fellow
Yeh, Peter	Data Collection and Recruitment	Obstetric Anesthesia Fellow
Balan, Samantha A	Research Recruiter	Recruits for studies on labor and delivery with over a year of experience

5.0 Initial Screening Questions - Updated 9/13

(Note: You must answer every question on this page to proceed.)
If you are converting to the new form, check questions 5.4, 5.6, 5.7, 5.8 and 5.10 before saving and continuing to the next section.

5.1 * Application type:

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

5.2 * Risk level (Help Text updated 9/13):

- ( ) Minimal risk
- (•) Greater than minimal risk

5.3 * Subject contact:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

5.4 * Funding (past or present):

- (•) Funded or will be funded (external sponsor, gift, program or specific internal or departmental funds)
- ( ) Unfunded (no specific funds earmarked for this project)
- ( ) Unfunded student project

5.5 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

( ) Yes (•) No

If **Yes**, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.6 * This is an investigator-initiated study:

(•) Yes ( ) No

5.7 * This study ONLY involves retrospective records review and/or identifiable biospecimen analysis:

( ) Yes (•) No

5.8 * This is a clinical trial:

(•) Yes ( ) No

Clinical Trial Registration
"NCT" number for this trial:

NCT02265965

5.9 * This is a multicenter study:

○ Yes ◉ No

5.10 * This application involves the study of unapproved or approved drugs, devices, biologics or in vitro diagnostics:

◉ Yes ○ No

5.11 * This application involves a Humanitarian Use Device:

◉ No
○ Yes, and it includes a research component
○ Yes, and it involves clinical care ONLY

5.12 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

◉ No
○ Yes, and requires CHR and GESCR review
○ Yes, and requires GESCR review, but NOT CHR review

5.13 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

○ Yes ◉ No

5.14 * This application includes a request to rely on another IRB (other than NCI CIRB):

○ Yes ◉ No

Note: If this request is approved, the CHR will **NOT** review and approve this study. Another institution will be the IRB of record.

6.0 Funding

6.1 Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor: **Note: we require only a P Number *OR* an A Number for funding coming through UCSF. Please avoid these common errors in funding documentation:**

- **DO NOT add the A Number if a P Number was already provided OR update the A Number field when a new funding cycle begins. The IRB does NOT use this information or want these changes made.**
- **DO NOT add a grant continuation as a new funding source.**

External Sponsor:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number"	UCSF RAS System Award Number

					or eProposal number	("A" + 6 digits)
No Sponsor has been added to this IRB Study						

Gift, Program, or Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☑ Specific departmental funding (specify source below, if applicable)

List the gift, program, or departmental funding source:

Departmental funding through Department RFA

6.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps:

- **If funding has already been awarded or the contract is being processed by the Office of Sponsored Research (OSR) or Industry Contracts Division (ICD), your sponsor is already in the system and the project has an eProposal Proposal or Award number. Check with your department's OSR Staff or ICD Officer to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is. Click here to find your OSR staff and here to find your ICD staff.**
- **If your sponsor is not yet in the list, enter it in the box below.**

○ Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

6.3 * This study is currently supported in whole or in part by Federal funding OR has received ANY Federal funding in the past (Help Text updated 9/13):

○ Yes ◉ No

If **yes**, indicate which portion of your grant you will be attaching:

- ☐ The Research Plan, including the Human Subjects Section of your NIH grant or subcontract
- ☐ For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- ☐ The section of your progress report if it provides the most current information about your human subjects work
- ☐ The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

7.0 Sites

7.1 Institutions (check all that apply):

- ☑ UCSF
- ☐ China Basin

- [ ] Helen Diller Family Comprehensive Cancer Center
- [ ] Mission Bay
- [ ] Mount Zion
- [ ] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno (Community Medical Center)
- [ ] Gallo
- [ ] Gladstone
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)

7.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project (Help Text updated 9/13):

- [ ] Other UC Campus
- [ ] Other institution
- [ ] Other community-based site
- [ ] Foreign Country

List the foreign country/ies:

7.3 Check any research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

8.0 Study Design

8.1 * Study design (Help Text updated 9/13):

