# Optimizing and validating an EMG-based fetal monitor to identify true preterm labor

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## 1. PURPOSE OF THE STUDY AND BACKGROUND

### 1.1. Purpose of the study

This research is a traditional feasibility study designed to clinically characterize PreTel's uterine EMG/ECG fetal monitor for regional contraction detection and synchronization in laboring and non-laboring patients.

### 1.2. Background

**Fetal monitoring**

Fetal monitoring is the primary method used by obstetricians for moment-to-moment assessment of the health of the fetus. Fetal heart rate and uterine contractions together comprise the two elements of a fetal monitor. Fetal monitors are used in 90% of all deliveries in the United States during labor [1]. Even in the outpatient setting, fetal monitoring is used to assess fetal well-being in pregnancies with common conditions, such as obesity [2]. Fetal monitoring tests are, thus, routinely performed in the outpatient and inpatient settings.

**Maternal Heart Rate monitoring**

Maternal heart rate data are sometimes confused with fetal heart rate data, and it is clinically useful to independently measure the maternal heart rate. If different rates are obtained, it is clear that the fetal heart rate reported by the monitor does indeed come from the fetus. Legacy recording of the maternal heart rate occurs through use of a pulse oximeter placed on the maternal finger.

**Legacy fetal monitoring - Non-invasive method**

Uterine contractions can be measured using a plunger-type mechanical device (called the Tocodynamometer, or "Toco"), and the fetal heart rate can be measured using an electronic stethoscope device (called the Doppler). To obtain tracings, each device is held firmly against the maternal abdomen by straps, which causes discomfort to the patient after several hours. To maintain accurate recordings each device must be correctly aligned, and the alignment needs frequent adjustment by nursing staff. Patient movements, including ambulation, can displace the sensors, so patients are commonly asked to lie still in bed.

Accurate monitoring while ambulating is difficult or impossible. Even with patients lying still and with dedicated nursing attention, this technology is ineffective on average 15% of the time, with even poorer performance in obese patients [3].

**Legacy fetal monitoring - Invasive fetal monitoring.**

Because ongoing assessment of the fetus is critically important, invasive monitoring is often performed when non-invasive legacy methods fail. Here, a fetal scalp electrode (FSE) is used to measure the fetal heart rate, and an intrauterine pressure catheter (IUPC) is used to measure uterine contractions.

For the FSE, a silver wire is attached to the fetal scalp. This provides direct electrical contact with the fetus and allows recording of a reliable ECG signal for heart rate determination. The IUPC is a tube that is inserted through the vagina and cervix, and into the uterine cavity. The IUPC reports the pressure generated inside the uterus, which is a direct measure of the contraction forces produced. The use of these internal direct measurements is considered the gold standard for fetal monitoring.

Use of invasive monitoring requires that the amniontic membranes be ruptured (either naturally or intentionally). Thus, there are potential complications that arise in the setting of IUPC/FSE monitoring, most commonly maternal fever [4], which is suggestive of intrauterine infection.

**The need for a more reliable non-invasive fetal monitor**

If a more reliable non-invasive fetal monitor was available, it would reduce the need to use invasive (IUPC/FSE) methods, and thereby reduce the risks to mother and baby.

Additionally, a reliable non-invasive fetal monitor not requiring straps would allow for improved patient comfort and for patient and care provider desired maternal ambulation.

**An alternative to the legacy non-invasive fetal monitor (Toco/Doppler)**

Most are familiar with electrocardiography (ECG, or EKG in German), where electrical impulses causing contractions of the heart are assessed using sensor pads on the chest. The pads "sense" the signals created by the heart, and do not create or store any electricity. The uterus is a muscle emitting electrical signals when it contracts. Uterine signals (here called EMG, for electromyography) can be separated from heart signals because the uterus and heart create signals at different frequencies. Thus, both heart and uterine signals appear in each sensor and then the signals can subsequently be amplified and separated by filtering. Like the Toco and Doppler, EMG and ECG are non-invasive. Non-invasive methods by definition do not pose a risk to the patient.

