Does the Cerebroplacental Ratio (CPR) Predict Adverse Outcomes in Low Risk Pregnancies?

Protocol Identifying Number: RU10312017

Principal Investigator: Mayra Cruz-Ithier, MD

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LIST OF ABBREVIATIONS

AFI	Amniotic Fluid Index
BPP	Biophysical Profile
C/S	Cesarean Section
CPR	Cerebroplacental Ratio
EFW	Estimated Fetal Weight
EGA	Estimated Gestational Age
IRB	Investigational Review Board
MCA	Middle Cerebral Artery
N/A	Not Applicable
NICU	Neonatal Intensive Care Unit
PHI	Personal Health Information
PI	Pulastility Index
PRC	Perinatal Research Consortium
SGA	Small for Gestational Age
UA	Umbilical Artery

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name:

Title:

PROTOCOL SUMMARY

Title	**Does the CPR predict adverse outcomes in low risk pregnancies?**
Précis	Ultrasound Doppler studies are used during pregnancy to help manage

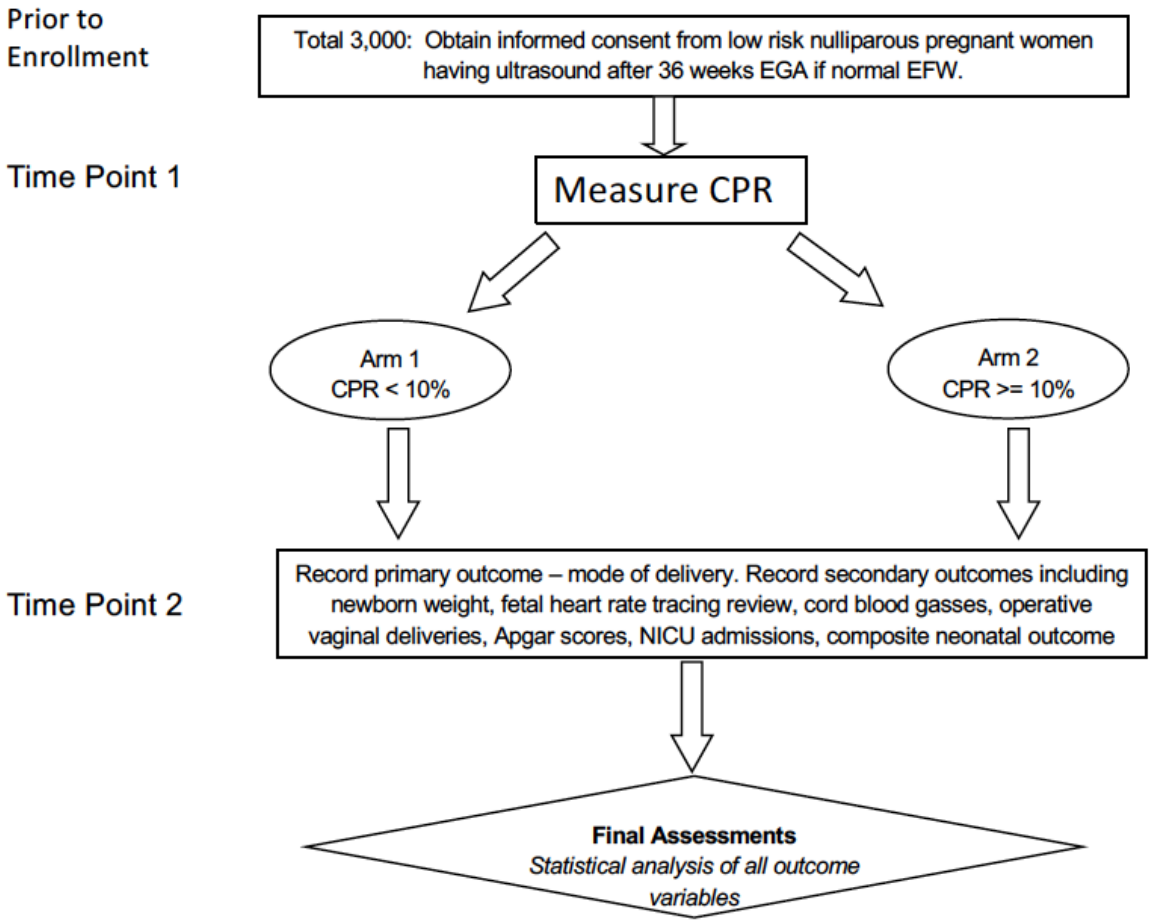
	pregnancies complicated by IUGR. The CPR may predict adverse outcomes in low risk pregnancies. In a prospective study, we will examine whether fetuses with an abnormal CPR at or near term are at increased risk for being delivered by cesearan
Objective	To assess whether women with appropriately grown fetuses in otherwise low risk pregnancies with an abnormal CPR are more likely to be delivered by cesarean section