This is a study of the effect of IV nitroglycerin on the ease of fetal extraction during cesarean delivery in the second stage of labor and thus reducing the incidence of uterine extension. Nitroglycerin IV is often given during cesarean delivery for women who are diagnosed with arrest of descent for uterine relaxation and aid in delivery of the fetal head. This is standard obstetric practice, but the use of this medication has not been shown to have a significant effect on maternal outcomes in previous studies, and its use has not been standardized among obstetric and anesthesia providers. However, in our retrospecitve review of our data from our perintatal database in a small subset of women who received nitroglycerin (28/309) there was an increase risk of neontal admission to NICU, metabolic acidosis on cord blood gas, and lower apgar scores. In an attempt to clarify and standardize the utility and efficacy of this practice, we propose a cluster randomized trial of the use of IV nitroglyerin on hysterotomy extension during cesarean delivery performed in the second stage of labor. Prior to the start of a new month all cesarean deliveries performed in the second stage of labor will undergo randomization to receive nitroglycerin for the entire month vs saline for that month. The nitroglycerin or placebo will be administered to the patient at the time of hysterotomy prior to fetal extraction. It has become routine in many cases with prolonged second stage to administer nitroglycerin during cesarean delivery at the time of fetal head deliver after the obstetrician has deemed the delivery difficult, therefore at the time of uterine incision prior to the extraction the obstetric anesthesiologist will give a bolus dose of 400mcg nitroglycerin or placebo followed by infusion of 400mcg

/min of nitroglycerin until delivery of the neonate is complete. If during the delivery the obstetrician makes an additional request for nitroglycerin the obsetric anesthesiologist will give a 400mcg bolus of known nitroglycerin to the patient.

8.2 If this is a clinical trial, check the applicable phase(s) (Help Text updated 9/13):

- ☐ Phase I
- ☐ Phase II
- ☐ Phase III
- ☑ Phase IV

9.0 Scientific Considerations

9.1 Hypothesis (Help Text updated 9/13):

This study has a hypothesis:

◉ Yes ○ No

If yes, state the hypothesis or hypotheses:

H1-IV nitroglycerin will decrease uterine incision extensions and blood loss compared to placebo
H2- IV nitroglycerin will decrease overall operative time compared to placebo
H3-IV nitroglycerin will decrease the fetal extraction time (time from hysterotomy to delivery of infant) compared to placebo
H4-IV nitroglycerin will have no difference in fetal outcomes compared to placebo

9.2 * List the specific aims:

Aim-1 Uterine relaxation providing ease of delivery of fetal head would result in reduction of uterine extensions and allow for shortened operative times for cesaran delivery. We would like to evaluate the role of IV nitroglycerin for improved maternal outcomes in cesearean delivery for arrest of descent.
Aim 1a.To test the hypothesis that use of IV nitroglycerin during the time of cesarean delivery for difficulty delivering fetal head is effective in reducing hysterotomy extensions, blood loss, and improved cord blood gases. Measurment of blood loss, if any uterine extensions, and cord blood gas values will be analyzed.
Aim 1b. To test the hypothesis that use of IV nitroglycerin during the time of cesarean delivery for difficulty delivering fetal head is effective in reducing total operative time. Monthly IV nitroglycerin randomization for cesearen delivery will be performed. Measurement of total operative time will be analyzed.
Aim 1c. To test the hypothesis that use of IV nitroglycerin during the time of cesarean delivery for difficulty delivering fetal head is effective in reducing fetal extraction. Monthly IV nitroglycerin randomization for cesearen delivery will be performed. The obstetrician will be blinded. Measurement of time of hysterotomy to delivery of neonate will be analyzed.

9.3 Statistical analysis:

Sample size- 270 patients per arm based on power calculation of hysterotomy uterine extension alpha = 0.05, power 0.8
Univariate- We will perform a chi square for the nonparametric outcomes and t-test for the continuous outcomes
multiple comparisons performed post-hoc will include bonferroni correction, where applicable.
Mutivariate-We will perform a a logistic regression for the primary and seconary outcomes

9.4 If this study has undergone scientific or scholarly review, please indicate which entity performed the review:

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Center (CRC) advisory committee
- [x] Departmental scientific review
- [ ] Other:

Specify **Other**:

10.0 Background

10.1 Background:

The use of nitroglycerin has become routine in breech extraction during twin delivery and recently become routinely requested by the obstetricians who are having difficulty delivering a neonate through a hysterostomy for both arrest of descent and active phase arrest for cesarean deliveries. Addtionally it has been studied as an alternative and for terbutaline for external cephalic version. Both IV niroglycerin and sublingual nitroglycerin have been used in cases of tachysystole with fetal bradycardia during labor. In uterine inversion it is considered the drug of choice prior to induction of volatile anesthetics and is given at bolus doses of 1000 mcg IV without any safety concerns. It is a standard medication during open fetal surgeries where there is concern of uterine contractions and as such given in bolus IV doses of 200-400mcg if there is concern of fetal bradycardia secondary to increased uterine tone. The safety profile of IV nitorglycerin has been studied and given the broad range of uses in Obstetrics. Recently there is thought based on anecdotal evidence that IV nitroglycerin boluses prior to fetal head extraction ease delivery of a potential difficult delivery, and has become routinely requested by the obstetrician if there is a stuggle to deliver the head during cesarean delivery. Prior to this becoming adopted based on only anecdotal evidence and utilized after time has been lost during a difficult delivery, we propose evaluating IV nitroglycerin administration prior to delivery of the neonate and blind obstetricians to the administration to better evaluate whether there are benefits of nitroglycerin during fetal head extraction during cesaren delivery for arrest of descent.