Hence, as an alternative to the plunger-based Toco, it is possible to use EMG to measure the bioelectrical signals that originate from the uterus, and then convert these signals to into tracings that mimic the Toco tracing [5]. Similarly, it is possible to measure the ECG of the fetal heart, then convert these signals to a fetal heart rate tracing. In this manner, an EMG/ECG –based fetal monitor can be constructed. Additionally, the EMG/ECG monitor can detect the maternal ECG, and hence the maternal heart rate can be determined. This could then replace the additional finger pulse oximeter, reducing the number of lines attached to the patient.

The clinical impetus to convert to an EMG/ECG fetal monitor is that it would overcome many of the limitations of the Toco/Doppler [6]. Specifically, an EMG/ECG monitor should be more reliable, require less nursing intervention, be more comfortable to patients, and more easily allow ambulation.

**First generation EMG/ECG fetal monitors**

Because of these potential benefits, fetal monitors using EMG/ECG technology (including display of maternal heart rate) have been developed. These first-generation devices use traditional, circular ECG pads to record fetal ECG, maternal ECG, and uterine signals. However, ECG pads were specifically designed to record heart signals, and yield only small signals from the uterus. Small signals require a moderate amount of data processing suggesting sub-optimal reliability. Reporting of false positive contractions is a problem with EMG reliability that is not seen with legacy methods, and this creates a problem that clinicians have no experience in accommodating.

**PreTel's next generation regional contraction uterine EMG (uEMG)/ECG fetal monitor**
The next generation EMG/ECG fetal monitor will need to overcome the limitations of the first-generation monitors. Furthermore, PreTel's regional contraction uEMG/ECG monitor provides information that previously was unavailable with any non-invasive technology. Three components of PreTel's monitor exhibit advantages over the first generation. They are (1) the sensors, (2) the amplifier, and (3) the method of data analysis.

**Area uEMG sensors**
In our research, we discovered that ECG-type pads are poorly suited to record uterine signals because of major differences of physiology between the organs [7]. In brief, heart signals travel parallel with the skin, while uterine signals arise from below. This phenomenon results in circular pads detecting only very small signals that are difficult to separate from background noise. To more efficiently measure the rising uterine signals, we developed a directional sensor, (which we call "area sensor"). These were evaluated at URMC under RSRB#59426 in 2016-2017. These uEMG sensors are made from the same material as standard ECG pads, but differ only in shape – an open hexagon, measuring 6 cm x 6 cm, (i.e. the hexagon surrounds an open "area"). The unique shape confers directionality to the sensor, efficiently sensing signals that arise from below. This gives our sensors the ability for typical signal detection of 1500 μV, which is 5 times greater voltage than the largest voltage reported using pad-type sensors. Furthermore, our sensors provide for, the first time, spatial resolution to identify local uterine contractile activity.

Not surprisingly, both the fetal and maternal ECG is also observable using our area sensors.

Further study is required to convert and display these signals into clinically useful fetal and maternal heart rates.

Though this study, we anticipate that by measuring the extent of synchronization of several regions on the uterus, we will be able to determine which contractions represent true labor, and which represent false labor. First generation EMG analysis measures the relative power of the signals coming from the uterus. Our method analyzes the timing of events from the many sensors/regions that sample a large surface of the uterus, a procedure called "event analysis". Furthermore, we hypothesize that a transition from unsynchronized regional contractions to fully synchronized contractions will represents the onset of true labor.

## 2. STUDY DESIGN

### 2.1. Overview
This is an NIH SBIR feasibility and efficacy study. This study seeks to validate the reliability of the PreTel Regional Contraction uEMG/ECG Fetal Monitor in accurately determining contraction and the fetal heart rate. The study also seeks to validate the reliability with which the monitor is able to determine true labor contractions from false labor contractions. The study will achieve these goals by utilizing the PreTel Regional Contraction uEMG/ECG Fetal Monitor concurrently with standard fetal and uterine monitoring prior to and during labor.

