# Study protocol 09-014-07
# STUDY PROTOCOL

**Randomized study to compare the Cook Cervical Ripening Balloon plus Pitocin to Pitocin alone in PROM patients**

**Global Clinical Number 09-014**

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# STUDY PROTOCOL SIGNATURE PAGE

This clinical investigation will be conducted in accordance with the study protocol, 21 CFR 812, ICH-GCP, and other applicable requirements as appropriate. The protocol will be revised, as appropriate, based on new information.

Signatures:

Sponsor Contact

Jennifer L. Kerr — Signature
27 Apr 2018 — DD/MM/YYYY

JENNIFER L. KERR — Printed Name
PRESIDENT — Title

Principal Investigator

I hereby confirm that I approve of this Study Protocol and agree to comply with its terms as laid out in this document.

Signature
DD/MM/YYYY

Printed Name
Title

# CONFIDENTIALITY STATEMENT

**This document shall be treated as a confidential document for the sole information and use of the clinical investigation team and the Institutional Review Board (IRB).**

**Introduction:**

Cervical ripening and induction of labor continues to be a significant problem for patients with premature rupture of membranes (PROM) at term and near term with an unfavorable cervix. Despite the fact that some chemical means of effecting cervical ripening exist, their effectiveness is unpredictable in PROM patients. The purpose of this study is to compare the Cook Cervical Ripening Balloon (CRB) plus Pitocin to Pitocin alone in term and near term PROM patients not in labor.

**Objectives:**

To evaluate the safety and effectiveness of the CRB to expedite labor in term and near term PROM patients not in labor in conjunction with Pitocin compared to Pitocin alone.

The primary effectiveness endpoint is the time from start of labor induction to delivery.

The primary safety endpoint is the incidence of protocol-defined chorioamnionitis.

**Study Design:**

This is a prospective, controlled, randomized, multicenter study to compare the safety and effectiveness of the CRB plus Pitocin to Pitocin alone in term and near term PROM patients not in labor.

This study intends to enroll up to 200 patients, randomized 1:1 into two treatment groups, at up to five investigational sites.

**Inclusion Criteria:**

1. Intrauterine pregnancy ≥ 34 0/7 and ≤ 42 0/7 weeks
2. PROM not in labor
3. Bishop score ≤ 6
4. Maternal age ≥ 18 years old

**Exclusion Criteria:**

1. Patient unwilling or unable to provide informed consent
2. Evidence of chorioamnionitis at enrollment
3. Malpresentation (e.g., transverse fetal orientation, breech presentation)
4. History of prior cesarean section or uterine surgery
5. Major fetal anomaly or aneuploidy (anomalies that require immediate medical or surgical intervention)
6. Significant vaginal bleeding
7. Multiple gestation
8. Contraindication to vaginal delivery (e.g., placenta previa, vasa previa, placenta percreta, prolapsed umbilical cord, active genital herpes infection, invasive cervical cancer)
9. Contraindication to labor induction
10. Abnormal (Category III) fetal heart rate patterns
11. Maternal heart disease requiring medication or resulting in significant cardiac dysfunction
12. Severe maternal hypertension (chronic or preeclampsia)
13. Patient receiving or planning to undergo exogenous prostaglandin administration
14. Polyhydramnios
15. Pelvic structural abnormality that would preclude labor
16. Presenting part above the pelvic inlet (i.e., - 4 station and above)

**Study Considerations:**

The CRB is indicated for mechanical dilation of the cervical canal prior to labor induction at term when the cervix is unfavorable for induction. The CRB is cleared for commercial use and is routinely used in labor and delivery patients at many institutions for cervical ripening. It has been adopted over the past several years as an important method of ripening the cervix in nulliparous and multiparous women who have an indication for delivery.

Although it has been used more frequently in term or near term patients, the CRB has also been used at other gestational ages where delivery is sought in a patient who has an unfavorable cervical exam, i.e., the cervix is not ripe or is unlikely to respond to the normal labor stimulants. In many of these circumstances the contraindications to the use of this device are discounted because of the inherent benefits the device affords in achieving labor in a reasonable time period. One of these conditions is the event of rupture of membranes (ROM), which is listed as a contraindication in the CRB Instructions for Use (IFU). This contraindication is based on the idea that anything that breeches the cervix might increase a woman's risk for infection. Several devices that impose the same risk and are approved for this indication are already in use: the fetal scalp electrode, which actually attaches to the fetus, and the intrauterine pressure catheter. Both of these devices have been part of clinical practice for over 30 years. In each of these cases the device is being used during labor to improve the quality of monitoring or safety of labor.

