Document Coversheet

Study Title: Role of ASpirin in Placental and Maternal Endothelial Cell Regulation IN Pre-eclampsia

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	6/27/2025
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IMPORTANT NOTE:

If you accidentally select the wrong IRB type or "Protocol Process Type" while your Initial Review (IR) application is in draft form (unsubmitted), you may change your selections. Please contact the Office of Research Integrity (ORI) at 859-257-9428, IRBsubmission@uky.edu, or request a consult to resolve any questions regarding your selections *prior* to submitting your Initial Review application.

If your **submitted IR application has been returned to you for requested revisions or additional information,** to streamline the review process **do not make changes** to your selections here **unless instructed to do so by the ORI/IRB.**

Changes to this section cannot be made after initial approval has been issued (the option is not available for MR or CR).

For guidance, see:

- Which IRB?
- Which Protocol Process Type?
- "Getting Started"

Which IRB

- (•) Medical ( ) NonMedical

Protocol Process Type

- ( ) Exemption
- (•) Expedited (Must be risk level 1)
- ( ) Full

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

EXPEDITED CERTIFICATION

0 unresolved comment(s)

To Be Completed Only If Protocol is to Receive Expedited Review

Applicability

A. Research activities that (1) present no more than *minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
B. The categories in this list apply regardless of the age of subjects, except as noted.
C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
D. The expedited review procedure may not be used for classified research involving human subjects.
E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

**"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. 45 CFR 46.102(i)*

Check the appropriate categories that apply to your research project:

☑ Study was originally approved by the full IRB at a convened meeting.

☐ 1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

A. Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
B. Research on medical devices for which (i) an investigational device exemption application is not required*; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.**

* Study must meet one of the IDE Exempt categories listed on the Device Form Attachment.
** An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements.
NOTE: Select Category 1 for compassionate use medical device applications or individual patient expanded access investigational drug applications for which FDA has waived the requirement for full review.

☐ 2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

A. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
B. From other adults and children* considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

NOTE: Intravenous (IV), Port, Central, or any other lines are NOT eligible under this category even if the research involves "minimal risk".

*In Kentucky, "child/children" refers to all individuals less than 18 years of age unless the individual(s) is/are legally emancipated. (See Informed Consent SOP for discussion of "Emancipated Individuals" under Kentucky state law.) Individuals less than 18 years of age who are not emancipated meet the federal definition for "child" (e.g., DHHS, FDA, and U.S. Department of Education). Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." If conducting research outside the state of Kentucky, you are responsible for complying with applicable state law.

☐ 3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

A. Hair and nail clippings in a nondisfiguring manner;
B. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
C. Permanent teeth if routine patient care indicates a need for extraction;
D. Excreta and external secretions (including sweat);
E. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
F. placenta removed at delivery;
G. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
H. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
I. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
J. Sputum collected after saline mist nebulization.

☐ 4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:

A. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
B. Weighing or testing sensory acuity;
C. Magnetic resonance imaging;
D. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
E. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

☐ 5) Research involving materials (data, documents, records, or specimens) that have been or will be collected solely for non-research purposes (such as medical treatment or diagnosis) as well as research involving existing information or specimens that were previously collected for research purposes, provided they were not collected for the currently proposed research. (Note: Some research in this category may qualify for Exempt review. This listing refers only to research that is not exempt.)
(Note: If submission includes materials previously collected for either non-research or research purposes in a protocol for which IRB approval expired, you may check Category 5. However, a separate category must also be selected for prospective collection of data/specimens obtained solely for research purposes)

☐ 6) Collection of data from voice, video, digital, or image recordings made for research purposes.

☐ 7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.)

MODIFICATION REQUEST SECTION

0 unresolved comment(s)

***** If this modification changes the scope of your activities to include COVID-19 related research, please insert "COVID19" at the start of your Project and Short Titles.*****

Select One:

- (•) This modification does not increase risk to study participants.
- ( ) This modification may or will increase risk to study participants.

Is this modification request due to an Unanticipated Problem/Adverse Event, or Protocol Violation?

( ) Yes (•) No

In your professional opinion, does this modification involve information that might relate to a subject's willingness to continue to take part in the research?

( ) Yes (•) No

If yes, state how the information will be communicated to subjects (i.e., re-consent, send letter, etc.):

For each proposed modification, include a justification.

Example: Jane Doe, MD, is being added as co-investigator because she has expertise with the subjects on this protocol. She has completed human subject protections training, and is authorized to obtain consent.

Greg Hawk , Katie Thompson and Tori Stanton are being added as project assistance for data analysis because they have expertise with the subjects on this protocol.

PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Role of aspirin in maternal endothelial dysfunction and uterine artery blood flow in women at risk for preeclampsia

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

ASPERIN Trial

Anticipated Ending Date of Research Project: 3/31/2026

Maximum number of human subjects (or records/specimens to be reviewed) 209

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? ○ Yes ◉ No

Are you requesting that the UK IRB serve as the lead IRB for a multi-site study, **OR** that the UK IRB defer review to another IRB? [Click here for "IRB Reliance" help]
○ Yes ◉ No
If "Yes," before completing your IRB application, fill out the Reliance Request Form and submit it to irbreliance@uky.edu.

PI CONTACT INFORMATION

0 unresolved comment(s)

Principal Investigator (PI) role for E-IRB access
The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

1. Read;
2. write/edit;
3. receive communications; and
4. submit to the IRB (IR, CR, MR, Other Review*).

If research is being submitted to or supported by an extramural funding agency such as NIH, a private foundation or a pharmaceutical/manufacturing company, the PI listed on the grant application or the drug protocol must be listed as PI here.

Please fill in any blank fields with the appropriate contact information (gray shaded fields are not editable). Required fields left blank will be highlighted in pink after you click "Save".

To change home and work addresses, go to myUK and update using the Employee Self Service (ESS) portal. If name has changed, the individual with the name change will need to submit a 'Name Change Form' to the Human Resources Benefits Office for entering into SAP. The new name will need to be associated with the individual's Link Blue ID in SAP before the change is reflected in E-IRB. Contact the HR Benefits Office for additional information.

The Principal Investigator's (PI) contact information is filled in automatically based on who logged in to create the application.

If you are not the Principal Investigator, do NOT add yourself as study personnel.
To change the PI contact information on an application in Researcher edit status:

- click "Change Principal Investigator";
- search for the PI's name using the search feature;
- click "Select" by the name of the Principal Investigator, then "Save Contact Information".

  You will automatically be added as study personnel with editing permissions to continue editing the application.

Change Principal Investigator:

First Name:	John	Room# & Bldg:	C374 A B CHANDLER MEDICAL CENTER
Last Name:	O'Brien	Speed Sort#:	405360293
Middle Name	Michael		
Department:	Obstetrics & Gynecology - 7H…	Dept Code:	7H500
PI's Employee/Student ID#:	10796931	Rank:	Professor
PI's Telephone #:	8592180765	Degree:	MD
PI's e-mail address:	john.obrien2@uky.edu	PI's FAX Number:	859-218-7577
PI is R.N.	○ Yes ◉ No	HSP Trained:	Yes
		HSP Trained Date:	7/31/2023
		RCR Trained:	Yes

Do you, the PI/researcher, have a significant financial interest related to your responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2)?

○ Yes ◉ No

RISK LEVEL

0 unresolved comment(s)

Indicate which of the categories listed below accurately describes this protocol

- (●) (Risk Level 1) Not greater than minimal risk
- ( ) (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ( ) (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ( ) (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

*****For Expedited and Exempt Applications, the research activities must be Risk Level 1 (no more than minimal risk to human subjects).*****

Refer to UK's guidance document on assessing the research risk for additional information.

SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 to 45

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

The study population will include pregnant women between the ages 18 and 45 years enrolled as cases and controls. Women at high risk for preeclampsia will be enrolled as cases and those without risk factors for preeclampsia will be approached to serve as a control population. Approximately 250 eligible women will be enrolled in this study (50 in the normal control arm, 100 in the low dose 81 mg per day arm, and 100 in the 162 mg per day arm). Eligible patients will be recruited from UK clinics and the UK Good Samaritan ultrasound unit at the time of their scheduled prenatal visits or ultrasound appointments. Women who plan to deliver at University of Kentucky Chandler Hospital will be approached for enrollment.