Patients will be approached as they present for evaluation of labor in Triage and Labor and Delivery. After obtaining consent, we will have the subject sit, slightly reclining. We will place up to 15 EMG electrode pads over her abdomen, spanning most of the surface of the uterus, plus one ground electrode. The arrangement of the electrodes will be documented. If the patient consents to photo-documentation of the arrangement, then a de-identified photo of the sensor arrangement will be taken and stored electronically. The purpose of the image is to assess the

overall abdominal coverage of all EMG/ECG sensors and the placement of the legacy (traditional) monitors. The photograph may be taken before, during or after the completion of testing, so long as it accurately represents the locations of the area and pad sensors of the study device, and the Toco and Doppler of the legacy devices. Should significant adjustments of the study or legacy recording devices occur, such that the locations change, additional photographs may be taken to provide additional information of sensor locations at different times during testing. If the subject requests that a photograph not be taken, or if there is a technical reason that a photograph cannot be obtained, no photograph will be taken, and the subject will continue as a research subject (i.e. She will not be withdrawn from the study.) Failure to obtain an image will not be considered a breach of protocol and will not be reportable as such.

We will record multichannel EMG signals for 60 minutes for each subject. The subject will be eligible for compensation as outlined in section 10.1.

All health care management decision will be based on the standard obstetrical testing.

At the conclusion of the recording, the pads will be removed from the subject. Pads will also be removed at patient request at any time during the study procedure.

We will examine the subjects' medical record for the following PHI, which will be recorded in the Case Report form (CRF):

1. Documentation of key elements of the consent process
2. Date and time of study
3. Patient BMI (weight and height)
4. Patient age, race/ethnicity
5. Due date
6. Cervical dilation prior to start of study, any cervical dilation measurements recorded for clinical purposes during study (noting times)
7. Copy of the legacy (standard) fetal monitor strips obtained during study
8. Placement and location of the sensors on the subject (Photo, if patient consents to photo)
9. If labor was spontaneous or induced/augmented
10. Mode of delivery (vaginal vs Cesarean section) and delivery time and date.
11. Any medications administered before or during EMG recordings, such as Pitocin, nifedipine, magnesium sulfate, terbutaline, etc.

Should data be missing, a decision regarding the applicability of the recording will be made on a case-by-case basis by the sponsor.

2.2. **Rationale for Study Design**

There is a clinical need to develop a non-invasive fetal monitor that has greater reliability than both the Toco/Doppler monitor and first-generation EMG/ECG fetal monitors. In response, PreTel has created the regional contraction uEMG/ECG fetal monitor. PreTel's fetal monitor is based on new understanding of uterine physiology, which confers the following advantages: 1) 5X larger EMG signals; 2) ability to localize uterine activity to specific regions of the uterus; 3) an analysis that is based on function of the whole organ. Together, we hypothesize that PreTel's fetal monitor will provide more accurate reporting of contractions, and the ability to non-invasively separate contractions of true labor from false labor.

## 3. CHARACTERISTICS OF THE RESEARCH POPULATION

### 3.1. Subject Characteristics

a) **Number of Subjects:**
We plan to recruit up to 50 study subjects to complete the entire 60 minutes of testing and consent to have their chart reviewed after delivery to collect all objective outcome data as outlined in our study plan. Data from those who start the uEMG recordings but are unable to complete the full duration will still be analyzed so long as the reason for their withdrawal is not secondary to their withdrawal of consent. Those who withdraw consent will be excluded for data collection and analysis.

b) **Gender and Age of Subjects:**
Pregnant females over 24 weeks gestation age, and age 18 or older (to avoid consenting minors - we do not wish to study pregnant women under the age of 18).

c) **Racial and Ethnic Origin:** Women will not be excluded on the basis of racial or ethnic origin. The patients enrolled in the study should represent the distribution of racial and ethnic origins encountered at URMC.

d) **Vulnerable Subjects:** The study will include pregnant women. There is no way to perform this study in a non-pregnant population. Since the "intervention" is observational only, there is minimal risk and no need for additional safeguards.