It is known that a longer latency period, the period from ROM to delivery, increases the chance for infection in the form of chorioamnionitis, neonatal sepsis, or postpartum endometritis. It is for this reason that once ROM has occurred in the term or near term pregnancy, it is important to expedite the course of labor to avoid this infectious outcome. In the current clinical environment there are approved products and products used off-label to achieve delivery. The use of Pitocin, Cytotec®, Cervidil® and the CRB have been the primary methods to achieve this goal.

**Risks and Foreseeable Adverse Device Effects:**

Please reference the CRB IFU for a list of adverse events that may be considered potential risks to patients participating in this study. Additional risks unique to the use of the CRB in term and near term PROM patients include intrapartum infection, adverse material reaction and entanglement of the umbilical cord.

Appropriate obstetric care and standard procedures will be used to manage the risks unique to the use of the CRB in term and near term PROM patients.

**Study Procedure Initiation:**

Patients meeting all inclusion criteria and no exclusion criteria will be invited to participate in the study. Patient eligibility for enrollment will be based on known information at the time of enrollment; information obtained at a later date may contradict this information but will not be considered a noncompliance with the study protocol. Patients will have the study procedures, risks and benefits explained to them and will have the opportunity to ask questions. Point of enrollment occurs when the patient is randomized into the study.

For patients who have not received any prenatal care or who, for any other reason, have not been assessed for abnormal placentation, it is recommended that an ultrasound be performed prior to study enrollment to assess the location of the placenta. Enrolled patients will be randomized 1:1 to treatment with the CRB plus Pitocin (Group A) or Pitocin alone (Group B). Randomization will utilize a computer generated randomization assignment that is stratified for parity, i.e., nulliparous and multiparous women will be accounted for in the randomization assignment. Approximately 200 pregnant women who meet the eligibility criteria will be enrolled into the study.

Both groups A and B will receive Pitocin in accordance with ACOG recommendations to be started within 90 minutes of study enrollment. Limit ambulation per site’s standard of care following administration of Pitocin.

Patients randomized to Group A will undergo CRB placement within 90 minutes of study enrollment. Please reference the CRB IFU for a description of patient preparation and suggested instructions for use. In this study, the intrauterine balloon should be inflated with 60 cc of saline, and the vaginal balloon should be inflated with 30 cc of saline.

**Pitocin Administration:**

Pitocin will be administered in accordance with current ACOG recommendations and following institutional protocols. Details of Pitocin administration, including the maximum amount of Pitocin administered, amount of Pitocin administered at the time of delivery (prior to post-delivery bolus) and total amount of Pitocin infused, will be recorded for each patient. Providers are permitted to suspend Pitocin for periods of time at their discretion for maternal or fetal indications.

**Intrapartum Procedure Management:**

The CRB will remain *in situ* for up to 12 hours or until it falls out of the vagina or when it is determined that the intrauterine balloon has descended past the cervix; please reference the IFU for a description of device removal. The removal of the CRB will have no impact on the use of Pitocin, its dosage, or its continued use. Those decisions will be made based on progress of labor and institutional standard of care, and in accordance with the Pitocin Administration guidelines described above.

All other aspects of labor management will be at the discretion of the primary obstetrical provider. Patients known to be group B streptococcus (GBS) positive will receive prophylaxis in accordance with CDC guidelines. A cervical exam including Bishop score should be completed at baseline (i.e., within 90 minutes of point of enrollment and prior to start of labor induction) and every 6 hours until delivery.

The use of fetal scalp electrodes and intrauterine pressure catheters will also be at the discretion of the obstetrical provider. Women will be able to choose analgesia or regional anesthesia depending on their preference. If a spontaneous delivery is not possible the ultimate decision to deliver by an operative vaginal procedure versus cesarean section will be made by the obstetrical provider using institutional and national criteria.

Uterine activity relative to contraction frequency and cervical change will be monitored along with fetal wellbeing (e.g., fetal heart tones assessment) per the discretion of the obstetrical provider.

**Statistical Considerations:**

Primary Effectiveness Hypothesis

The primary effectiveness endpoint, the time from start of labor induction to delivery, will be analyzed on a per-patient basis based on the intent-to-treat population. The primary effectiveness hypothesis is that patients treated with the CRB and Pitocin will experience decreased time from start of labor induction to delivery than patients treated with Pitocin alone.