The risk factor assessment to screen women at high risk for preeclampsia include:
1. History of preterm preeclampsia, especially when accompanied by an adverse outcome
2. Chronic hypertension
3. Type 1 and Type 2 diabetes
4. Renal diseases
5. Autoimmune disease

Exclusion criteria include:
1. Pregnant women younger than 18 years or older than 45 years
2. Multiple gestations
3. History of allergy (urticaria or anaphylaxis) to aspirin or aspirin related products asthma that worsens after aspirin use
4. Patients with gastrointestinal or genitourinary bleeding
5. Patients with peptic ulcer disease
6. Patients with severe liver dysfunction
7. Patients who have undergone bypass surgery
8. Patients on anticoagulant medication(s)
9. Women with anomalous fetus

Recruitment and data collection is expected to last throughout 2018-2022 academic years. Data analysis is expected to be accomplished during 2019-2022 academic years.

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:	0	2		
Asian:	0	10		
Black/African American:	0	35		
Latinx:	0	25		
Native Hawaiian/Pacific Islander:	0	2		
White:	0	166		
American Arab/Middle Eastern/North African:		1		
Indigenous People Around		1		

the World:				
More than One Race:		8		
Unknown or Not Reported:	0	0		

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☑ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

PREGNANT WOMEN/NEONATES/FETUSES

0 unresolved comment(s)

For studies involving pregnant women, human fetuses and/or neonates, check the option that best fits your research, then address the questions and requests for information.

Section 1: Research Involving Pregnant Women or Fetuses

Research Involving Pregnant Women or Fetuses

A. Explain why the proposed research is scientifically appropriate, including descriptions of any pre-clinical studies on pregnant animals and any clinical studies on non-pregnant women that have been conducted and have provided data for assessing potential risks to pregnant women and fetuses.

The etiology of preeclampsia is multi-factorial. Endothelial dysfunction and defective placental vascularization are key features of the proposed underlying etiology in the pathogenesis of preeclampsia. In 1987, an endothelium dependent relaxing factor, nitric oxide was identified as one of the important factors involved in maintaining underlying vascular tone. In pathological states like preeclampsia, due to vascular endothelial dysfunction, decreased nitric oxide production leads to vasoconstriction. Initial tests to determine endothelial dysfunction were invasive and were done in non-pregnant women in the context of cardiovascular risk assessment. Celermajer and colleagues later developed a non-invasive screening tool called flow mediated dilation (FMD) that measured nitric oxide dependent reactive hyperemia in brachial artery after a 5-minute occlusion with a blood pressure cuff. This technique served as a surrogate marker for coronary endothelial dysfunction. Cockell et al and Dorup et al applied the technique to the pregnant population under the hypothesis that preeclampsia is associated with profound nitric oxide dependent vascular endothelial dysfunction.
FMD is now a validated tool to assess vascular endothelium reactivity in pregnant women. The second biophysical biomarker we are focusing on as part of our study is ultrasonographic Doppler assessment of the uterine artery at 3 different time points in pregnancy. This technique is also noninvasive and does not pose any maternal or fetal risk. Measurement of flow mediated dilation in the forearm requires inflating the blood pressure cuff for 5 minutes which might cause discomfort to the patient. This test has been extensively studied in pregnancy and is very useful in the prediction of pre-eclampsia. The test is incorporated routinely in other countries (most notably England) as a screening test for all women with low dose aspirin therapy given to those with evidence of poor placental vascular invasion. This is not the standard of care for routine prenatal ultrasound assessment in United States but will be done for the purpose of this study.
1. Tayyar A, Guerra L, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history. Ultrasound Obstet Gynecol 2015; 45: 689-97.
2. O'Gorman N, Tampakoudis G, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. Ultrasound Obstet Gynecol 2016; 47: 565-72
The standard of care dose for preeclampsia prophylaxis is 81 mg per day. Roberge et al.(2018) showed aspirin conferred a greater benefit in the reduction of preterm preeclampsia at a dose of = 100 mg when initiated < 16 weeks of gestation. ASPRE trial showed a 60% reduction in the risk of preeclampsia when 150 mg of aspirin was used for prophylaxis.
Low dose aspirin is defined as dosages between 50 mg and 325 mg of aspirin. The dose of 162 mg, which we intend to use in our study for preeclampsia prophylaxis, lies in the low dose range (Berger et al., 2008) and no maternal risks have been identified.

B. Select the option that best describes the anticipated risk to the fetus:

- ○ Not greater than minimal; or
- ◉ Greater than minimal risk and the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus.

C. Provide a rationale for anticipated risk:

Evidence for effectiveness of 162 mg vs. 81 mg of aspirin to reduce neonatal complications including intraventricular hemorrhage (IVH): The rate of IVH, necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and neonatal mortality are all dependent upon the gestational age and delivery and a reduction in early preterm birth will reduce the frequency of these adverse events.
a. Meta-analysis has documented exposure to low dose aspirin reduced the rate of preterm birth in indicated population (PARIS Collaboration trial)
b. Aspirin confers a greater benefit in the reduction of preterm preeclampsia at a dose of = 100 mg when initiated < 16 weeks of gestation (Roberge et al., 2018)
Low dose aspirin is defined as dosages between 50 mg and 325 mg of aspirin. The dose of 162 mg, which we intend to use in our study for preeclampsia prophylaxis, lies in the low dose range (Berger et al., 2008). Systematic reviews of randomized control trials of use of low dose aspirin in pregnancy have not demonstrated any maternal or fetal risks. ASPRE trial showed no difference in the rates of intraventricular hemorrhage (IVH) when pregnant women identified as high risk for preeclampsia received 150 mg of aspirin compared to those who received placebo (0.3% vs. 0.1%; OR 2.23, 95% CI: 0.09 -52.70). No significant differences were noted in other neonatal morbidities like anemia requiring blood transfusion and necrotizing enterocolitis between the aspirin and the placebo groups. With altered pharmacokinetics of aspirin in pregnancy, there is no physiological basis to believe a 12 mg increment in aspirin dose to 162 mg in our study poses a significantly increased risk for neonatal intraventricular hemorrhage.
In fact, a study currently underway at the University of Kentucky involves the use of Indomethacin, which is a stronger NSAID than aspirin in the prophylaxis of neonatal IVH in preterm infants. Several trials with 162 mg of aspirin in pregnancy for preeclampsia prophylaxis are currently registered in clinicaltrials.gov. Other institutions in United States and other countries have approved this dose for testing given the safety findings above as no fetal risks have been

identified.

D. Explain why any risk is the least possible for achieving the objectives of the research:

Other than the discomfort patient might experience at the time of inflating the blood pressure cuff to record the flow mediated dilation of the brachial artery, use of low dose aspirin and ultrasound doppler assessments are not associated with maternal and fetal risk. The interventions in our study are extensively validated in pregnant population with no risks

E. Select the options that apply:

(●) Yes ( ) No 1) This research holds out the prospect of direct benefit to the pregnant woman.

(●) Yes ( ) No 2) This research holds out the prospect of a direct benefit both to the pregnant woman and the fetus; or

( ) Yes (●) No 3) This research does not hold out the prospect of direct benefit for the woman or the fetus, but the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.

If "Yes" to any of these three questions, informed consent must be obtained from the pregnant woman or her legally authorized representative, but consent from the father is not required. The informed consent process should include a clear explanation regarding the reasonably foreseeable impact of the research on the fetus.

( ) Yes (●) No 4) This research holds out the prospect of a direct benefit solely to the fetus.

If "Yes", informed consent must be obtained from the pregnant woman AND the father. The informed consent process should include a clear explanation regarding the reasonably foreseeable impact of the research on the fetus. NOTE: The father's informed consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or the pregnancy resulted from rape or incest.

( ) Yes (●) No 5) This research will involve individuals under the age of 18 who are pregnant and are not considered emancipated minors.

If "Yes", assent from the pregnant child and permission from her parent or legal guardian must be obtained.

( ) Yes (●) No 6) Will there be any inducements, monetary or otherwise, offered to terminate a pregnancy?

( ) Yes (●) No 7) Will individuals performing research procedures have any part in any decisions as to the timing, method, or procedures used to terminate a pregnancy?

( ) Yes (●) No 8) Will individuals performing research procedures have any part in determining the viability of a fetus?