### 3.2. Inclusion and Exclusion Criteria

a) **Inclusion Criteria:**

- Age 18 or greater
- At least 30 weeks gestation
- English reading and speaking
- Female gender
- Singleton fetus
- Experiencing contractions and <3cm dilated
- Patients' primary complaint or primary reason for seeking evaluation is uterine contractions and/or suspected labor.
- May be undergoing induction or augmentation of labor (Induction or augmentation refers to any mechanical or medical technique except artificial rupture of membranes (AROM). Subjects undergoing AROM alone, without other induction or augmentation techniques being used concurrently, will be included as a special category within spontaneous labor)
- May have clinical indications for internal monitoring (IUPC and/or FSE)
- Subjects may have intermittent fetal and uterine monitoring as a part of their overall birth plan; however for the 60 minutes of monitoring with EMG required for participation in the study, the subject must be willing to utilize continuous uterine and fetal monitoring.
- Subjects may be scheduled for induction of labor or Cesarean section delivery
- Patients must be able to review and sign informed consent to participate in the study.
- Trial of labor after cesarean section are eligible for participation
- Subjects with premature rupture of membranes in whom labor is augmented are eligible for inclusion in the study

b) **Exclusion Criteria:**

- Twins, triplets and larger number multifetal gestations
- Age less than 18 years
- Humans without a uterus
- Non-English reading and/or speaking
- Significant uterine anomalies such as didelphys or bicornuate uterus (women with small, clinically insignificant anomalies such as uterine fibroids are not excluded).
- Participants cannot be participating in any other research study or protocol regarding uterine contraction monitoring during the same study period as required for our study.
- Known allergy to ECG pad adhesive
- Non-living fetus
- Major fetal malformation
- Fetal distress, or other indications for emergent delivery

### 3.3. Discussion of Subject Population

This study can only be performed on pregnant subjects. To avoid the need for the consent of subjects under the age of 18 who are pregnant, minors will be excluded from this study.

## 4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

### 4.1. Method Of Subject Identification And Recruitment

Women who present for routing obstetrical care at URMC affiliated outpatient sites (i.e., Women's Health Practice, University OBGYN, Strong Perinatal Associates, and Special Care Clinic) and those women who present for evaluation of labor at URMC will be screened for participation. Screening will be performed by regular hospital staff (resident physicians, nurses, other obstetricians) or study coordinators screening subjects on L&D. Patients who meet criteria will be offered participation in the study. Not all patients who meet criteria will be offered the study. This will largely depend on the availability of research personnel (availability of a study coordinator to consent the subject) and the acuity on Labor and Delivery at the time of presentation.

BMI stratification will require us to enroll equal numbers of patients in each BMI category.

Subjects approached in the office by a study coordinator prior to their presentation in labor will be eligible to complete the consent prior to being in labor, presenting to URMC with suspected labor, presenting for an induction of labor or cesarean section. A note regarding their consent to participation in the study will be placed in their medical record in the Provider "Sticky Note" to inform hospital staff that the subject is in the study (see risk section). This notification will help to facilitate contacting the study coordinator at the time of the subjects' hospital admission.

All potential subjects will be told that we are investigating new methods to monitor the baby's heart beat and uterine contractions during labor, and that they will simultaneously receive standard-of-care clinical monitoring. Patients who refuse participation will receive the standard-of-care.

The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's study case history. The Primary Investigator at URMC (Neil

Seligman) will retain the original copy of the signed informed consent form and a copy will be provided to the subject or the subject's authorized representative.

Study personnel will also record the participants name and Medical Record Number in an I-Drive password protected database in order to select a unique identifier code, which will be used to label all EMG data and record the study data points as outlined above. Each subject will be coded per the following: mm/dd/yy-xx, where mm/dd/yy is the date of study, and xx refers to subject #01 through 50. All data sets, including the EMG tracings, fetal ECG tracing, and the CRF will be coded by the number.

Recording of the MRN and name is necessary in order to facilitate accessing the subjects' delivery records after completion of the study. Electronic accessibility to this key is necessary so that study investigators can enroll patients in triage, L&D and the birth center as well as at the out-patient URMC-affiliated obstetric offices, which are not in close proximity to the locked office of the PI.

All collected data will be recorded on Case Report Forms (CRF), attached in appendix 2. These will be copied and sent to Dr. Roger Young (recipient of NIH SBIR grant). A copy will be saved at URMC in the locked office of the local PI Neil Seligman.

At the completion of the study all patient-identifying information will be kept in a secure locked filing cabinet. The time line for destruction will be no less than 10 years following study completion based on institutional protocol.