10.2 Preliminary studies:

Retrospective analysis was performed at UCSF, evaluating the use of nitroglycerin during cesarean delivery during the second stage of labor. nitroglycerin was used in 9% of the total cesarean deliveries and was not significantly associated with increased risk of uterine exension. Although the absolute rate of extension was lower in the nitroglycerin group a small sample size limited our ability to detect a difference between these groups. One finding associated with sublingual nitroglycerin group was the increased rate of NICU admissions, metabolic acidosis in cord blood, and lower apgars, however this was not found with intravenous nitroglycerin. Given the sample size was small and this was a retrospective review it is unclear whether this is a real effect of sublingual nitroglycerin or is sublingual nitroglycerin a surrogate for difficulty delivery and prolonged second stage of labor.

10.3 References:

Alexander et al., Obstet & Gynecol, 2007
David et al., 1997 Obstet & Gynecol
Hilton et al., 2009
Clark et al, 2004 Obstet & Gynecol

If you have a separate bibliography, attach it to the submission with your other study documents.

11.0 Sample Size and Eligibility

11.1 Number of subjects that will be enrolled at UCSF and affiliated institutions:

540

11.2 Total number of subjects that will be enrolled at all sites (Help Text updated 9/13):

540

11.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

160/month

11.4 Explain how and why the number of subjects was chosen (Help Text updated 9/13):

Estimates are based on our perinatal databse calculations for cesarean delivery in the second stage over the last 3 years. We conducted a power calculation to determine amount of subjects needed to see a difference in hysterotomy extension during fetal extraction. This sample size was calculated using standard alpha of 0.05, this sample size would allow us 80% power to find reduction in hysterotomy extension from baseline risk of 25% to 15% with treatment. This was chosen as it is considered a clinically significant difference in this outcome.

11.5 * Eligible age range(s):

- ☐ 0-6 years
- ☐ 7-12 years
- ☐ 13-17 years
- ☑ 18+ years

11.6 Inclusion criteria:

We plan to include all women with a term (>/= 37weeks) gestation, undergoing cesarean delivery in the second stage of labor. This would also include those who underwent a failed assisted vaginal delivery with forceps or vaccuum and need to undergo cesarean delivery.

11.7 Exclusion criteria:

Women who delivery vaginally either via operative vaginal delivery or spontaneous vaginal delivery
Any cesarean delivery under general anesthesia
Primary or repeat cesarean delivery electively perfomred or in the first stage of labor

11.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

◉ Yes ○ No

If **yes**, please explain the nature and rationale for the restrictions:

This is a study that requires women who are pregnant underoing cesarean delivery, therefore their gender needs to be female.

12.0 Drugs and Devices

12.1 * Investigational drugs or biologics will be used OR approved drugs or biologics will be studied under this application:

◉ Yes ○ No

12.2 * Investigational medical devices or in vitro diagnostics will be used OR approved medical devices or in vitro diagnostics will be studied under this application:

○ Yes ◉ No

12.3 * A Non-Significant Risk (NSR) determination is being requested for an investigational device:

○ Yes ◉ No

12.4 Verification of IND/IDE numbers: If the sponsor's protocol does not list the IND/IDE number, you must submit documentation from the sponsor or FDA identifying the IND/IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.

13.0 Study Drug Details

13.1 List the drugs or biologics that will be studied:

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** NITROGLYCERIN **Generic Drug Name:** NITROGLYCERIN **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	NITROGLYCERIN
Generic Drug Name:	NITROGLYCERIN
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	American Regent, inc
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	The drug is currently used for this obstetrical clinical scenario and has been for over 20 years.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No

If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug /biologic:	

14.0 Other Approvals and Registrations

14.1 * Do any study activities take place on patient care units:

◉ Yes ○ No

If **Yes**, attach a letter of support for the study from the involved patient care manager(s).