☐ **Section 2. Research Involving Neonates**

Research Involving Neonates

A. Viable Neonates - A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accordance with the requirement of 45 CFR 46 Subpart A and Subpart D.

( ) Yes ( ) No Does your research involve viable neonates?

If yes, you will need to complete the Children subsection before submitting this application (if the Children subsection is not visible, go to the "Subject Demographics" section, checkmark "Children", and save).

B. Neonates of Uncertain Viability AND Nonviable Neonates - Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by 45 CFR 46 Subpart B unless the IRB determines that certain conditions are met. Your responses to the following will help the IRB determine whether the conditions are met.

Explain why the proposed research is scientifically appropriate and provide a description of any pre-clinical and clinical studies that have been conducted which provide data for assessing potential risks to neonates.
If not applicable, please enter "N/A".

( ) Yes ( ) No Will individuals engaged in the research have any part in determining the viability of a neonate?

C. Neonates of Uncertain Viability - Additional Requirements - Select the option that applies to your research.

☐ Not Applicable

○ The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, **AND** any risk is the least possible for achieving that objective.

○ The research has the main purpose of the development of important biomedical knowledge, which cannot be obtained by other means **AND** there will be no added risk to the neonate resulting from the research.

Explain the procedures that will be used to obtain legally effective informed consent of either parent of the neonate.

NOTE: If neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative will be obtained. **These procedures must ensure that each individual providing informed consent will be fully informed regarding the reasonably foreseeable impact of the research on the neonate. The father's informed consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.**

D. Nonviable Neonates – Additional Requirements - After delivery, a nonviable neonate may not be involved in research covered by 45 CFR 46 Subpart B unless the IRB determines that the following additional conditions are met.

☐ Not Applicable

○ Yes ○ No 1) Will the vital functions of the neonate be artificially maintained?

If "Yes", please explain:

○ Yes ○ No 2) Does the research include procedures to terminate the heartbeat or respiration of the neonate?

○ Yes ○ No 3) Will there be any added risk to the neonate resulting from this research?

If "Yes", please explain:

○ Yes ○ No 4) Is the sole purpose of the research for the development of important biomedical knowledge that cannot be obtained by other means?

If "Yes", please explain:

5) Explain the procedures that will be used to obtain legally effective informed consent of both parents of the neonate.

Note: *If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice. The consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice.* ***These procedures must ensure that each individual providing informed consent will be fully informed regarding the reasonably foreseeable impact of the research on the neonate.***

☑ **Section 3. Research Involving After Delivery, The Placenta, The Dead Fetus, Or Fetal Material**

Research Involving After Delivery, The Placenta, The Dead Fetus, Or Fetal Material

A. This research proposes to use the following: (Check all that apply)

- ☑ Placenta
- ☐ The Dead Fetus
- ☐ Macerated Fetal Material
- ☐ Cells Excised from Dead Fetus
- ☐ Tissue Excised from Dead Fetus
- ☐ Organs Excised from Dead Fetus
- ☐ Other

If 'Other' Describe:

NOTE: The use of any of the above must be conducted in accordance with any applicable Federal, State, or local laws, regulations, and institutional policies regarding such activities.

B. ◉ Yes ○ No Will any information associated with the material identified above be recorded for research purposes in such a manner that living individuals can be identified, directly or through identifiers linked to those individuals?

If "Yes", provide a rationale for the recording of identifiable information [Note: those individuals are considered to be research subjects and all pertinent human subject regulations are applicable to their participation.]:

All identifiable information will be removed from the samples. All information will be de-identified and assigned unique identification codes before storing the specimens. Only the bank staff will have access to the master list that links the code to you. We will store the coded information in a secured computer behind locked doors. We will protect the information with passwords/encryption. Encryption changes your information to another format to protect it from being accessed by anyone outside of the approved staff

Section 4. Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Human Fetuses, or Neonates

If the study is Department of Health and Human Services (HHS) funded, or funding by HHS is sought, review by the Secretary of HHS and posting in the Federal Register for public comments and review is required. If this category is applicable, the Office of Research Integrity will prepare and submit a report of IRB review to the appropriate HHS institutional official.

Select all that apply:

- Neonates
- Pregnant Women
- Fetal Material

INFORMED CONSENT/ASSENT PROCESS/WAIVER

0 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a "Reliance Consent Form" so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a read-only PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☐ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☑ Stamped Consent Doc(s) Not Needed

Attachments

Informed Consent Process:

Using active voice, in the text box below, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)

- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Will electronic consent form/process be utilized on-site or remotely for this study?

○ Yes ◉ No

If yes, in addition to addressing the above bullet points, describe the e-consent method and platform, including any hyperlinks, videos, or enhancements used to convey information, if applicable. Attach a representation of the e-consent with signature fields. For guidance, see the ORI E-Consent web page.

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

After identifying eligible patients for this study, the risks and benefits of the study will be discussed with the participant prior to obtaining consent. Certified Spanish translators identified as study personnel will be available onsite for recruiting and consenting Hispanic patients. Potential participants will be notified of their right to decline study participation without any consequences to the standard healthcare they will otherwise receive. Women will be recruited into the study and will be provided with a written, informed consent prior to 16 weeks of gestation. For Hispanic patients, Spanish consent form will be made available. Only the study personnel will be obtaining consent A research repository with the blood, urine and cord blood specimens will be created to store the samples for a period of 2 years after the current study ends. Patients will be notified of this at the time of their consenting process.
The person in charge of the study is Dr. John O'Brien of the University of Kentucky, Department of Maternal Fetal Medicine. If the subjects have questions, suggestions, or concerns regarding this study his contact information is: Dr. John O'Brien at 859-218-0765
If subjects have any questions, suggestions or concerns about their rights as a volunteer in this research, the research staff can be contacted at the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

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

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the ***Cover Letter Template*** *as a guide. There is an English and a Spanish version.*

Option 1

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

STUDY PERSONNEL **0 unresolved comment(s)**

Do you have study personnel who will be assisting with the research?
After selecting 'Yes' or 'No' you must click the 'Save Study Personnel Information' button.
(•) Yes ( ) No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is required for a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed below. ***Residents and students who are PI's are encouraged to designate the faculty advisor or at least one other individual as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature:

- Search for personnel;
- Click "select" by the listing for the person you want to add;
- For each person, specify responsibility in the project, whether authorized to obtain informed consent, AND denote who should receive E-IRB notifications (contact status).

NOTE: Study personnel must complete human subject protection (HSP) and Responsible Conduct of Research (RCR) training before implementing any research procedures. For information about training requirements for study personnel, visit UK's HSP FAQ page, the RCR Getting Started page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (HSPTrainingSupport@uky.edu) for credit.

Study personnel assisting in research project:

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI	Active
Cockerham-Morris	Cynthia	Study Coordinator	DP	Y	Y	BSN	P	Y	04/09/2025	Y	N	09/14/2022	N	Y
Hawk	Gregory	Data Analysis/Processing	SP	N	N		P	Y	03/01/2023	Y	N	04/28/2025	N	Y
Shrestha	Asmita	Project Assistance/Support	DP	N	Y	MPH	P	Y	10/10/2022	Y	N	07/06/2022	N	Y
Stanton	Victoria	Data Analysis/Processing	SP	N	N		P	Y	08/12/2024	Y	N	04/28/2025	N	Y
Thompson	Katherine	Data Analysis/Processing	SP	N	N		P	Y	11/08/2024	Y	N	04/28/2025	N	Y
Whitley	Wendy	Study Coordinator	DP	Y	Y	BSN	P	Y	11/06/2023	Y	N	02/02/2021	N	Y
Armstrong	Alexandra	Project Assistance/Support	DP	Y	N	BSN	P	Y	12/27/2023	N	Y	05/20/2024	N	N
Bauer	John	Faculty Advisor	SP	Y	N	PhD	P	Y	07/30/2023	Y	Y	03/14/2025	N	Y
Bidros	Patrick	Project Assistance/Support	SP	N	N		P	Y	08/30/2023	Y	Y	09/22/2021	N	Y
Boerrigter	Ashley	Project Assistance/Support	DP	Y	N	MD	P	Y	07/21/2022	Y	Y	03/14/2025	N	Y
Butler	Sara	Data Collection	SP	N	N		P	N	03/13/2021		Y	09/14/2022	N	N
Chavan	Niraj	Faculty Advisor	DP	Y	N	MD, MPH	S	N	03/03/2021		Y	09/22/2021	N	N
Critchfield	Agatha	Recruitment	SP	Y	N		P	N	04/20/2017		Y	12/02/2019	N	N
D'Alessandri	Brianna	Project Assistance/Support	SP	Y	N	MSN	P	N	04/11/2022	N	Y	05/20/2024	N	Y
Hammond	Tyler	Sub-Investigator	SP	Y	N	MS		N	04/05/2022	N	Y	03/14/2025	N	N
Hansen	Wendy	Recruitment	SP	Y	N	MD	P	Y	01/17/2023	Y	Y	05/20/2024	N	Y
Hendrix	Nancy	Recruitment	SP	Y	N		P	Y	11/14/2024	Y	Y	05/20/2024	N	Y
Huang	Hong	Data Analysis/Processing	SP	N	N		P	Y	07/28/2022	Y	Y	03/14/2025	N	Y
Joseph	Rahul	Project Assistance/Support	SP	N	N	MD	P	Y	02/07/2023	Y	Y	03/14/2025	N	Y
Lewis	Regina	Project Assistance/Support	DP	Y	N	MS	P	Y	03/06/2023	Y	Y	05/20/2024	N	Y
MacLeod	Erin	Project Assistance/Support	SP	Y	N	MD	P	N	12/28/2020		Y	09/14/2022	N	Y
McKinley	Brittany	Data Collection	SP	Y	N	MD	S	N	11/02/2020		Y	09/22/2021	N	N
McKinney-Whitlock	Alisa	Project Assistance/Support	SP	N	N	CCRP	P	Y	12/10/2024	Y	Y	03/14/2025	N	Y
Mirsky	Elizabeth	Project Assistance/Support	SP	Y	N	MD	P	Y	07/09/2023	Y	Y	03/14/2025	N	Y

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI	Active
Patel	Neil	Project Assistance/Support	SP	Y	N	MD	P	N	07/15/2021	N	Y	05/20/2024	N	N
Playforth	Karen	Recruitment	SP	Y	N		P	Y	06/28/2022	N	Y	03/08/2022	N	Y
Schanbacher	Avery	Project Assistance/Support	SP	N	N		P	N	07/08/2019		Y	09/14/2022	N	Y
Schanbacher	Brandon	Data Analysis/Processing	SP	N	N	MS	P	Y	10/09/2023	Y	Y	03/14/2025	N	Y
Sepulveda	Norma	Project Assistance/Support	SP	Y	N		P	N	01/01/2019		Y	10/27/2020	N	N
Sharma	Deepti	Data Collection	SP	Y	N		P	N	01/25/2021		Y	10/27/2020	N	N
Shoemaker	Robin	Faculty Advisor	SP	N	N	PhD	P	Y	12/30/2022	Y	Y	03/14/2025	N	Y
Srinivasan	Aarthi	Co-Investigator	SP	Y	N	MD, MS	P	N	09/21/2019		Y	09/14/2022	N	N
Stanley	Zachary	Project Assistance/Support	SP	Y	N	MD	S	N	04/16/2020		Y	09/14/2022	N	N
Su	Leon	Project Assistance/Support	SP	N	N		S	Y	11/13/2023	N	Y	09/14/2022	N	N
Vignes	Katherine	Co-Investigator	DP	Y	Y	MD	P	N	02/02/2020		Y	07/10/2023	N	N
Ward	Calvin	Project Assistance/Support	SP	Y	N	MD	P	N	04/28/2021		Y	07/10/2023	N	N

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Preeclampsia is a part of the spectrum of hypertensive disorders of pregnancy and is the leading cause of significant maternal and fetal morbidity and mortality. The incidence ranges from 3% to 8% of all pregnancies. The pathophysiology can involve multiple organ systems and the etiology is multi-factorial. Defective placental implantation, endothelial dysfunction, defective placental angiogenesis, platelet activation, oxidative stress and autoimmunity are some aberrant physiologies that contribute to preeclampsia. The potential role of endothelial dysfunction in the pathogenesis of disease was initially described in the pathogenesis of atherosclerosis and as a risk marker for cardiovascular events in non-pregnant adults. Ludmer et al demonstrated a paradoxical vasoconstriction with intracoronary infusion of acetyl choline in coronary atherosclerosis. This sentinel study led to an appreciation of a possible defect in endothelial vasodilation in human atherosclerosis. Furchgott and Zawadski demonstrated the vascular endometrium released a substance named endothelial-derived relaxing factor (EDRF) which had the ability to influence the action of the underlying smooth muscle in the vascular wall. This substance was later identified as nitric oxide (NO). The existence of a nitric oxide dependent pathway, L-arginine-NO-CGMP pathway in pregnancy has been demonstrated in animal models (Weiner et al.). Yallampalli et al. examined the human endometrium at various gestational ages and demonstrated that the L-arginine-NO-cGMP pathway helped regulate myometrial contractility throughout gestation. Normal pregnancy is associated with profound cardiovascular changes with increase in cardiac output and heart rate and decrease in peripheral vascular resistance and mean arterial blood pressure. While endothelium-derived prostacyclin has shown to have a role, nitric oxide has been identified as an important regulator of blood pressure in pregnancy. Molnar and Hertelendy used animal models to show prolonged blockade of nitric oxide synthase inhibitor leads to a preeclampsia like state with sustained hypertension, thrombocytopenia, a reduced intravascular compartment, fetal growth retardation and potentially fetal demise. Additional evidence of endothelial dysfunction in preeclampsia in humans was provided by Mccarthy et al. Small arteries from the subcutaneous fat were examined at the time of cesarean section in normal pregnant women and women with preeclampsia. The authors showed acetylcholine(endothelial) mediated relaxation of the arteries was impaired in women with preeclampsia compared to normotensive pregnant women providing evidence of endothelial dysfunction in preeclampsia.

Many invasive and non-invasive techniques were developed as surrogate markers for coronary endothelial function. Such tests were later expanded to assess both macrovascular and microvascular endothelial function. Celermajer and colleagues demonstrated that the reactive hyperemia produced in the brachial artery after an occlusion with a blood pressure cuff was endothelial, NO dependent and was termed as Flow mediated dilation (FMD). FMD was originally developed to assess coronary artery endothelial function. Preeclampsia is a condition associated with profound dysfunction of NO dependent vascular endothelium relaxation. Several studies have validated the use of flow mediation dilation of brachial artery to evaluate maternal vascular endothelial function in women with preeclampsia. Increased blood pressure and increased peripheral vascular resistance is partly due to decreased NO production by a dysfunctional vascular endothelium resulting in decreased FMD.

Defective placental trophoblast invasion is associated with incomplete spiral arterial remodeling. Ultrasound assessment of the uterine arteries can provide an objective evidence of this underlying dysfunction. Role of Doppler ultrasound in the comprehensive risk assessment for preeclampsia has been extensively described in the literature. In 2018, the International Society for Ultrasound in Obstetrics and Gynecology (ISUOG) described practice guidelines on the use of ultrasound in the screening and follow-up tool for preeclampsia. Pulsatility index (PI), Resistance index (RI) and Systolic/Diastolic (S/D) ratio) are the doppler indices available to interrogate the impedance to the flow in the uterine artery. Of these, mean PI is the most predictive index and is the preferred methodology in the screening for preeclampsia. This measure incorporates the variability of blood velocity in a cardiac cycle rather than just a two-point measurement as in RI. Bilateral uterine artery notching in the second trimester has a similar sensitivity as PI and the combination can be used as an effective ultrasound screening tool for preeclampsia.