### 4.2. Process of Consent

Once a potential participant has been identified as fitting the inclusion criteria, without any exclusionary criteria, the study will be verbally described to the potential participant to assess their interest in participation. This will be done by the study PI or a study coordinator, who will then provide the subject with written information regarding the study and complete the consent form with the subject. The individual obtaining consent will be selected based on the time of day and their subsequent availability. The entire consent form will be reviewed with the participant and the participant will be given additional time to re-read the forms and ask any questions. The participant will then sign the consent form if they are still interested in participating. Consent forms will be stored in the locked office of Dr. Neil Seligman.

## 5. METHODS AND STUDY PROCEDURES

<u>Monitoring before and during scheduled induction or Cesarean Section.</u>

In many cases, patients present to labor and delivery for a clinically-indicated induction of labor or Cesarean Section. Following consent, study monitoring will be performed prior to initiation of labor induction or Cesarean Section. If the subject and the research personnel agree, study monitoring may be periodically discontinued, and restarted at a later time without requiring subject withdrawal.

For a scheduled induction, monitoring will occur when the patient is contracting and <3cm dilated. Recordings may be stopped and restarted multiple times for a single subject if needed.

For cesarean sections, the subject can undergo 60 minutes of EMG monitoring just prior to her planned cesarean delivery, if this would not otherwise delay delivery.

Triage patients:
Some patients (not scheduled for delivery), present to labor and delivery for evaluation of labor. They may perceive contractions, but may or may not be in active labor as defined by cervical change, or may or may not have experienced rupture of membranes.

Some patients present with rupture of membranes or a small abruption, in the preterm setting, and for these cases, the decision is usually made to not augment or induce labor. Alternatively, in the term setting, the decision to proceed with delivery via augmentation or induction for those noted conditions, is often made. For cases where the decision to not induce or augment labor is made, study monitoring can initially be performed for 60 minutes. In cases where the decision to deliver via induction, augmentation or expectant management is made, the protocol will be the same as in the sections describing monitoring before and during scheduled induction of labor.

For both the preterm or term subjects who present to triage, there is the possibility that is they may not ultimately progress in labor. These subjects are also eligible for an EMG study session for 60 minutes while their labor status is being evaluated. If they are deemed to not be in labor (i.e. no cervical change) and are discharged (or admitted for extended monitoring, as may occur in the preterm setting or at term for "therapeutic rest"), they will not be excluded from analysis, and they will be allowed to participate in another session either when they begin laboring (i.e. if admitted) or if they are discharged and then return to Triage for another labor evaluation. Recordings may be stopped and restarted multiple times for a single subject if needed.

During the 60+ minutes of EMG pad placement, subjects must also have standard tocometry monitoring and fetal heart rate monitoring. The standard monitoring can consist of either external tocodynamometry (Toco) or an intra-uterine pressure catheter (IUPC) and either external Doppler monitoring of the fetal heart rate or a fetal scalp electrode (FSE). Which type of monitoring is used will be at the discretion of her regular obstetric care team and will not be altered by participating in the study (i.e., the study will not require the patient to have internal monitoring IUPC/FSE). Participation during the 60 minutes of recording does however require some form of continuous monitoring, and therefore subjects desiring intermittent fetal heart rate auscultation or intermittent palpation for contractions, will not be eligible for participation unless they are willing to having standard monitoring for the duration of the study period. Clinical decisions will only be made based on standard uterine and fetal monitoring and examinations.

Uterine EMG recordings, along with the fetal monitoring paper record, will be sent to PreTel. Assessment of the recordings for uterine contractility and fetal heart rate will then be performed by those investigators trained in the analysis (Dr. Young). The EMG data will be compared to the tocometry data to determine correlation or "R" value.

The Case Report Form (CRF) (Appendix 2) will be completed for each subject enrolled in the clinical study. The local investigator will review, approve and sign/date each completed CRF; the local investigator's signature serving as attestation of the local investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

5.1. **Safety Assessments**

The investigational device carries the same risk as obtaining an adult ECG, hence qualifying for the IDE 21 CFR Part 812.3(k) non-invasive. We anticipate that no serious adverse events will occur due to monitoring. It is possible that some subjects may experience slight skin irritation from the gel associated with the sensors; however, these reactions are not severe, are self-limited, and resolve without specific treatment.