Endpoints

Primary outcome variable:	Cesarean for non-reassuring fetal heart tracings
Secondary outcome variables:	Total cesarean delivery rate Umbilical cord blood pH Unidentified small for gestational age births Birthweight percentile Prevalence of category 2 or 3 fetal heart tracings Distribution of CPR by EFW Rate of operative vaginal delivery NICU admission Apgar scores at 1 and 5 minutes Composite neonatal outcome

Population	Healthy women with low-risk pregnancies receiving care at study institutions
Number of Sites enrolling participants	8
Description of Study Agent	Prenatal ultrasound Doppler assessment of the umbilical and middle cerebral arteries
Study Duration	12 months
Participant Duration	Between 1 day and 6 weeks

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

Mayra Cruz-Ithier, MD
Co-Principal Investigator
Rutgers Robert Wood Johnson Medical School
Clinical Academic Building Room 2131
New Brunswick, NJ 08901

Todd Rosen, MD
Co-Principal Investigator
Rutgers Robert Wood Johnson Medical School
Clinical Academic Building Room 2140
New Brunswick, NJ 08901

Shama Khan, MS
Study Coordinator

Rutgers Robert Wood Johnson Medical School
Clinical Academic Building Room 2126
New Brunswick, NJ 08901

Chia-Ling Nhan Chang, MD
Columbia University
622 West 168th Street, PH 12-15
New York, NY 10032

Kristy Palomares, MD, PhD
Saint Peters University Hospital
254 Easton Ave
4th Floor Medical Office Building
New Brunswick, NJ 08901

Wendy Kinzler, MD
Winthrop University Hospital
101 Mineola Blvd
3rd floor, 3-002
Mineola, NY 11501

Jessica Scholl, MD
NewYork-Presbyterian/ Queens Hospital
Lang Research Center
56-45 Main St.
Flushing, NY 11355

David Vettori, MD
Virtua Health System
239 Hurffville-Crosskeys Road,
Suite 245
Sewell, NJ 08080

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND

The CPR was first described in the 1980's. The CPR is calculated by dividing the Doppler indices of the middle cerebral artery (MCA) by the umbilical artery (UA). Most commonly, the pulsatility index (PI) is used to calculate the CPR. The CPR represents alterations in blood flow to the brain as a result of cerebrovascular dilation in response to hypoxia and increased placental resistance. The CPR has been best studied as a predictor of adverse pregnancy outcomes in fetus diagnosed with growth restriction. Newer studies have suggested the use of the CPR as an alternative approach for appropriately grown fetuses suffering from placental insufficiency who haven't reached their full growth potential but do not appear to be growth restricted (Morales-Rosello et al, Ultrasound Obstet Gynecol Jan 2015).

There is preliminary evidence that an abnormal CPR predicts adverse outcomes in otherwise low risk pregnancies. In a study by Prior et al. (Amer J Obstet Gyn February 2013) appropriately grown fetuses with an abnormal CPR (less than the 10th percentile) were 4 times more likely to be delivered by cesareansecondary to fetal distress in labor. A second study published by Morales-Roselló et al (Journal of Ultrasound in Obstetrics and Gynecology in

January of 2015) showed that appropriately grown fetuses with abnormal CPR were more likely to have lower cord blood gas pH levels.

The current standard of care is only to perform Doppler studies in growth restricted fetuses. Currently there is not data to support Doppler studies in the low risk obstetrical population. Our primary aim to investigate the value of assessing the CPR in fetuses that are at low risk for adverse outcomes.

While these limited data suggest that the CPR may be useful in predicting which women need cesarean and are at increased risk for abnormal fetal heart rate tracings and fetal acidosis, these data are only preliminary and further study is necessary.