The anti-platelet action, and altered thromboxane/prostacyclin ratio relate to low dose aspirin therapy have been extensively explored for the prevention of preeclampsia. One of the proposed theories for development of preeclampsia is that defective placental invasion and spiral arterial remodeling leads to activation of platelets and the coagulation cascade. The hypothesis is that aspirin can prevent or delay the onset of platelet aggregation. The role of aspirin in the prevention of preeclampsia was first investigated by Crandon et al. The incidence of preeclampsia was significantly lower in patients who frequently took aspirin or aspirin related products in pregnancy. Since then several studies have evaluated the efficacy of low dose aspirin prophylaxis in the prevention of preeclampsia in doses ranging from 50 mg to 150 mg. In 2014, a United States Preventive Services Task Force (USPSTF) guidelines supported the use of low dose aspirin based on a meta-analysis that showed a 2-5% absolute risk reduction for preeclampsia. USPSTF defines high and

moderate risk factors for preeclampsia. The American College of Obstetrics and Gynecology (ACOG) and the Society of Maternal Fetal Medicine (SMFM) endorse the USPSTF recommendations. Low dose aspirin is supported for women who have one or more of the high-risk factors or multiple moderate risk factors for preeclampsia. This prophylaxis is prescribed initially between 12 and 28 weeks of gestation (optimally before 16 weeks). In support of the USPSTF recommendations, a meta-analysis in 2017 showed a significant reduction in the incidence of preeclampsia when aspirin was initiated =16 weeks and at a dose of 100 mg. Furthermore, in 2017, the ASPRE trial, a large multi-center, double-blind, placebo controlled trial was published demonstrating women who were stratified as high risk for preeclampsia by means of first trimester screening including uterine artery Doppler assessment, and who received a daily dose of 150 mg of aspirin, had a 60% reduction in the incidence of preterm preeclampsia (< 37 weeks of gestation) .

Despite this abundance of evidence on the beneficial role of aspirin to prevent preeclampsia, relatively few mechanistic studies have been performed to understand better how aspirin modifies the pathogenesis of the disease. Hashemi et al showed a significant increase in FMD in preeclamptic women who were placed on low dose aspirin which was observed throughout pregnancy and persisted until 2 months postpartum. These findings suggest aspirin's ability to decrease endothelial dysfunction by selective inhibition of thromboxane A2 may impact the peripheral vasculature in pregnancy. There is also sparce data on how aspirin modifies the impedance to flow centrally in the uterine arteries when impaired placental implantation is observed. One study identified a non-significant trend towards reduced placental resistance in women treated with aspirin by assessing uterine arterial Doppler indices at 32-34 weeks of gestation. However, other evidence suggests aspirin may not alter abnormal uterine artery flow even when initiated early on in the gestation.

The therapeutic benefits or the toxicological effects of drugs during pregnancy is best studied with a two compartment (maternal – fetal) unit. This is a simple kinetic model that can used to study the rate, distribution and duration of drug exposure in the mother and the fetus. The volume of distribution has been noted to be increased when the 2 compartment model has been studied. The pharmacokinetics of a drug is also influenced by the metabolism in a third compartment, placental compartment and the by the kinetics of the drug metabolite itself.

Szeto, H.H. Pharmacokinetics in the ovine maternal-fetal unit. Annu Rev Pharmacol Toxicol 2:221-243, 1982

In a non-pregnant state, following ingestion of 162 mg of aspirin, the mean maximum plasma concentrations of acetyl salicylic acid and salicylic acid was 1.8 ± 0·6 mg mg /L and 7.6 ± 1·4 mg/L respectively. The lowest measured plasma concentration of salicylic acid to fully inhibit arachidonic acid induced platelet aggregation was 5.7 mg/L seen when 162 mg of aspirin was used per day.
Hobl, E. L., Schmid, R. W., Stimpfl, T., Ebner, J., & Jilma, B. (2015). Absorption kinetics of low-dose chewable aspirin–implications for acute coronary syndromes. European journal of clinical investigation, 45(1), 13-17.

Aspirin pharmacokinetics have been studied in pregnancy. The metabolism of aspirin is altered in pregnancy due to physiological changes in gastrointestinal absorption, accumulation in body fat and decreased drug binding to plasma proteins and changes in renal excretion due to increase renal plasma flow and glomerular filtration rate. Jacobson and colleagues investigated the transfer of acetylsalicylic acid in a perfused human placental cotyledon and its effects on fetal placental unit. When isolated perfused human cotyledons were treated with acetyl salicylic acid, 60% of acetyl salicylic acid was extracted from the maternal perfusate when steady state was reached and less than 15% was noted in the fetal circulation. These levels were much lower than those known to inhibit thromboxane or alter fetal perfusion pressure. The much lower concentrations seen in the fetal circulation than what is extracted from the maternal perfusate might be presumably due to placental metabolism
Jacobson, R. L., Brewer, A., Eis, A., Siddiqi, T. A., & Myatt, L. (1991). Transfer of aspirin across the perfused human placental cotyledon. American Journal of Obstetrics & Gynecology, 165(4), 939-944.

Although this intervention is well supported and low risk, aspirin has several pharmacokinetic mechanisms of action and the way it modifies disease in some pregnant patients is unclear5. Aspirin triggered lipoxins (ATL/LXA4) are lipid mediators produced from arachidonic acid that are thought to work through anti-oxidant and anti-inflammatory roles to result in tissue specific, and possibly, systemic change. These mediators occur naturally but are increased by aspirin administration and pregnant mouse models show reduction of pre-eclamptic disease with administration6. Further, a cohort study of pregnant women showed lower circulating levels of ATL/LXA4 and placental receptor (ALX) expression in pre-eclamptic women7. As pre-eclampsia is a disease of widespread endothelial damage and inflammation triggered by placental dysfunction, we surmise that aspirin's effectiveness as a prophylactic therapy could be through alteration of ATL/LXA4 and receptor (ALX) expression at the placental level.

The pharmacokinetics of aspirin in pregnancy has not been clearly defined and existing sparce data from animal and some human placental models therefore supports the construct that the efficacy of the intervention may be dependent upon dose and volume of distribution.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

The objective of our study is to determine if low dose aspirin has a dose dependent response to modify maternal endothelial dysfunction and impedance in uterine arteries when used in the prophylaxis of preeclampsia prevention in women identified as at high risk for development of preeclampsia.

Another objective of our current study is to understand the important mechanism of prevention of pre-eclampsia with the ultimate goal to improve targeting of therapy to pregnant women who will benefit from aspirin exposure in pregnancy. We will accomplish this by evaluating ATL/LXA4 concentrations as a mechanism of aspirin benefit.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

This is a single center, prospective, randomized, open-label clinical trial. The experimental group will include pregnant women who are identified at high risk for preeclampsia either by history, presence of risk factors, or abnormal uterine artery Doppler impedance. They will be divided into two groups based on their body mass index (BMI) (<30 and =30). Patients in each group will be randomized to receive either aspirin 81 mg (1 tablet of baby aspirin) or aspirin 162 mg (2 tablets of baby aspirin) daily initiated between 11 and 16 weeks of gestation and continued until 36 weeks of gestation. There will be a third control group of pregnant women at low risk for preeclampsia based on their risk factor assessment to provide baseline data. The control group will not receive aspirin. Both of the experimental and control groups will be assessed with uterine artery Doppler studies and FMD of the brachial artery at three different time points in pregnancy: at enrollment between 11 and 16 weeks, between 18 and 22 weeks (+/- 7 days), and between 28 and 32 weeks of gestation(+/- 7 days). We will obtain baseline blood and urine samples at the time of enrollment and later between 28 and 32 weeks (+/- 7 days) to assess salicylate levels, thromboxane and endothelin-1 levels. We will also obtain cord blood and placental samples from the experimental and control population at the time of delivery.

Attachments

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

Participants will be recruited from UK Polk Dalton clinic, Good Samaritan Obstetrics and Gynecology clinic, and the Good Samaritan Ultrasound unit. Patients will be greeted in person and recruitment will be done in a private room. Study personnel who work in the clinics listed above with access to patients' identity and information will be involved in patient recruitment and consenting processes. Recruitment of Hispanic patients will be accomplished by certified Spanish translators identified as support staff under study personnel who will be present onsite. The initial recruitment process will not involve any Hispanic patients until a modification is submitted to the IRB with a detailed Spanish consent. The recruitment of the Hispanic patients will begin after the consent form in Spanish has been approved by the IRB.
There will be no advertising.