14.2 * Does your protocol involve any radiation exposure to patients/subjects? The UCSF Radiation Safety Committee requires review of your protocol if it includes administration of radiation as part of standard of care OR research exposures:

○ Yes ◉ No

14.3 * This study may generate genetic data that may be broadly shared (e.g. submitted to NIH for Genome-Wide Association Studies (GWAS) in dbGaP, TCGA, etc):

○ Yes ◉ No

14.4 * This study involves administration of vaccines produced using recombinant DNA technologies to human subjects:

○ Yes ◉ No

14.5 * This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to CHR approval):

○ Yes ◉ No

14.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Radiation Safety Committee

Specify RUA #:

☐ Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

☐ Controlled Substances

15.0 Procedures

15.1 * Procedures/Methods (Help Text updated 9/13) For clinical research list all study procedures, test and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the Methods:

At the time of cesarean delivery, all consented patients that meet the inclusion criteria subjects undergoing cesarean delivery in the second stage will be moved to the operating room for cesarean delivery. The anesthesia providers will have the study drug on an infusion pump, based on monthly randomization. Standard procedures for cesarean delivery will be undertaken. Standard procedure for cesarean delivery in the second stage with an epidural in place include bolusing local anesthetic for anesthesia effect, typically the drug utilized in 2% lidocaine in amounts of 15-20 ml to achieve an anesthetic block to T4 dermatome level. This level of anesthesia typically produces hypotension in the patient and the standard practice is to start an infusion of phenylephrine in typical infusions of 25-50mcg /min titrated to acheive the patient's normal blood pressure level prior to labor. This is typicall done whether patient receives IV NTG or not. At the announcement of uterine incision by the obstetrical team, the anesthesia provider will bolus through the infusion pump 2ml (400 mcg NTG or saline) of study drug and will start the infusion at 800mcg/min immediately following the bolus dose. An equal amount ml of saline will be given for the placebo group. The infusion of the study drug will be discontinued after delivery of the infant or when 1600mcg total NTG is reached. In addition, when we give NTG the anesthesia provider will give IV phenylephrine (a standard vasopressor) to prevent any potential hypotension at the dose of 100mcg for every 400mcg of IV NTG. The anesthesia provider will not give the phenylephrine dose if the study patient has blood pressure above their baseline and will not give the bolus of phenylephrine if the study patient is receiving saline (control) drug. The patient will otherwise be treated under the standard care for cesarean delivery which includes can include the use of phenyleprhine infusion titrated to patients normal blood pressure prior to the induction of local anesthesia for cesarean delivery. This study was designed specifically such that the anesthesia provider will not be blinded to the drug.
If the neonatal extraction is difficult and the attending obstetrician attempts delivery and is unable to deliver the neonate, he or she may request that the anesthesia provider give known IV NTG at 400mcg bolus and continue the infusion at 800mcg/min until delivery of the neonate. However, this will only be given if they previously received saline. If the patient has already received NTG the team will be told that NTG has been given and continue the infusion until the maximum dose of 1600mcg has been given.

If you have a procedure table, attach it to the submission with your other study documents.

15.2 Interviews, questionnaires, and/or surveys will be administered or focus groups will be conducted:

○ Yes ◉ No

List any standard instruments used for this study:

Attach any non-standard instruments at the end of the application.

15.3 Conduct of study procedures or tests off-site by non-UCSF personnel:

○ Yes ◉ No

If yes, explain:

15.4 Sharing of experimental research test results with subjects or their care providers:

○ Yes ◉ No

If yes, explain:

15.5 * Specimen collection for future research and/or specimen repository/bank administration:

○ Yes ◉ No

15.6 Time commitment (per visit and in total):

None

15.7 Locations:

Labor and Delivery

15.8 Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

All outcome information is currently being collected in a secured/maintained in a perinatal database.

16.0 Alternatives

16.1 Study drug or treatment is available off-study:

◉ Yes
○ No
○ Not applicable

16.2 * Is there a standard of care (SOC) or usual care that would be offered to prospective subjects at UCSF (or the study site) if they did not participate:

◉ Yes ○ No

If yes, describe the SOC or usual care that patients would receive if they choose not to participate:

Patients who choose not to participate in the study will undergo cesarean delivery according to the institutional standard. The provider may choose to use nitroglycerin during the surgery based upon his /her clinical judgement. If the patient does not agree to enrol in the study the obstetrics provider will attempt to delivery the neonate and if they have trouble with the neonatal extraction they can request nitroglycerin which is the current standard. They will be given the standard does which is 400mcg bolus of IV nitroglycerin followed by a 800mcg/min infusion until maximum dose of 1600mcg total of nitroglycerin is given.