For subjects experiencing internal monitoring, there is added medical risk to the subject. If internal monitoring is clinically indicated, the risk to those subjects is not attributable to the study.

All subjects undergoing internal monitoring will have clinical indications for the procedure. Subjects will not undergo internal monitoring expressly for purposes of this study, and the risk of internal monitoring is not attributable to the study.

5.2. **Costs to the Subject**

There will be no cost to the patient or the patient's insurance as a result of study enrollment. The electrodes, EMG, and computer are being provided by the study Sponsor.

5.3. **Payment for Participation**

There is a small stipend ($50) given to subjects to defray the time-cost, potential discomfort, and slight risk for participation. Subjects who initiate the study but who are unable to complete a full 60 minute session will be compensated the full amount if any recording has already been initiated.

**Compensation to Subjects**

Subjects who complete a 60 minute study will receive $50 compensation in the form of a gift card, to defray the cost of additional monitoring time and inconvenience of simultaneously monitoring with EMG/ECG.

6. **Return of Individual Research Results**

Research results will not be directly provided to the subjects. See safety (above) regarding the incidental finding of non-reassuring fetal heart rate patterns.

7. **CONCOMITANT AND DISALLOWED MEDICATIONS**

There are no required treatments or disallowed medications.

8. **SUBJECT WITHDRAWALS**

Subjects will be advised in the written informed consent that they have the right to withdraw from the study at any time without prejudice. Subjects may be withdrawn by the investigator if the clinical circumstances require immediate delivery (e.g. non-reassuring fetal heart rate, abruption, etc.). If a subject requires withdrawal by the study investigator, uEMG recording will be stopped at that time and no further data will be collected.

9. **STUDY DEVICE**

9.1. **Study Device**

The study will utilize body surface electrodes, an 8-channel EMG, and computer. The system being used is the PreTel Regional Contraction uEMG/ECG Fetal Monitor. This device was reviewed by URMC Engineering Department for RSRB#59426 and was approved for external use in the study design. The PreTel Monitor is manufactured by Cooper Consulting Services to

meet electromagnetic compliance (EMC) and safety IEC 60601-1 for medical devices, development and process documentation ISO 14971 (hardware) and IEC 62304 (software).

Each physiological amplifier will be tested for equivalence to the Porti Physiological Amplifier which has been cleared by the FDA for use as per #K063599 for the intended use by or under the direction of a physician for the acquisition of EMG/ECG signals. All of the study equipment will be supplied by the study investigator, Roger Young, at PreTel, Inc. and will be returned upon completion of enrollment.

All PreTel sensors (pads) utilized in this protocol have been manufactured to the requirement of this document, and more specifically in accordance with ISO 13485:2003, section 7.5 and with the Food, Drug, and Cosmetic Act Good Manufacturing Practices regulation and the Code of Federal Regulations (CFR) Title 21 Part 820 (and part 211 where applicable). All EMG sensors to be utilized in this study have been manufactured as per the above requirements by Katecho (Des Moines, IA). Additionally, commercially available ECG pads, such as those supplied by AMBU Corporation, will be used as the reference and fetal ECG sensors.

The device will be stored in the locked storage cabinet in the Ultrasound Suit for labor and delivery at Strong Memorial Hospital. Only study personnel will have access to the device.

### 9.2. Accountability of Investigational Supplies

The principal investigator at the University of Rochester, Neil Seligman, will be responsible for receipt, storage, dispensing, collection, accountability and disposal of the investigational supplies as applicable.

## 10. SAFETY AND REPORTABLE EVENTS

The investigational device carries the same risk as obtaining an adult ECG, hence qualifies for the IDE 21 CFR Part 812.3(k) non-invasive. We anticipate that no serious adverse events will occur due to monitoring. It is possible that some subjects may experience a slight skin irritation due to the gel associated with the sensors; however, these reactions are not severe, are self-limited, and resolve without specific treatment.

For subjects experiencing internal monitoring, there is added medical risk to the subject. If internal monitoring is clinically indicated, the risk to those subjects is not attributable to the study.