Attachments

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

The research procedures including patient enrollment will happen at the time of their routine prenatal visits and no additional visits for the purpose of this research are anticipated. The procedures patients will undergo during their visits and the timeline are shown in the attached table. The experimental group will include pregnant women who are identified at high risk for preeclampsia either by history, presence of risk factors, or abnormal uterine artery Doppler impedance. They will be divided into two groups based on their body mass index (BMI) (<30 and >=30). Patients in each group will be randomized to receive either aspirin 81 mg (1 tablet of baby aspirin) or aspirin 162 mg (2 tablets of baby aspirin) daily initiated between 11 and 16 weeks of gestation and continued until 36 weeks of gestation. There will be a third control group of pregnant women at low risk for preeclampsia based on their risk factor assessment to provide baseline data. The control group will not receive any aspirin.
After their initial enrollment, patients in the experimental group will be divided into 2 groups based on their body mass index (BMI) : <30 and >=30. Patients in each group will be randomized to receive aspirin 81 mg(1 low-dose aspirin tablet) or aspirin 162 mg (2 low dose aspirin tablets per day) daily until 36 weeks of gestation. Prescribing low dose aspirin is part of the standard prenatal care for women who are identified as at high risk for preeclampsia.

The prescription for aspirin for the patients enrolled in the study will be sent to the UK Good Samaritan Hospital outpatient pharmacy. When patients are randomized to Aspirin 162 mg (2 tablets of baby aspirin) and there is an additional cost to the patient due to the higher dose. The Division of Maternal Fetal Medicine at UK will receive a monthly statement from UK Good Samaritan Hospital pharmacy for every dose of 162mg that was filled during the previous month.

Patients in both the experimental and control groups will undergo two sets of ultrasound assessments - uterine and brachial arteries, during their routine prenatal ultrasound evaluation at different time points in their pregnancy at UK Good Samaritan hospital. Initial assessment would be during their initial enrollment less than 16 weeks of gestation. The other two would be between 20 and 22 weeks (+/- 7 days) and between 28 and 32 (+/- 7 days) weeks during their routine ultrasound evaluation for fetal anatomy and fetal growth respectively. During their ultrasound visit, after completion of their routine evaluation indicated for that visit, doppler assessment of the uterine arteries will be done. Following this, Doppler assessment of the brachial artery will be performed known as the flow mediated dilation (FMD).

The baseline diameter of the brachial artery will be first recorded using the ultrasound transducer probe. Thereafter a blood pressure cuff will be placed around the forearm distal to the ultrasound probe and inflated to 25-50 mm Hg above the systolic arterial pressure for 5 minutes to elicit a reactive hyperemic stimulus. The cuff will then be deflated and the longitudinal image of the brachial artery will be obtained continuously from 30 seconds before and 2 minutes after the cuff deflation. Flow mediated dilation will be calculated using the following equation: FMD (%) = (Peak diameter - Baseline diameter) / Baseline diameter

Patients will also provide an extra tube of blood and urine specimen collected during their routine prenatal laboratory evaluation performed at the time of first trimester screening and for gestational diabetes screening in the late second/early third trimester. Finally, cord blood and will be collected in 15 patients from each group to assess whether the variation in dose results in appreciably greater fetal cord blood concentrations. The first 15 deliveries from each group in the study will be selected for cord blood and placental collection at the time of delivery. Medical records will be abstracted to collect demographic information, medical and prenatal history, treatment course, ultrasound information, information related to delivery and neonate after birth (Birth weight, gender, APGARS and neonatal complications).

The urine, maternal blood, cord blood and placental samples collected during the study will be stored in a locked freezer behind locked doors in Dr. John Bauer's laboratory at the Medical Science building #472. All identifiable information will be removed from the samples. All information will be de-identified and assigned unique identification codes before storing the specimens. Only the bank staff will have access to the master list that links the code to you. We will store the coded information in a secured computer behind locked doors. We will protect the information with passwords/encryption. Encryption changes your information to another format to protect it from being accessed by anyone outside of the approved staff.

Attachments

Attach Type	File Name
ResearchProcedures	Research procedures timeline pdf.pdf

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Please find the data collection sheet attached

Attachments

Attach Type	File Name
DataCollection	Data Collection highlighted copy.docx
DataCollection	Data Collection clean copy.docx

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

The facilities that will be used for the study will be UK Chandler hospital, UK Polk Dalton clinic, UK Good Samaritan hospital, UK Good Samaritan ultrasound unit, UK Good Samaritan Radiology unit and UK laboratories. The blood and urine samples will be de-identified and stored in Dr. John Bauer's lab at the University of Kentucky. The participants will continue to receive prenatal care as per her their standard prenatal care from their obstetricians. If any medical concerns are addressed they will be immediately be referred back to their obstetrician.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

The most common side effects seen with aspirin use are but not limited to nausea, vomiting, heartburn in the mother seen in about 10% of the patients. There is no increased risk for bleeding during antepartum, intrapartum or postpartum period and there are no known fetal risks with low dose aspirin. There is no risk to the control group involving low risk pregnant women as they do not meet criteria to receive aspirin during the study or outside of it.
The ultrasound assessments of the uterine and brachial arteries are non-invasive and do not pose any maternal or fetal risks. Patients may experience discomfort using ultrasound assessment of the brachial artery which involves inflating the blood cuff around the forearm for 5 minutes.
Possible side effects from blood draws include redness, swelling, pain or bruising at the blood draw site. There are no maternal or fetal risks from ultrasound assessments during pregnancy.
There are no identifiable social, legal and economic risks associated with participation in this study.
There is a possibility of direct benefit to the group of patients randomized to receive 162 mg of aspirin as we might see a greater reduction in the risk preeclampsia. The knowledge gained from this study will potentially help the medical community understand the pharmacodynamics of aspirin for the prevention of preeclampsia. The information may be further used to tailor women's prenatal care to improve maternal and fetal outcomes related to the dose of aspirin.
For the experimental groups, there is no known maternal and fetal risks from aspirin use in pregnancy. The control group with low risk pregnant women will not receive aspirin as they do not meet criteria to receive preeclampsia prophylaxis for the study or outside of it

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

There are no alternative treatments or procedures if the subjects do not wish to participate in the study. They will however continue to receive standard prenatal and other indicated care and ultrasounds without being enrolled in this study

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Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

Research materials include: Socio-demographic patient characteristics, medical chart abstraction, ultrasound assessments of brachial arterial pressures and uterine artery, blood and urine samples. This information is vital to this study to achieve the objectives outlined above. For incidental findings affecting the health of a subject, the participant will be contacted via demographic data that was disclosed at the time of enrollment.
All identifying information will be separated from data and all data will be assigned a coded identification number. Women will be told during enrollment that all their data will be kept either in a locked file cabinet behind a locked door or on a password protected computer in the PI's office located in the Chandler Medical Center, Pavilion H, C-369. The data collected during this study will be maintained for a period of 6 years following the completion of this study. All possible safety measures described above will be initiated to prevent of breaches of confidentiality.

The urine, blood, cord blood and placental samples collected during the study will be stored in a locked freezer behind locked doors in Dr. John Bauer's laboratory at the Medical Science building #472. All identifiable information will be removed from the samples. All information will be de-identified and assigned unique identification codes before storing the specimens. Only the bank staff will have access to the master list that links the code to you. We will store the coded information in a secured computer behind locked doors. We will protect the information with passwords/encryption. Encryption changes your information to another format to protect it from being accessed by anyone outside of the approved staff.
Women will be screened for any history of allergy to aspirin or aspirin related products, history of gastrointestinal or genitourinary bleeding, history of gastric bypass surgery, peptic ulcer disease or liver dysfunction prior to initiating aspirin to minimize undesirable side effects of aspirin. Patients on anticoagulant medication(s) will be excluded from this study. A data and safety monitoring plan will be implemented.
They can choose to leave the study at any time without any consequences to the standard prenatal care they would receive. Risk of breech of confidentiality - Patients' data will be de-identified and will be assigned a coded identification number. Women will be informed that their data will be stored in a locked cabinet behind a locked door or on a password protected computer behind a locked door in the PI's office located in the Chandler Medical Center, Pavilion H, C-369. All possible safety measures will be initiated to protect patient information. Despite all this, should any breech occur, we will contact patients immediately and work with IRB to correct any problems

☑ **UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Check this item to confirm that you will retain all IRB-related records for a minimum of 6 years after study closure.**

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered,

indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

The subjects will not be offered any incentives for their time during participation in the research study

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

Patients' insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that they would normally receive for any conditions they may have. These are costs that are considered medically necessary and will be part of the care they receive even if they do not take part in this study.