$H_0$: $t_{CRB + PITOCIN} > t_{PITOCIN}$

$H_1$: $t_{CRB + PITOCIN} \leq t_{PITOCIN}$

Where:

$t_{CRB + PITOCIN}$: Mean time from start of labor induction to delivery in patients treated with the CRB and Pitocin

$t_{PITOCIN}$: Mean time from start of labor induction to delivery in patients treated with Pitocin alone

The null hypothesis will be rejected in favor of the alternate hypothesis indicating that the treatment with the CRB and Pitocin is more effective than Pitocin alone at a *p*-value < 0.025.

Primary Safety Hypothesis

The primary safety endpoint, the incidence of protocol-defined chorioamnionitis, will be analyzed on a per-patient basis based on the per-protocol population. The primary safety hypothesis is that patients treated with the CRB and Pitocin will experience non-inferior rates of protocol-defined chorioamnionitis than patients treated with Pitocin alone.

$H_0$: $\pi_{CRB + PITOCIN} > \pi_{PITOCIN} + \delta$

$H_1$: $\pi_{CRB + PITOCIN} \leq \pi_{PITOCIN} + \delta$

Where:

$\pi_{CRB + PITOCIN}$: Incidence of protocol-defined chorioamnionitis in patients treated with the CRB and Pitocin

$\pi_{PITOCIN}$: Incidence of protocol-defined chorioamnionitis in patients treated with Pitocin alone

$\delta$: Margin of non-inferiority, set at 10% for this study

The null hypothesis will be rejected in favor of the alternate hypothesis indicating that the treatment with the CRB and Pitocin is as safe as Pitocin alone at a *p*-value $< 0.025$.

Secondary Endpoints

The following secondary endpoints will be analyzed on a per-patient basis based on the per-protocol population:

- Incidence of failed induction,
- Incidence of cesarean section,
- Incidence of post-partum endometritis, and
- Incidence of cord prolapse.

For each outcome, the CRB and Pitocin will be compared to Pitocin alone, to assess for a significantly reduced rate. *P*-values will be adjusted using the Holm method controlling the family-wide Type I error rate at 0.05.

Additional Measures

The following additional measures will be reported:

- Time from PROM to delivery,
- Length of each stage of labor,
- Amount of Pitocin used,
- Incidence of post-partum hemorrhage,
- 1 minute, 5 minute, and 10 minute Apgar scores,

- Time from start of labor induction to delivery in patients with vaginal births,
- NICU admission rate,
- Total maternal hospital stay,
- Total newborn hospital stay,
- General cost analysis based on service utilization, and
- Maternal and newborn resource allocation.

Sample Size Calculations

Sample size calculations for the primary effectiveness hypothesis were performed using data from Sanchez-Ramos, et al.[1] using a one-tailed t-test with α=0.025, power=0.80 and a pooled standard deviation of 300. The expected mean time from start of labor induction to delivery was 416 minutes for the CRB and Pitocin and 539 minutes for Pitocin alone. This resulted in a required sample size of 190 patients, or 95 per group.

Sample size calculations for the primary safety hypothesis were performed using an expected rate of 4% for each group, derived from the rate of chorioamnionitis observed in the literature. [1,2,3,4,5,6,7] A one-sided exact test, α=0.025, power=0.80 and non-inferiority margin of 10% resulted in a required sample size of 124 patients, or 62 per group.

[1] Sanchez-Ramos L, Chen AH, Kaunitz AM, Gaudier FL, Delke I. Labor induction with intravaginal misoprostol in term premature rupture of membranes: a randomized study. Obstet Gynecol. 1997;89(6): 909-912.
[2] Guinn DA, Davies JK, Jones RO, Sullivan L, Wolf D. Labor induction in women with an unfavorable Bishop score: randomized controlled trial of intrauterine Foley catheter with concurrent oxytocin infusion versus Foley catheter with extra-amniotic saline infusion with concurrent oxytocin infusion. Am J Obstet Gynecol. 2004;191(1): 225-229.
[3] Hannah ME, Ohlsson A, Farine D, Hewson SA, Hodnett ED, Myhr TL, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. TERMPROM Study Group. N Engl J Med. 1996;334(16):1005-1010.
[4] Hartling L, Chari R, Friesen C, Vandermeer B, Lacaze-Masmonteil T. A systematic review of intentional delivery in women with preterm prelabor rupture of membranes. J Matern Fetal Neonatal Med. 2006;19(3):177-187.
[5] Heinemann J, Gillen G, Sanchez-Ramos L, Kaunitz AM. Do mechanical methods of cervical ripening increase infectious morbidity? A systematic review. Am J Obstet Gynecol. 2008;199(2):177-188.
[6] Kehl S, Ehard A, Berlit S, Spaich S, Sutterlin M, Siemer J. Combination of misoprostol and mechanical dilation for induction of labour: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):315-319.
[7] Wolff K, Swahn ML, Westgren M. Balloon catheter for induction of labor in nulliparous women with prelabor rupture of the membranes at term. A preliminary report. Gynecol Obstet Invest. 1998;46(1):1-4.