16.3 Describe other alternatives to study participation that are available to prospective subjects:

If the patient choses to not enroll in the study the obstetrics provider will attempt to delivery the neonate and if they have trouble with the neonatal extraction from the uterus they can request IV nitroglycerin which is the current standard. They will be given the standard dose which, is 400mcg bolus of IV nitroglycerin followed by a 800mcg/min infusion until the neonate is delivered or the maximum dose of 1600mcg total of nitroglycerin is given.

17.0 Risks and Benefits

17.1 * Risks and discomforts:

Nitroglycerin is currently being used at the obstetrician's request after prolonged struggle to deliver neonatal head. Nitroglycerin half life is 2.3 minutes. There is no evidence of embryotoxic or tetatogenic effects, although those would be of limited significance given administration in labor. It is typically tolerated well as it is short-acting; the most common side effects are headache and hypotension in volunteer (non-obstetric) patients.
Phenyleprhine insfusion is a standard vasopressor used in obstetrics for hypotension during induction of local anesthestic anesthesia for neuraxial technique it is standardly started with the local anesthetic bolus. Risk fo phenyeprhine infusion is hypertention and bradycardia, however, the dose it titrated by anesthesia provider to maintain patents pre labor blood pressure. Phenyleprhine has been widely studied in obstetrics literature and compared to ephedrine which was previoulsy thought to be the drug of choice, however extensive RCT studies have shown phenyleprhine to be a superior drug as it has favorable fetal metabolism and improved umbilical blood gases compared to ephedrine. Ref: *Lee A, Ngan Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2002; 94: 920–6.*
review of randomized controlled trials of ephedrine versus
phenylephrine for the management of hypotension during
spinal anesthesia for cesarean delivery. Anesth Analg 2002;
94: 920–6.
Currently this is being utilized as a standard by many obstetricians after they struggle with neonatal head extraction. In our limited retrospective review of data at our institution we have found in the patients who received sublingual (SL) nitroglycerin after the obstetrcians had struggled fetal extraction delivery there were increased rates of NICU admission, metabolic acidosis in cord bloods, and lower apgar scores, but not for IV- nitroglycerin. In this same retrospective review we have found that there was no difference in maternal outcomes, fetal extraction time, blood loss, need for tranfusion compared to control for either nitroglcerin group (IV or SL). It is unclear in this retrospective review whether this is due to intrinsic effects of sublingual nitroglycerin or secondary to other factors, e.g. prolonged pushing in the second stage, difficult fetal extraction, etc. Given that this medication is utilized in many clinical scenarios in obstetrics and for this particular clinical scenario a randomized control trial is warranted to evaluate any benefits or risks of nitroglycerin in cesarean delivery for second stage arrest.
In a retrospective review of patients at our institution who received nitroglycerin compared to a cohort who did not recieve nitroglycerin there was no difference in mean arterial blood pressure between groups and some patients in both group (nitoglycerin and no nitroglycerin) received phenyephrine.

17.2 Steps taken to minimize risks to subjects:

all information will be stored on a secured maintained database already in existence.

17.3 Benefits to subjects:

(●) Yes ( ) No

If yes, describe:

Potential reduction in uterine hysterotomy extension, which may impact long term maternal/neonatal outcomes. Given that this medication is utilized in many clinical scenarios in obstetrics and for this particular clinical scenario a randomized control trial is warranted to evaluate any benefits nitroglycerin in cesarean delivery for second stage arrest.

17.4 Benefits to society:

Potential improved understanding of obstetric options/care women in this clinical scenario and better understand whether this currenlty standardly utilized treatment poses any neonatal risks.

17.5 Explain why the risks to subjects are reasonable:

This is a widely used drug in obstetrics and has been used for this exact clinical scenario for years and has not shown any maternal risks. A randomized controlled clinical trial of nitroglycerin in this clinical scenario at this point is necessary to evaluate any potential negative neotnatal effects and to ellucidate whether there are any potential benefits to a standard route, timing, and dose of nitroglycerin.

18.0 Data and Safety Monitoring Plan

18.1 Describe the plan for monitoring data and safety (Help Text updated 9/13):

We will have a data and safety monitoring group comprised of an Ob-anesthesia and Maternal Fetal Medicine specialist who will review the data and discuss any adverse effects every 6 months during the trial.

18.2 This study requires a Data and Safety Monitoring Board:

- (•) Yes
- ( ) No or not sure

If **yes**, press **SAVE and CONTINUE** to move to the next section of the application.

18.3 If No, provide rationale:

- ( ) Social/Behavioral research
- ( ) Phase I trial
- ( ) Treatment IND/Compassionate Use Trial
- ( ) Other (explain below)

If **Other,** explain:

.