2.2 RATIONALE

A major contributor to the increasing cesarean rate in the United States is abnormal fetal heart rate tracings leading to concerns for intrapartum hypoxia. Measuring the CPR close or at term may predict which fetuses are at greatest risk for fetal distress in labor and lead to better strategies to reduce the number of cesarean in this group. We aim to study whether an abnormal CPR in low risk women with normally grown fetuses predicts the need for cesarean and other adverse outcomes

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Women enrolling in the study will be having obstetric ultrasound ordered by their health care provider as part of their clinical care. The only additional intervention will performance of umbilical and middle cerebral artery Doppler studies at the time of this ultrasound. Because this study would not be performed as part of routine clinical care, providers caring for this patient will be blinded to the result of the study with the exception that the prinicipal investigator deems that the pregnancy is at high risk for adverse outcome. Because providers caring for the patient will be blinded to the results, there should be no influence on the patient's care.

The only risk to study subjects is the inadvertent release of PHI, but safeguards will be put in place to minimize this risk.

2.3.2 KNOWN POTENTIAL BENEFITS

Study subjects will not gain any benefit from enrolling in this observational study. Data gleaned from this work may be of benefit to pregnant women in the future.

3 OBJECTIVES AND PURPOSE

To determine whether the cerebroplacental ratio (CPR) performed after 36 weeks estimated gestational age predicts adverse obstetrical outcomes in low risk pregnancies

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a multicenter prospective study of low-risk women who will be recruited if they are having an ultrasound at 36 weeks EGA or greater or if they are presenting to Labor and Delivery for induction of labor. As part of the study, women will have umbilical and middle cerebral artery Doppler studies and the CPR will be calculated by dividing the MCA PI by the UA/PI. Providers caring for study subjects will be blinded to this result. Pregnancy outcomes in women with CPR values less than the 10th percentile for gestational age will be compared to those with CPR values above the 10th percentile.

A secondary aim to our study is to analyze CPR as a continuous variable.

4.2.1 PRIMARY ENDPOINT

The primary endpoint is the cesarean delivery.

4.2.2 SECONDARY ENDPOINTS

Secondary outcomes will be obtained by chart abstraction after delivery. These include the following:

- Total cesarean section rate
- Cord blood gases
- Cases of SGA undetected prenatally.
- Birthweight/ birthweight percentile
- Incidence of category 2 or 3 tracings
- Distribution of CPR by EFW
- Rate of operative vaginal delivery
- NICU admission
- Apgar scores at 1 and 5 minute
- Composite neonatal outcome

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Pregnant women between the ages of 18 and 45 years with low risk pregnancies who present for obstetrical ultrasound at 36 weeks of gestation or later.

5.2 PARTICIPANT EXCLUSION CRITERIA

- Multifetal pregnancy at the time of presentation

- Known fetal chromosomal anomaly
- Known fetal malformation
- Preeclampsia
- Fetal growth restriction
- Prior cesarean section
- Placental abnormalities such as previa or accreta
- Pregestational diabetes

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Pregnant women presenting to an obstetrical ultrasound unit or those women on labor and delivery who are not in active labor at or beyond 36 weeks EGA will be approached for enrollment in the study. Women from all ethnic backgrounds will be approached to participate. The actual percentage of minority patients will not be known until patient recruitment is completed. It is expected that there the study population will include adequate representation from a large variety of ethnic groups.

Study subjects are only being asked to undergo two additional measurements during ultrasound after they consent to the study, and we anticipate that this additional work will take no more than 5 minutes of the subject's time. Subjects will not be compensated for participating in the study.

Target sample size is for 3,000 women to enroll, which will give approximately 300 women with CPR < 10^{th} percentile for gestational age.

Accrual rate will depend upon the number of sites participating in the research. There are currently 36,000 deliveries annually within the consortium.

No advertisements to potential study subjects are planned.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

An subject may request that she be withdrawn from the study. If ultrasound has already been performed, she may request that her data not be used and that data not be abstracted from her clinical record.

An investigator may termination participation in the study if the participant meets an exclusion criterion (which may be newly developed that precludes further pariticpation in the study.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Participant withdrawals will be recorded and described in the final report of the study. Study data generated by a patient who has withdrawn will not be included in the final study of CPR effects on either the primary or secondary outcome variables.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the PI and/or the IRB.

6 STUDY PROCEDURES AND SCHEDULE

6.1 STUDY PROCEDURES/EVALUATIONS

6.1.1 STUDY SPECIFIC PROCEDURES

- Study personnel will identify subjects who meet inclusion criteria and none of the exclusion criteria and approach them for informed consent to participate in the study.
- Once a subject agrees to participate, a brief obstetrical history will be obtained.
- If subjects' clinically indicated ultrasound study is normal, Doppler measurements of the umbilical and middle cerebral arteries will be obtained three times each and the mean value of the PI will be used to determine the CPR. Data will be recorded on study forms.
- The subject's medical record will be abstracted to obtain relevant data on study forms. Mode of delivery, whether this was a diagnosis of fetal compromise and managing physician's diagnoses will be obtained from the maternal chart. Birthweight, 1 and 5 minute Apgars scores, cord blood gasses (if done) and NICU admission will be recorded. The newborn birth record will also be reviewed for specific complications including need for supplemental oxygen, intracranial hemorrhage, hypoglycemia, jaundice, an unspecified complications.