Cook intends to enroll 200 patients to account for those patients who might withdraw.

General Statistical Analyses

Statistical analyses will be performed using SAS® for Windows® (release 9.3 or higher) or other widely accepted statistical software. Clinically relevant baseline variables will be tabulated and compared between the treatment groups. Categorical variables will be assessed using appropriate contingency table analyses (chi-square test or Fisher's exact test) and logistic regression to assess the importance of covariates. Continuous variables will be tested using appropriate tests such as ANOVA, unpaired Student's t-test, or Wilcoxon rank-sum test, depending on variable distribution, and linear regression and repeated measure where appropriate. Survival analysis techniques such as Kaplan-Meier or Cox Proportional Hazards will be incorporated if censoring of data occurs.

Measures to be Taken to Avoid or Minimize Bias

This study is designed as a prospective, randomized, controlled clinical trial to minimize bias in both assigning patients to treatments and in analyzing the results.

Randomization

Assignment of patients to a treatment group will be by block randomization within each site and stratum. Sites will not be informed of the block size.

Missing Data

Due to the short-term follow-up of this study, a minimal amount of missing primary safety and effectiveness data is expected. Ten additional patients have been added to the required sample size to account for missing data. If necessary, multiple imputation will be used where the imputed values will be samples from the empirical distribution of the separate treatment groups.

The intent-to-treat population is defined as all patients who are randomized. The per-protocol population is defined as those patients who received the treatment as specified in their randomization.

Site-level Poolability

Poolability of data from multiple sites will be verified by examining the interaction between treatment arm and study site for the primary effectiveness and safety endpoints. Site-level poolability will be considered appropriate provided that these results are non-significant at the 0.05 level.

**Adverse Event Definitions and Reporting:**

Adverse events (AEs) are to be reported to the Data Coordinating Center using the appropriate case report form. In case of adverse device effects, completed forms will be submitted to the Data Coordinating Center as soon as possible upon knowledge of the event.

The Data Coordinating Center will review the information submitted for possible reporting to the Sponsor. The Sponsor shall, if required according to applicable regulations, report the event to the appropriate Regulatory Authority. The Principal Investigator (PI) or designee will notify his/her IRB of applicable events according to institutional guidelines.

**Device Identification and Tracking:**

Devices under investigation will be tracked throughout the course of the study through use of a Product Log, upon which lot numbers, quantity and disposition of devices will be recorded. Product Logs will be maintained in the site's Investigator File. Additionally, the lot number of each device used in a subject will be recorded on the case report forms.

**Deviations from the Study Protocol:**

Investigators are not allowed to deviate from this protocol without prior authorization by the Sponsor except under emergency situations when necessary to preserve the rights, safety and well-being of human subjects.

Deviations and noncompliances will be recorded together with an explanation. Deviations or noncompliances that impact the rights, welfare, or safety of patients shall be reported to the Sponsor and IRBs as required and as soon as possible.

**Data Collection:**

All primary, secondary and tertiary data will be collected and entered by the investigative site into an electronic case report form (eCRF) system. This is a secure, web-based system, allowing those with permission to access data from any location at any time.

The eCRFs will reflect maternal events until the mother is discharged from the hospital and newborn events until the newborn is discharged from the hospital. If the newborn remains hospitalized at 60 days after birth, the eCRFs will reflect all events in the first 60 days of life. The data to be collected will include, but not be limited to:

1. Prenatal history,
2. Relevant medical and surgical history,
3. Antimicrobial medications administered during the course of the study and Pitocin from start of induction to delivery,
4. Basic biometric markers such as weight and height,
5. Intrapartum events, times and treatments, and
6. Maternal and newborn adverse events, duration of stay and treatments.

**Research Staff:**

All investigators and research staff will observe 21 CFR regulations and Good Clinical Practices (GCP) guidelines in the securing of patient consent, the

documentation of the consent process, data recording, security of protected health information, entry of data in the eCRF system and maintenance of clinical data in general. It is the PI's obligation to ensure that documentation of all relevant data such as relevant medical history, date of study enrollment, visit dates, results of examinations or tests and adverse events are correctly entered in each participant's file.