19.0 Data and Safety Monitoring Board

19.1 Provide details from the Data and Safety Monitoring Board's charter, including meeting frequency, and affiliations and qualifications of members:

Obstetric Anesthesiologist Dr. Mark Rosen Professor Emeritus and Maternal Fetal Medicine specialist, Dr. Mary Norton who will meet every 6 months

Dr. Rosen has had significant clinical experience in Obstetric Anesthesia and the use of both intravenous and sublingual nitroglyerin thoughout his career. Dr. Mary Norton is a leader in Maternal Fetal Medicine and has implementated several clinical trials both at UCSF through the UC consortium and at Stanford . These individuals are not part of the study personnel and have significant experience in clinical research.

19.2 All of the members of the Data and Safety Monitoring Board are independent of the sponsor:

(•) Yes ( ) No

20.0 Confidentiality and Privacy

20.1 Plans for maintaining privacy in the research setting:

all patient information is part of the secure and maintaned perinatal database

20.2 Possible consequences to subjects resulting from a loss of privacy:

loss of patient confidentiality

20.3 Study data are:

- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [ ] Added to the hospital or clinical medical record
- [x] Created or collected as part of health care
- [ ] Used to make health care decisions
- [ ] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained from a foreign country or countries only
- [ ] Obtained from records open to the public
- [x] Obtained from existing research records
- [ ] None of the above

If **derived from a medical record**, identify source:

20.4 Identifiers may be included in research records:

(•) Yes ( ) No

If **yes**, check all the identifiers that may be included:

- [ ] Names
- [x] Dates
- [ ] Postal addresses
- [ ] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier

* Required for studies conducted at the VAMC

20.5 Identifiable information might be disclosed as part of study activities:

( ) Yes (•) No

If **yes**, indicate to whom identifiable information may be disclosed:

- [ ] The subject's medical record
- [ ] The study sponsor
- [ ] Collaborators
- [ ] The US Food & Drug Administration (FDA)
- [ ] Others (specify below)

☐ A Foreign Country or Countries (specify below)

If **Others**, specify:

20.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

☐ Data are stored securely in My Research
☐ Data are coded; data key is destroyed at end of study
☑ Data are coded; data key is kept separately and securely
☐ Data are kept in a locked file cabinet
☐ Data are kept in a locked office or suite
☑ Electronic data are protected with a password
☑ Data are stored on a secure network
☐ Data are collected/stored using REDCap or REDCap Survey
☐ Data are securely stored in OnCore

20.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

20.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

○ Yes ◉ No

Explain:

20.9 This study will be issued a Certificate of Confidentiality:

○ Yes ◉ No

21.0 Subjects

21.1 Check all types of subjects that may be enrolled:

☑ Inpatients
☐ Outpatients
☐ Healthy volunteers
☐ Staff of UCSF or affiliated institutions

21.2 Additional vulnerable populations:

☐ Children
☐ Subjects unable to consent for themselves
☐ Subjects unable to consent for themselves (emergency setting)
☐ Subjects with diminished capacity to consent
☐ Subjects unable to read, speak or understand English
☑ Pregnant women
☑ Fetuses

- [x] Neonates
- [ ] Prisoners
- [ ] Economically or educationally disadvantaged persons
- [ ] Investigators' staff
- [ ] Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

This is evaluating our routine use of nitroglycerin for cesarean delivery and requires pregnant women for cesarean delivery

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Those subjects included in the study will will undergo the usual standard of care on the obstetric suite. The data collected is already part of the perinatal database that is secure.

22.0 Inclusion of Children in Research

22.1 This study will enroll children who can legally consent for themselves:

○ Yes ◉ No

If **yes,** explain why they can consent for themselves in the research setting:

If you will **ONLY** be enrolling children who can legally consent for themselves, press **SAVE and CONTINUE** to skip the rest of this section.

22.2 Select all the regulatory categories that apply:

- [ ] No greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)
- [x] Greater than minimal risk but presenting prospect of direct benefit (45 CFR 46.405, 21 CFR 50.52)
- [ ] Greater than minimal risk (though only a minor increase over minimal risk) and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- [ ] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 21 CFR 50.54)

Explain why the research in this study falls under the above category or categories:

22.3 Parental permission or waiver:

- [x] Parental permission will be obtained
- [ ] Waiver of parental permission is requested: Parental permission is not a reasonable requirement
- [ ] Waiver of parental permission is requested: The waiver meets the provisions for a waiver of consent set forth in 45 CFR 46.116, Subpart A

If you are requesting a **waiver of parental permission**, explain why the study meets the regulatory criteria for this waiver:

22.4 Assent of children or waiver:

- [ ] Assent of children old enough to provide assent will be obtained
- [ ] Waiver of assent is requested: Children cannot be consulted or the research has prospect of direct

benefit only available in the study

☑ Waiver of assent is requested: The waiver meets the provisions for a waiver of consent set forth in 45 CFR 46.116, Subpart A

If you are requesting a **waiver of child's assent**, explain why the study meets the regulatory criteria for this waiver:

Neonates are involved in the study and will not be able to assent.