6.1.2 STANDARD OF CARE STUDY PROCEDURES

Standard of care will not be impacted by a subjects' enrollment in the study. The only difference in care will be assessment of the middle cerebral and umbilical artery by Doppler in women who consent to participate in the study. Clinical care providers will be blinded to the Doppler results. There will be no involvement of study personnel on Labor and Delivery. All data recorded for maternal and neonatal outcomes will be obtained by chart abstraction after delivery has occurred.

6.2 LABORATORY PROCEDURES/EVALUATIONS

6.2.1 CLINICAL LABORATORY EVALUATIONS

With the exception of the Doppler measurements of the fetal middle cerebral and umbilical arteries, no additional assessment will be performed for subjects in the study. Data of laboratory results will abstracted from the medical record. Specifically, umbilical artery and venous cord pH measurements will be recorded if they were performed by the clinical team as part of their routine obstetric care.

6.2.2 OTHER ASSAYS OR PROCEDURES

Not applicable.

6.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE
6.2.4 SPECIMEN SHIPMENT

Not applicable.

6.3 STUDY SCHEDULE

6.3.1 SCREENING

Potential subjects will be approached to enroll in the study if they present to an obstetrical ultrasound unit at a participating site. If subjects meet inclusion criteria but not of the exclusion criteria they will be offered enrollment in the study and asked to sign an informed consent form if they agree to participate. They will have their ultrasound along with study Doppler measurements immediately following the consent process.

6.3.2 ENROLLMENT/BASELINE

When the study subject has her ultrasound, the fetus must not be growth restricted as defined by a composite EFW of less than the 10^{th} percentile to continue participation in the study.

The ultrasound assessment of Doppler studies must be complete. If the sonographer cannot obtain satisfactory measurements of both vessels, this information will be recorded but additional subjects will need to be recruited to meet sample size requirements.

6.3.3 FOLLOW-UP

After study subjects deliver, maternal and neonatal charts will be reviewed and relevant study data will be abstracted.

6.3.4 FINAL STUDY VISIT

There is only a single study visit when the ultrasound Doppler measurements are obtained. All additional data will be obtained through chart abstraction.

6.3.5 EARLY TERMINATION VISIT

Subjects have the right to withdraw from the study at any point. No early termination visit will be required as all necessary procedures would have been performed during the solitary study visit.

6.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Enrollment (Only Subject Visit)	Delivery Chart Abstraction	
Informed Consent	X		
Demographics	X		
Medical History			
Height			
Weight	X		
Middle Cerebral Artery Doppler	X		
Umbilical Artery Doppler	X		
CPR Calculation	X		
Maternal data		x	
Neonatal data		x	

6.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable.

6.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

6.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

6.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

6.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

6.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

6.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable.

7 ASSESSMENT OF SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

Diagnostic ultrasound studies of the fetus are generally considered safe during pregnancy. The lowest possible ultrasonic exposure setting should be used to gain the necessary diagnostic information under the ALARA (as low as reasonably achievable) principle. The 3 additional measurements of the umbilical and middle cerebral arteries are not thought pose additional risk to the study subject or the fetus. There cannot be adverse events related to the study.

7.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Not applicable.

7.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Not applicable.

7.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Not applicable.

7.2 CLASSIFICATION OF AN ADVERSE EVENT

7.2.1 SEVERITY OF EVENT

Not applicable.

7.2.2 RELATIONSHIP TO STUDY AGENT

Not applicable.

7.2.3 EXPECTEDNESS

Not applicable.

7.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Not applicable.

7.4 REPORTING PROCEDURES

7.4.1 ADVERSE EVENT REPORTING

Not applicable.

7.4.2 SERIOUS ADVERSE EVENT REPORTING

Not applicable.

7.4.3 UNANTICIPATED PROBLEM REPORTING

Not applicable.

7.4.4 EVENTS OF SPECIAL INTEREST

Not applicable.