All subjects undergoing internal monitoring will have clinical indications for the procedure. Subjects will not undergo internal monitoring expressly for purposes of this study, and the risk of internal monitoring is not attributable to the study.

### 10.1. Responsibilities for Reporting Serious Adverse Events

The Principle Investigator will record all serious adverse experiences that occur during the study period in an adverse event log. The study period for reporting serious adverse events (e.g., from the time of signing consent to final study visit) will be indicated, as will the personnel who needs to be notified and the time frame for notification. The Principle Investigator will comply with regulations and RSRB policy regarding the reporting of adverse events.

## 11. RISK/BENEFIT ASSESSMENT

### 11.1. Potential Risks

All monitoring is passive in nature and is done in concert with standard monitoring. Therefore there is no risk of applying the additional EMG pads. As noted in section 9, there is a theoretical risk of irritation from the gel on the pads, which is no different from the pads used for standard EKG recordings.

A breach of confidentiality is a risk of participation, as the medical record will need to be reviewed to gather the necessary clinical information.

### 11.2. Protection Against Risks

If a participant has any irritation from the uEMG pads, they may ask for their removal and withdraw from study participation.

Protection against a breach of confidentiality: A note regarding their consent to participation in the study will be placed in their medical record in the Provider "Sticky Note" to inform hospital staff that the subject is in the study. This will be done only if the subject would like to participate in the study beyond the first uterine EMG recording session. If subjects are only participating in a single uEMG monitoring session, then no information will be recorded in their medical record. The "Sticky note" is not a part of the patient's permanent medical record and is removed after the pregnancy episode is complete (which occurs following delivery). The information in the sticky note will state: "subject enrolled in UEMG Study". No other identifying information will be recorded in the medical record. This note is necessary to ensure that study personnel are notified when the patient presents to triage at future dates/times to determine if the subject would like to proceed with additional uterine EMG monitoring per the protocol. The risk of a confidentiality breech will also be mitigated, by using only a unique ID code on all documentation. Without the ID code key, it will be impossible to link the subjects' participation information to their confidential information. Only URMC study investigators will have access to the key code. Information sent to the study sponsor for data analysis will have no individual identifying information.

### 11.3. Potential Benefits to Subjects

There are no other potential benefits to the subjects

### 11.4. Alternatives to Participation

None

## 12. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

Participants' consent forms will be kept in a secure locked filing cabinet in Neil Seligman's locked office.

Patients' names and medical record numbers will be linked to a code by date as follows: mm/dd/yy-xx, where mm/dd/yy is the date of study, and xx refers to subject #01 through 50. A master key will be maintained on a password-protected spreadsheet on the secure OB/GYN I-Drive at URMC.

The CRF's will be kept in a locked file in the office of Dr. Neil Seligman.

Uterine EMG recordings will be labeled with the participants' unique identifier codes and not with their names, MRNs or birthdates.

Access to the I-Drive Key will be available only to those personnel responsible for consenting participants. Once all data is collected and EMG recordings have been completed this EMG data will be sent to the PreTel, Inc. electronically via e-mail, as there is no identifying patient information recorded on these. The data sheet is also de-identified, with only the unique identifier listed; this data sheet will also be sent to PreTel, Inc., (a.k.a. Dr. Young) via URMC email. The Key spreadsheet will remain at URMC in the password protected file on the encrypted I-Drive. Following completed enrollment the password to the Key sheet will be changed so that only the PI's have access to this key and study coordinators will no longer have access.

## 13. RESEARCH INFORMATION IN MEDICAL RECORDS

No research data will be included in the participants' medical records.

## 14. DATA ANALYSIS AND MONITORING

### 14.1. Sample Size Determination

This project is a pilot study to assess the reliability of uEMG compared to tocodynamometry for recording uterine contractions. Patient-to-patient variations include body habitus, uterine size, contraction strength and the amount of cervical dilation. We are not capable of controlling for all clinical variables, but assume that term patients carrying one baby in active labor will have contractions that are nearly uniform in producing uterine EMG signals. Thus, for these analyses, we assume that there are no subcategories of patient variables in the study population.