22.5 Documentation of permission and assent (select all that will be used):

☑ Permission form addressed to the parents
☐ Simplified assent form addressed to the child, 7-12 years old (parents get separate form)
☐ Assent form addressed to the child, 13 years and older (for subjects and parents)
☐ Assent form addressed to the child, 13 years and older (parents get separate form)

Check one:

◉ One parent's signature will be obtained
○ Two parents' signatures will be obtained

If this study is approvable under .404 or .405 and you plan to get permission from only one parent, explain why you think one parent's permission is sufficient:

The data collected is currenlty collected in a secure form as part of the perinatal database and is related to the obstetrical record and is the following: APGAR scores, umbilical cord blood gases, and admission to the NICU. These are currenlty found in the obstetrical record and startdardly collected as part of the perinatal database. No additional information will be collected from tne neonate or the neonatal record. We will not need access to the neontal record.

22.6 This study may enroll wards of the state:

○ Yes ◉ No

23.0 Inclusion of Pregnant Women, Fetuses, and/or Neonates

23.1 Review the regulatory categories by clicking on the Help bubble and identify all sections of 45 CFR 46 Subpart B under which you believe the research falls and provide study-specific information showing why the research falls within those sections:

Pregnant women as this group will be the only subject group undergoing cesarean delivery

24.0 Recruitment

24.1 * Methods (check all that apply):

☑ Study investigators (and/or affiliated nurses or staff) recruit their own patients directly in person or by phone.
☐ Study investigators recruit their own patients by letter. Attach the letter for review.
☐ Study investigators send a "Dear Doctor" letter to colleagues asking for referrals of eligible patients. If interested, the patient will contact the PI or the PI may directly recruit the patients (with documented permission from the patient). Investigators may give the referring physicians a study information sheet for the patients.
☐ Study investigators provide their colleagues with a "Dear Patient" letter describing the study. This letter can be signed by the treating physicians and would inform the patients how to contact the study investigators. The study investigators may not have access to patient names and addresses for mailing
☐

Advertisements, notices, and/or media used to recruit subjects. Interested subjects initiate contact with study investigators. Attach ads, notices, or media text for review. In section below, please explain where ads will be posted.

- [x] Study investigators identify prospective subjects through chart review. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Large-scale epidemiological studies and/or population-based studies: Prospective subjects are identified through a registry or medical records and contacted by someone other than their personal physician. (Study investigators request a Waiver of Authorization for recruitment purposes.)
- [ ] Direct contact of potential subjects who have previously given consent to be contacted for participation in research. Clinic or program develops a CHR-approved recruitment protocol that asks patients if they agree to be contacted for research (a recruitment database) or consent for future contact was documented using the consent form for another CHR-approved study.
- [ ] Study investigators list the study on the School of Medicine list of UCSF Clinical Trials website or a similarly managed site. Interested subjects initiate contact with investigators.
- [ ] Study investigators recruit potential subjects who are unknown to them through methods such as snowball sampling, direct approach, use of social networks, and random digit dialing.
- [ ] Other

If **Other**, explain:

24.2 * How, when, and by whom eligibility will be determined:

Recruiters will review the charts of patients who are coming into the prenatal clinics at UCSF. The charts will be viewed on APeX and patients who meet eligibility criteria will be approached in the waiting area before their visit and given the opt-in form to review. We have found this approach method to be very successful in multiple studies during pregnancy and prenatal care. Recruitment will not interrupt usual clinic flow and patient care. In addition to outpatient recruitment, pregnant women who are admitted to labor and delivery are seen by anesthesia for a analgesic consultation who have not been already been evaluated during our outpatient recruitment will be approached. The study team will only approach women who are not in labor and will discuss the study and obtain consent. Of those patient's that consent for the study only 5-10% will be eligible fo the study. Eligbility for the study requires the subject to need a cesarean delivery in the second stage of labor. As such many women may consent for the study, but not become eligible as they will deliver vaginally.