7.4.5 REPORTING OF PREGNANCY

All study subjects will be pregnant

7.5 STUDY HALTING RULES

Not applicable.

7.6 SAFETY OVERSIGHT

Study procedures will be reviewed by the common IRB at Columbia University and implemented by IRBs at other PRC sites.

8 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- A central webinar training for research staff will be performed for initial start-up of participating sites.
- A standardized Doppler measurement training will be required for sonographers prior to acquisition of measurements for the study.
- Target or random review of data will be performed remotely. The data will be sent coded and encrypted from each site to Rutgers- Robert Wood Johnson Medical School for the review.
- Independent audits will not be conducted.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL AND ANALYTICAL PLANS

Statistical analysis is expected to be straight forward in this study. Chi-square or the Fisher exact test will be used to compare binary outcomes. Continuous variables will be compared with the Student *t* test or Mann-Whitney test as appropriate.

9.5 SAMPLE SIZE

To determine sample size we assumed a 20% cesarean rate for those women who have a CPR <10th percentile and a 10% cesarean rate in women with a CPR ≥10th percentile. With 90% power to detect a difference and $\alpha = 0.05$, 288 subjects with a CPR <10th percentile will need to be enrolled into the study. This means approximately 3,000 subjects will need to be screened.

9.6 MEASURES TO MINIMIZE BIAS

9.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Not applicable.

9.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

9.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

11 QUALITY ASSURANCE AND QUALITY CONTROL

Central Webinar trainings will be conducted for consistency and quality control. Sites will not enroll patients until the research staff and sonographer training is complete. There will be a random review of data from every site for quality assurance.

Paper data collection forms, de-identified and coded, will be completed at each site and sent to Rutgers- Robert Wood Johnson Medical School, the Data Coordinating Center (DCC). The data will be entered centrally at the DCC for quality control purposes. The sites will be responsible for data queries and assisting the DCC with data discrepancies for quality assurance.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The investigators will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Columbia UniversityIRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

All PRC sites have written agreements in place so that they will abide by the decision of the Columbia University IRB. Study protocol deviations will be reported to each institution's local IRB.

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study procedures, and risks are given to the participant and written documentation of informed consent is required prior to performing the additional measurements that a part of the study ultrasound.

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The only risk in this study is inadvertent release of PHI. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Data Coordinating Center.

The data may be shared with the Perinatal Research Consortium member sitesfor future research purposes.

12.4.1 RESEARCH USE OF STORED HUMAN SAMPLES,SPECIMENS OR DATA

N/A

12.5 FUTURE USE OF STORED SPECIMENS

N/A

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

13.2 STUDY RECORDS RETENTION

Study documents should be retained for 2 years after study completion.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 14 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to Dr. Cruz and the Data Coordinating Center. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

13.4 PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov , which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

14 STUDY ADMINISTRATION

14.1 STUDY LEADERSHIP

Mayra Cruz-Ithier, MD and Todd Rosen, MD will serve as co-PIs for the study. This will be a multicenter trial within the Perinatal Research Consortium. A site PI will be responsible for management of the research at their

institutions. The Data Coordinating Center at Rutgers will stored the data and it will be analyzed by Todd Rosen, MD and Mayra Cruz Ithier, MD of Rutgers and Cande Ananth, PhD of Columbia University.

15 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

16 LITERATURE REFERENCES

Morales-Rosello, J., Khalil, A., Morlando, M., Papageorghiou, A., Bhide, A., and Thilaganathan, B. **Changes in fetal Doppler indices as a marker of failure to reach growth potential at term.** *Ultrasound Obstet Gynecol*. 2014; 43: 303–310

Prior, T., Mullins, E., Bennett, P., and Kumar, S. **Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study.** *Am J Obstet Gynecol*. 2013; 208: 124.e1–124.e6

Figueras, F., Savchev, S., Triunfo, S., Crovetto, F., and Gratacos, E. **An integrated model with classification criteria to predict small-for-gestational-age fetuses at risk of adverse perinatal outcome.** *Ultrasound Obstet Gynecol*. 2015; 45: 279–285

DeVore, GR. **The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses.** *Am J Obstet Gynecol.* 2015;213:5-15

APPENDIX

Version	Date	Significant Revisions
1.0	10/31/2016	First draft of protocol
1.1	11/14/2016	Biostatistician's comments incorporated.
1.2	2/2/2017	Clinical Monitoring and Quality Assurance updates.
1.3	6/18/2017	Updated exclusion and inclusion criteria
1.4	12/11/2017	Update exclusion criteria