**Case Report Forms and Source Documentation:**

Every effort will be made to enter the data accurately and in a timely manner. Source data are to be retained for data entered into the eCRF system. Instances of missing or uninterpretable data will be discussed with the investigator and research staff for resolution. Checking the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, the FDA, IRBs, and/or the Sponsor and its designees may wish to carry out such source data checks and/or onsite audit inspections. Direct access to source data may be required for these inspections and audits; the audits will be carried out giving due consideration to data protection and medical confidentiality. The investigator agrees to give the auditor access to all relevant documents for review. The same applies in case of an inspection by the Regulatory Authority.

**Data Management and Monitoring:**

The study will be monitored through a combination of onsite and remote monitoring and in accordance with the International Conference on Harmonization (ICH)-GCP and 21 CFR 812.46. Written procedures for monitoring the study are maintained by the Data Coordinating Center. Data will be reviewed for missing data, data consistency and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. Standard operating procedures maintained by the Data

Coordinating Center will be followed for database management, data verification and data archiving and retention.

**Archiving Study Records:**

According to ICH guidelines and FDA regulations, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements and/or local IRB/institutional requirement.

**Good Clinical Practice:**

The procedures set out in this study protocol are designed to ensure that the Sponsor and investigator abide by the principles of the GCP guidelines of the ICH, the Declaration of Helsinki (2000, with clarification in 2004) and all applicable FDA regulations. The study also will be carried out in keeping with local legal requirements.

The PI is responsible for obtaining approval of this study by the relevant IRB for his/her institution; the investigation will not begin at a site until a favorable opinion of the relevant IRB has been obtained. The PI is responsible for complying with requirements imposed by his/her IRB. Furthermore, the investigator will ensure that local regulations concerning data protection are followed.

**Informed Consent:**

Prior to the administration of any study-specific tests or procedures required in this protocol, the investigator or designee will obtain informed consent in writing from all study participants. Each participant, investigator or designee and witness (as

applicable) must personally sign and date the informed consent form (ICF). Copies of the signed ICF for each patient will be retained at the investigative site.

A copy of the signed ICF will be given to the participant for her records. The ICF will explain the nature of the study, its objectives and its potential risks. Furthermore, it will detail the requirements of the participant, all trial procedures, alternative procedures and the fact that the participant is free to withdraw her consent at any time without reason. Details of indemnity and insurance may also be stated.

As required by ICH-GCP the participant will give in writing her authorization that the study data may be given for review to the responsible authorities and that Sponsor representatives may view the participant's medical records for verification of clinical data. The ICF will be available in a language understandable to the participant.

If a protocol amendment is required, the ICF will be revised if applicable to reflect the changes to the protocol. After the ICF is revised, it must be reviewed and approved by the appropriate IRBs, and signed by all participants subsequently enrolled in the study. Upon request of the IRBs, the revised ICF may also be signed by those previously enrolled in the study.

**Criteria and Procedures for Withdrawal:**

A patient may decide to withdraw from the study at any time either before or after undergoing the procedure without prejudice or loss of care. The PI may also decide to withdraw the patient from the study at any time based on medical judgment. In these instances, the appropriate study visit and study termination data will be submitted to the Data Coordinating Center, and will include the reason why the patient has been withdrawn from the study.

Patients who withdraw consent after study enrollment will be followed until the time of their withdrawal. Any data collected on the patient up to the point of withdrawal may be used in the study. No patient will be removed from the study unless the patient has withdrawn his/her consent before treatment or no treatment was ever attempted.

**Confidentiality:**

All study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor. The anonymity of participants must be maintained. Participants will be identified in the eCRF system and on other documents submitted to the Sponsor by their participant number, initials and/or birth date, not by name.

**Publication:**

At the conclusion of the study, the primary study outcomes will be published in a reputable scientific journal. Publication policy, rights and obligations for this study have been negotiated, detailed and defined in the study's contractual documents with the research sites and investigators.