The University of Kentucky may not be allowed to bill your insurance company, Medicare, or Medicaid for the medical procedures done strictly for research. There will be no additional costs to the patients.
There are no funds set aside to pay for the cost of any care or treatment that might be necessary for research related injury or care.There is no compensation for any wages lost from research related injuries. Medical costs related to care and treatment because of study-related harm will be the responsibility of the patients

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

1. Monitoring the progress of clinical investigations and the safety of participants:
Patient selection is facilitated by reviewing electronic health records and patient interviewing only by the authorized personnel in this study listed in the IRB. The criteria for patient enrollment will be clearly defined to all the study personnel to ensure efficient patient selection and minimize the risks of ambiguity and deviation from the study protocol. Various systematic reviews of RCTs have not shown any increased maternal and fetal risks associated with use of low dose aspirin in pregnancy.
The technique to measure flow mediated dilation has been validated and used extensively in research involving pregnant women. Patients may experience discomfort at the time of cuff inflation in their forearm for 5 minutes. We will continue to monitor patients during their hospitalizations and monitor for an increase between groups in adverse maternal and neonatal outcomes as defined as placental abruption, postpartum hemorrhage, epidural or spinal hematoma, fetal intracranial hemorrhages, premature closure of ductus or maternal deaths. PI will implement these monitoring procedures and data will be reviewed at 6- month intervals to determine if a significant increase in adverse events is noted between groups.

2. Assuring compliance with the requirements regarding the reporting of unanticipated problems or adverse experiences:
The PI will review the collected data at regular intervals to determine if adverse maternal or neonatal events are potentially related to the exposure. If a root cause analysis suggests that the adverse or unanticipated outcome is due to patient's participation in this research, then a severe adverse event will promptly be reported to IRB. The patient will also be notified and aspirin dosing will be changes as needed.

3. Any action resulting in a temporary or permanent suspension of the study is reported to the IRB promptly. This would include but not limited to a increase in serious maternal and neonatal adverse events as defined above

4. Assuring data accuracy and protocol compliance The PI will monitor data accuracy and protocol compliance

5. Assuring communication among multi-center sites adequately protects the participant (if this is a multi-center study in which the lead PI or UK is the coordinating institution) - Not applicable

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Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place

- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

1. list the biological specimens and/or information that will be kept: placenta, cord blood, maternal serum and urine for 2 years after study closure. Already outlined in previously approved consent.

2. briefly describe the types, categories and/or purposes of the future research- the mechanistic impact of low dose aspirin on body functions during pregnancy.

3. describe any risks of the additional use- None.

4. describe privacy/confidentiality protections that will be put into place. As outlined in the patient consent, samples are only marked with study ID and stored in a locked freezer, in a locked lab on UK's campus.

5. describe the period of time specimens/information may be used. 2 years after study closure.

6. describe procedures for sharing specimens/information with secondary researchers. All specimens and information sharing has to be done through the study coordinator, PI and the Director of Maternal Fetal Medicine. Data is stripped of identifiers and is placed in a excel sheet that is stored behind UK's firewall. It is not planned that we share the information with anyone outside of UK.

7. describe the process for, and limitations to, withdrawal of specimens/data- Verbally to study staff and then they facilitate the documentation and level of withdraw (In writing to the PI, from future participation or withdraw of samples and information too)

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

◉ Yes ○ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

The non-English speaking Hispanic population eligible for this study will be consented by certified Spanish translators listed as study personnel on this study. The consent form translated to Spanish equivalent to the English version will be provided. The translators will be present during the entire process of recruitment, consent and follow up prenatal and ultrasound visits.
The patients will be notified during the consenting process that they may choose not to be a study participant without any consequences to standard prenatal care she would receive

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?
○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?
○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?
○ Yes ○ No
If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

HIPAA

0 unresolved comment(s)

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

I have attached a HIPAA Waiver of Authorization. ○ Yes ◉ No

Attachments

STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

○ Yes ◉ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☐ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ○ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐	Held By:	
Investigator: ☐	Held By:	
Other: ☐	Held By:	

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any

applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.

Attachments

STUDY DEVICE INFORMATION

0 unresolved comment(s)

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer “no” above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ○ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor’s authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) being tested in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices being tested in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.

Attachments

RESEARCH SITES

0 unresolved comment(s)

To complete this section, ensure the responses are accurate then click "SAVE".

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☑ UK Classroom(s)/Lab(s)
- ☑ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☑ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky (UK) or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page), including:

- A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.
- Supportive documentation, including letters of support, can be attached below.
- NOTE: If the non-UK sites or non-UK personnel are engaged in the research, there are additional federal and university requirements which need to be completed for their participation. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK sites.

- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

List all other non-UK owned/operated locations where the research will be conducted:

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Please describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

Attachments

B) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

RESEARCH ATTRIBUTES

0 unresolved comment(s)

Instructions: For various reasons, it is necessary to determine whether your research activities meet the definition of clinical research and/or a clinical trial. Your responses to the next series of questions will make that determination. For more details on the definitions, go to ORI's clinical research vs. clinical trial web page or visit NIH's decision tree for the NIH Clinical Trial definition.

My research activities include one or more of the following:

Patient-oriented research regarding mechanisms of human disease, therapeutic interventions, clinical studies, or development of new technologies
◉ Yes ○ No

Material of human origin (such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects
◉ Yes ○ No

Epidemiologic or Behavioral Studies
○ Yes ◉ No

Outcomes Research or Health Services Research
◉ Yes ○ No

Does your research study involve one or more human subjects prospectively assigned into one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes?
◉ Yes ○ No

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

☐ Academic Degree/Required Research
☐ Alcohol/Drug/Substance Abuse Research
☐ Biological Specimen Bank Creation (for sharing)
☐ Cancer Research
☐ CCTS-Center for Clinical & Translational Science
☐ Certificate of Confidentiality
☑ Collection of Biological Specimens for banking and use
☐ Community-Based Participatory Research
☐ Deception
☐ Educational/Student Records (e.g., GPA, test scores)
☐ Emergency Use (Single Patient)
☐ Gene Transfer
☐ Genetic Research
☐ NIH Genomic Data Sharing (GDS) (databases such as GWAS, dbGaP, GenBank)
☐ Treatment with Human Cells, Tissues, and Cellular and Tissue Based Products
☐ Individual Expanded Access or Compassionate Use
☐ International Research
☐ Planned Emergency Research Involving Exception from

For additional requirements and information:

- Cancer Research (MCC PRMC)
- Certificate of Confidentiality (look up "Confidentiality/Privacy...")
- CCTS (Center for Clinical and Translational Science)
- Clinical Research (look up "What is the definition of....)
- Clinical Trial
- Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
- Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
- Community-Based Participatory Research (look up "Community-Engaged...")
- Data & Safety Monitoring Board (DSMB)

  *For Medical IRB: Service Request Form for CCTS DSMB

- Data & Safety Monitoring Plan
- Deception*

  *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"

- Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
- Genetic Research (look up "Specimen/Tissue

Informed Consent

- ☐ Recombinant DNA
- ☐ Registry or data repository creation
- ☐ Stem Cell Research
- ☐ Suicide Ideation or Behavior Research
- ☐ Survey Research
- ☐ Transplants
- ☐ Use, storage and disposal of radioactive material and radiation producing devices
- ☐ Vaccine Trials

Collection...")

- Gene Transfer
- HIV/AIDS Research (look up "Reportable Diseases/Conditions")
- Screening for Reportable Diseases [E2.0000] (PDF)
- International Research (look up "International & Non-English Speaking")
- NIH Genomic Data Sharing (GDS) Policy (PDF)
- Planned Emergency Research Involving Waiver of Informed Consent*

*For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"

- Use, storage and disposal of radioactive material and radiation producing devices

FUNDING/SUPPORT

0 unresolved comment(s)

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☑ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☐ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☐ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Click applicable listing(s) for additional requirements and information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Other:

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP and DoD Summary for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

Assurance/Certification Attachments

OTHER REVIEW COMMITTEES

0 unresolved comment(s)

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

○ Yes ◉ No

Additional Information

- ☐ Institutional Biosafety Committee
- ☐ Radiation Safety Committee
- ☐ Radioactive Drug Research Committee
- ☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
- ☐ Graduate Medical Education Committee (GME)
- ☐ Office of Medical Education (OME)

- Institutional Biosafety Committee (IBC) - Attach required IBC materials
- Radiation Safety Committee (RSC) - For applicability, see instructions and attach form
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

ADDITIONAL INFORMATION/MATERIALS

0 unresolved comment(s)

Do you want specific information inserted into your approval letter? ○ Yes ◉ No

Approval Letter Details:

If you wish to have specific language included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type that language in the box below exactly as it should appear in the letter. The text you enter will automatically appear at the top of all approval letters, identical to how you typed it, until you update it. Don't include instructions or questions to ORI staff as those will appear in your approval letter. **If these details need to be changed for any reason, you are responsible for updating the content of this field.**

Additional Materials:

If you have other materials you would like to include for the IRB's consideration, check all that apply and attach the corresponding documents using the Attachments button below.