24.3 * How, when, where and by whom potential subjects will be approached:

Recruitment will occur either of the following ways:
1-Recruiters will review the charts of patients who are coming into the prenatal clinics at UCSF. The charts will be viewed on APeX and patients who meet eligibility criteria will be approached in the waiting area before their visit. We have found this approach method to be very successful in multiple studies during pregnancy and prenatal care. Recruitment will not interrupt usual clinic flow and patient care.
2-The study team will approach after anesthesia consultation is completed and the potential candidate is deemed not in active labor.

24.4 * Protected health information (PHI) will be accessed prior to obtaining consent:

(•) Yes ( ) No

25.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when study investigators (and/or affiliated nurses or staff) recruit their own patients directly.

25.1 * Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified:

◉ Yes

If **no**, a waiver of consent/authorization is NOT needed.

25.2 * A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

◉ Yes

If **no**, a waiver of authorization can NOT be granted.

25.3 * Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

◉ Yes

If **no**, a waiver of authorization can NOT be granted.

25.4 * Check all the identifiers that will be collected prior to obtaining informed consent:

- ☑ Names
- ☐ Dates
- ☐ Postal addresses
- ☐ Phone numbers
- ☐ Fax numbers
- ☐ Email addresses
- ☐ Social Security Numbers*
- ☑ Medical record numbers
- ☐ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers
- ☐ Vehicle ID numbers
- ☐ Device identifiers or serial numbers
- ☐ Web URLs
- ☐ IP address numbers
- ☐ Biometric identifiers
- ☐ Facial photos or other identifiable images
- ☐ Any other unique identifier
- ☐ None

Note: HIPAA rules require that you collect the minimum necessary.

25.5 * Describe any health information that will be collected prior to obtaining informed consent:

Review of gestational age and reason for admission will be reviewed prior to obtaining consent, but will not be stored once reviewed

Note: HIPAA requires that you collect the minimum necessary.

25.6 * Describe your plan to destroy the identifiers at the earliest opportunity consistent with the research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law:

The patient information is stored on a secure/maintained perinatal database. Randomization will be performed based on month and once enrollment is complete the patient names and MRN will be destroyed.

26.0 Informed Consent

26.1 * Methods (check all that apply):

- [x] Signed consent will be obtained from subjects and/or parents (if subjects are minors)
- [ ] Verbal consent will be obtained from subjects using an information sheet or script
- [ ] Electronic consent will be obtained from subjects via the web or email
- [ ] Implied consent will be obtained via mail, the web or email
- [ ] Signed consent will be obtained from surrogates
- [ ] Emergency waiver of consent is being requested for subjects unable to provide consent
- [ ] Informed consent will not be obtained

26.2 * Process for obtaining informed consent:

Patient will be approached at admission to labor and delivery.

26.3 * How investigators will make sure subjects understand the information provided to them:

Confirm understanding by having the potential subject repeat back the general study plan and answer any additonal questions the potential subject may have.

27.0 Financial Considerations

27.1 Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [x] Subjects will not be paid
- [ ] Cash
- [ ] Check
- [ ] Debit card
- [ ] Gift card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

Specify **Other**:

27.2 Describe the schedule and amounts of payments, including the total subjects can receive for completing the study. If deviating from recommendations in Subject Payment Guidelines, include specific justification below.

no payments as this is part of standard of care

27.3 Costs to Subjects: Will subjects or their insurance be charged for any study procedures?

- ○ Yes
- ◉ No

If **yes,** describe those costs below, and compare subjects' costs to the costs associated with alternative care off-study. Finally, explain why it is appropriate to charge those costs to the subjects.

28.0 CTSI Screening Questions

28.1 * **This study will be carried out at one of the UCSF Clinical Research Services (CRS) centers or will utilize CRS services. CRS centers are at the following sites:**

- **SFGH Clinical Research Center**
- **Moffitt Adult Clinical Research Center**
- **Moffitt Hospital Pediatrics & NCRC**
- **Mount Zion Hospital Clinical Research Center**
- **Tenderloin Center**
- **CHORI Children's Hospital Pediatrics & Adult Clinical Research Center**
- **Kaiser Oakland Research Unit**
- **SF VA Medical Center Clinical Research Unit**

Please note: Effective 3/1/14, the CRS form will no longer be completed and submitted in iRIS. The CRS budget request form can be found at: https://accelerate.ucsf.edu/files/crs/BudgetRequest2015.docx. Follow the instructions on the form to submit. Even if you click 'Yes' to this question, the form will no longer proceed to the Clinical Research Services (CRS) Application Form section.

○ Yes ◉ No

28.2 This project involves community-based research:

○ Yes ◉ No

28.3 This project involves practice-based research:

○ Yes ◉ No

29.0 End of Study Application

29.1 **End of Study Application Form** **To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.**