**Definitions:**

***Apgar score***[8] – An objective scoring system used to evaluate the condition of a newborn after birth.

[8] Apgar V, Holaday DA, James LS, Weisbrot IM, Berrien C. Evaluation of the newborn infant: second report. JAMA. 1958;168:1985-1988.

| Score | Appearance (coloration) | Pulse (heart rate) | Grimace (reflex irritability) | Activity (muscle tone) | Respiration (breathing effort) |
|---|---|---|---|---|---|
| 0 | Blue or pale all over | Absent | No response | Limp | Absent |
| 1 | Blue or pale at extremities | < 100 bpm | Grimace or feeble cry | Weak, some movement | Weak or irregular |
| 2 | Pink all over | ≥ 100 bpm | Cry or pull away | Active movement | Strong cry |

***Arrest of descent*** – Failure of the presenting fetal part to continue to descend during the second stage of labor despite uterine contractions and maternal effort (pushing).

***Arrest of dilation*** – Failure of the cervix to progressively dilate despite active labor.

***Bishop score***[9] – A scoring system used to help predict the success of labor induction. For this study, a standard Bishop score will be calculated using the scoring system below. No additional modifiers will be used in the calculation of the Bishop score.

| Score | Dilatation | Effacement | Station | Position | Consistency |
|---|---|---|---|---|---|
| 0 | closed | 0 – 30% | -3 | Posterior | Firm |
| 1 | 1 – 2 cm | 40 – 50% | -2 | Mid-position | Medium |
| 2 | 3 – 4 cm | 60 – 70% | -1, 0 | Anterior | Soft |
| 3 | 5+ cm | 80+% | +1, +2 | - | - |

[9] Bishop E. Pelvic scoring for elective induction. Obstet Gynecol. 1962;24:266-268.

***Chorioamnionitis***[10] – A complication of pregnancy caused by bacterial infection of the fetal amnion and chorion membranes. A diagnosis of chorioamnionitis will include maternal fever ≥ 100.4°F (38.0°C) plus at least two of the following symptoms with no other documented source of infection:

- Sustained maternal tachycardia with heart rate ≥ 100 bpm,
- Fetal tachycardia with fetal heart rate ≥ 160 bpm for at least 10 minutes,
- Foul smelling amniotic fluid,
- White blood cell (WBC) count ≥ 15,000,
- C-reactive protein more than 2 mg/dL, or
- Uterine tenderness.

***Cord prolapse*** – A condition that occurs when the umbilical cord descends alongside or beyond the fetal presenting part.

***Dystocia*** – Pathologic or difficult labor, which may be caused by an obstruction or constriction of the birth passage or abnormal size, shape, position, or condition of the fetus.

***Febrile*** – Temperature ≥ 100.4˚F (38.0˚C).

***Labor*** – A patient will be considered in labor if she is having regular, painful uterine contractions ≥ 6/hr resulting in progressive cervical effacement and dilatation.

[10] Tita A, Andrews W. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 2010;37(2):339-354.

***Non-reassuring fetal heart tones (NR FHT)***[11] – For this study, only Category III NR FHT will be considered adverse events. NR FHT are considered Category III (abnormal) when the fetal heart rate tracing shows EITHER of the following:

- Sinusoidal pattern or
- Absent variability with recurrent late decelerations, recurrent variable decelerations, or bradycardia.

***Postpartum endometritis***[12] – An infection of the decidua (i.e., pregnancy endometrium). Evidence of postpartum endometritis will include maternal fever ≥ 100.4°F (38.0°C) on any two of the first 10 days postpartum, exclusive of the first 24 hours, with no other documented source of infection; symptoms generally include foul-smelling uterine discharge and uterine tenderness. A positive laboratory result may be obtained for verification of the diagnosis.

***Postpartum hemorrhage***[13] – The loss of greater than 500 mL of blood following vaginal delivery or 1000 mL of blood following cesarean section.

***Premature rupture of membranes (PROM)*** – Ruptured membranes prior to the onset of labor will be confirmed by one of the following methods:

- Non-invasive fetal membranes rupture diagnostic test (e.g., AmniSure),
- Amniocentesis with indigo carmine instillation, or

[11] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation and general management principles. Obstet Gynecol. 2009;114(1):192-202.
[12] Chen, Katherine T. Postpartum endometritis. UpToDate. Available at http://www.uptodate.com/contents/postpartum-endometritis. Accessed July 9, 2013.
[13] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 76. Clinical management guidelines for obstetricians-gynecologists: postpartum hemorrhage. Obstet Gynecol. 2006;108(4):1039-1047.

- Clinical indication of ruptured membranes, which will include at least two of the following symptoms:
  - Ferning,
  - Pooling, or
  - Visible leaking of amniotic fluid through the cervix.

***Tachysystole***[14] – More than five uterine contractions in 10 minutes, sustained ≥ 30 minutes.

[14] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol. 2009;114:386-397.