- ☐ Detailed protocol
- ☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
- ☐ Other Documents

Protocol/Other Attachments

NOTE: Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.

To view the materials currently attached to your application, click “All Attachments” on the left menu bar.

SIGNATURES (ASSURANCES)

0 unresolved comment(s)

Introduction

All IRB applications require additional assurances by a Department Chairperson or equivalent (DA), and when applicable, a Faculty Advisor or equivalent (FA). This signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans. The person assigned as DA *should not* also be listed in the Study Personnel section, and the individual assigned as FA *should* be listed in the Study Personnel section.

For a list of responsibilities reflected by signing the Assurance Statement, refer to "What does the Department Chairperson's Assurance Statement on the IRB application mean?"

For a detailed illustration of how to complete this section, please review the short online video tutorial "Signatures (Assurance) Section - How to Complete." Otherwise, follow the steps below.

Required Signatures:

Individuals chosen as signees may remove the application from their Inbox without signing the Assurance Statement by clicking "Return to PI" with a comment about why it is being returned (e.g., specific edits are deemed necessary).

The PI, and personnel chosen as a contact, will receive an email notification that edits are needed, and can find the draft application in both the "Draft" folder and the "Signatures Status" folder located in the menu in the left margin of the default Inbox page. The researcher does not have a 'reply' option to the signee's comments and must make the requested edits directly in the application, or communicate outside the E-IRB system as to why not. Once the response is finalized, the researcher must re-visit the "Assurances Required" section to click the "Return to Signee" button for their re-consideration; the signee will receive an email notification at that time.

Hover your mouse cursor here for additional instructions.

First Name	Last Name	Role	Department	Signee Return Comment	Date Signed	
Wendy	Hansen	Department Authorization	Obstetrics & Gynecology		11/13/2018 07:52 PM	View/Sign
John	O'Brien	Principal Investigator	Obstetrics & Gynecology		11/13/2018 09:25 PM	View/Sign

Department Authorization

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator has been notified of the additional regulatory requirements of the sponsor and by signing the principal investigator Assurance Statement, confirms he/she can comply with them.

*If the Principal Investigator is also the Chairperson of the department, the Vice Chairperson or equivalent should complete the "Department Authorization".

**IF APPLICABLE FOR RELIANCE: I attest that the principal investigator has been notified of the regulatory requirements of both the Reviewing and Relying IRBs, according to the information provided in the E-IRB application. The attached Reliance Assurance Statement, signed by the principal investigator, confirms that he/she can comply with both sets of IRB requirements.

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects and I agree:

1. To comply with all IRB policies, decisions, conditions, and requirements;
2. To accept responsibility for the scientific and ethical conduct of this research study;
3. To obtain prior approval from the Institutional Review Board before amending or altering the research protocol or implementing changes in the approved consent/assent form;
4. To report to the IRB in accord with IRB/IBC policy, any adverse event(s) and/or unanticipated problem(s) involving risks to subjects;
5. To complete, on request by the IRB for Full and Expedited studies, the Continuation/Final Review Forms;
6. To notify the Office of Sponsored Projects Administration (OSPA) and/or the IRB (when applicable) of the development of any financial interest not already disclosed;
7. Each individual listed as study personnel in this application has received the mandatory human research protections education (e.g., CITI);
8. Each individual listed as study personnel in this application possesses the necessary experience for conducting research activities in the role described for this research study.
9. To recognize and accept additional regulatory responsibilities if serving as both a sponsor and investigator for FDA regulated research.

☑ Furthermore, by checking this box, I also attest that:

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.
- If applying for an Abbreviated Application (AA) to rely on an external IRB, I understand that certain items above (1, 3, 4, 7-8) may not apply, or may be altered due to external institutional/IRB policies. I document my agreement with the Principal Investigator Reliance Assurance Statement by digitally signing this application.

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Once all Assurance Statement signatures have been acquired, return to this section to submit your application to ORI.

SUBMISSION INFORMATION

0 unresolved comment(s)

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed. Otherwise your submission for IRB review and approval cannot be sent to the Office of Research Integrity/IRB.

If applicable, remember to update the Approval Letter Details text box under the Additional Information section

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and you will receive a message to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Your protocol has been submitted.

Download all

	Document Type	File Loaded	Document Description	File Size	Modified By	Mod Date
	ApprovalLetter	ApprovalLetter.pdf		0.074	jchine2	4/28/2025 11:16:46 AM
	AdditionInfoConsiderations	Anticipated fetal risks - Additional considerations.pdf	Anticipated fetal risks	0.458	asr224	1/24/2019 11:32:56 AM
	DataCollection	Data Collection clean copy.docx	Data collection form - clean copy	0.014	asr224	12/28/2018 12:42:08 PM
	DataCollection	Data Collection highlighted copy.docx	Data collection form - highlighted copy	0.014	asr224	12/28/2018 12:40:28 PM
	ResearchProcedures	Research procedures timeline pdf.pdf		0.067	asr224	11/13/2018 5:54:05 PM

Protocol Changes

Protocol Number: 47841

Click link to sort Changed Date
ModificationJustification changed by ash231 on 4/28/2025 10:27:14 AM
Greg Hawk , Katie Thompson and Tori Stanton are being added as project assistance for data analysis because they have expertise with the subjects on this protocol.

Study Personnel Changes:

Status	PPIdentity	ProtocolID	PersonID	RoleInProtocol	IsContact	LastName	FirstName	Email	DeptCode	RoomBuilding	SpeedSort	PhoneNum	DeptDesc	AuthorizedConsent	ResponsibilityInProject	Degree	Rank	StatusFlag	IsRemoved	ModBy	ModDate	SFI	IsPIRN	MiddleName
Inserted	1031171	104560	10164730	SP	N	Thompson	Katherine	katherine.thompson@uky.edu						N	Data Analysis/Processing			P	N	ash231	4/28/2025 10:04:57 AM	N		
Inserted	1031172	104560	12170104	SP	N	Stanton	Victoria	victoria.stanton@uky.edu						N	Data Analysis/Processing			P	N	ash231	4/28/2025 10:05:43 AM	N		
Inserted	1031173	104560	10446600	SP	N	Hawk	Gregory	Greg.Hawk@uky.edu						N	Data Analysis/Processing			P	N	ash231	4/28/2025 10:06:22 AM	N		

Modification Comment by Joanne Hines - ORI to PI on 4/28/2025 10:13:11 AM
Please add the changes being made to "Hawk" - highlighted in study personnel section but not included here.

Statistical Analysis Plan NCT03893630 6/27/2025

To begin, continuous variables (age, BMI, gestational age at delivery, etc.) will be summarized with descriptive statistics (n, mean, standard error); categorical variables (e.g., pre-eclampsia, method of conception, etc.) will be summarized with counts and percentages.

The primary outcome, difference in uterine artery pulsatility index (PI) will be calculated as the difference in PI for each patient between each trimester visit. PI at each visit will be calculated by averaging left-side and right-side PIs from each of three (or all available) images on each side for each patient using ultrasound technology. For a very limited number of images identified using clinical expertise, the MATLAB code below will be used to produce PI values if ultrasound technology is insufficient.

An independent and automated image analysis pipeline will be developed using R to crop images and MATLAB to perform image analysis. For each available ultrasound image, an estimated mean PI will be calculated as the average of the PI from each analyzable waveform. For each patient at each visit, left- and right-side estimates will be obtained using the median of the available image-level estimates, since the median is more robust to outliers resulting from images that might be difficult to read. Finally, the mean PI for each patient at each visit will be calculated using the average of the left- and right-side estimates. Means and SDs of these indices will be compared to (1) ensure that there are no drastic differences from the values calculated using the ultrasound technology and the alternative pipeline, and (2) demonstrate the robustness of the calculated primary outcome values.