A sample size of 23 was determined using Odds Ratio statistics, assuming a 50% discrimination is clinically the minimum acceptable, $\alpha$=0.05; $\beta$=0.8; expected .75/.25 ratios. For each patient of 60 minutes of recording, we anticipate a minimum of 10 contractions could be observed. On average, we assume 10 contractions, for 23 patients, or 230 contractions.

However, to accommodate for patients who are enrolled in the study but who are subsequently excluded because of inability to complete the monitoring session, we will plan to recruit up to 50 patients.

### 14.2. Planned Statistical Analysis

**Fetal Heart Rate analysis**

Fetal heart rate tracings will be analyzed in 1.0 second epochs.

Endpoint 1.1 – FHR interpretability.

The fraction of epochs that report an interpretable value over the recording period will be determined for ECG and Doppler tracings for each subject as a modified sensitivity. Values for all subjects will be averaged to yield a mean modified sensitivity for each monitoring modality. We anticipate finding the fetal heart rate interpretability rate will equal or exceed the interpretability rate for Doppler.

Endpoint 1.2 – FHR accuracy.
Bland-Altman difference plots (using epochs) of ECG v Doppler will be created for each subject. RMS error will be calculated, where RMS = [average(delta^2)]^0.5. This calculation yields an RMS for each subject; a mean RMS error will then be calculated for ECG against Doppler as gold standard. We anticipate finding the fetal heart rate accuracy will equal or exceed the accuracy of Doppler.

**Contraction analysis**
Whether subjects are in true labor or false labor, or perhaps transitioning into labor, will clinically be uncertain at the time of testing. The EMG data will be analyzed to predict the labor status, then the prediction will be correlated with the subject's outcome. Subjects who subsequently deliver within 24 hours will be considered to have been in labor. Those who deliver after 72 hours or more will be considered to be not-in-labor. Subjects who deliver between 24 and 72 hours will be considered to be transitioning into labor.

Endpoint 1.3 – Contraction analysis. Standard methods for EMG analysis of uterine signals utilizes the power of the EMG signal at each time point. The power values are then mathematically converted to mimic the time-dependent tracing of the Toco. In the PreTel analysis, up to 15 sensors will be distributed across the maternal abdomen to measure uEMG activity at each location. Each sensor will detect uEMG events as a function of time, but the events will not be scaled by power. Instead, the bioelectrical activity of each channel will be converted to an assessment of the presence or absence of a bioelectrical event at each time point and in each location. At each time point, events in all channels will be summed to yield a single time-dependent event tracing. This tracing will be mathematically converted to mimic the time-dependent tracing of the Toco. The PreTel Contraction Analysis software program will perform this analysis.

The PreTel Contraction Analysis will be compared against the Toco/IUPC tracing for sensitivity and specificity.

Endpoint 1.4 – Synchronization Factor.
Prior to conversion to the time-dependent tracing that mimics the Toco, the summed time-dependent event tracing will be mathematically converted to the fraction of sensors showing simultaneous, or synchronized activity. This will be the "Synchronization factor", SF. The maximal SF for each contraction will be stored and reported as the SF associated with that contraction. We will compare the SF with the peak strength (in mmHg) as measured by the IUPC, anticipating that high values of SF are associated with a strong contraction, and consistently high SF values in sequential contractions are indicative of true labor.

For example, if half the sensors are simultaneously active during a given contraction, then SF = 0.50 for that contraction. For the next contraction, it is possible that SF = 0.25. Over time, if the average SF trends to SF < 0.25, the subject will be predicted to be not in-labor. Alternately, if SF trends to SF > 0.75, those subjects will be predicted to be in-labor. The purpose of this research is to quantify this relationship, and determine the specific values and trends of SF that are associated with labor and not-in-labor, and in both pre-term and term pregnancies.

**Maternal Heart Rate analysis**
Maternal heart rate will be calculated from the maternal ECG as recorded by the PreTel Monitor. These maternal heart rates will be compared with the corresponding maternal heart rates obtained from the gold standard pulse oximeter. Heart rate data will be analyzed in 0.25 second epochs, and the epochs will be analyzed for interpretability and accuracy in an identical manner as the fetal heart rate endpoints 1.1 and 1.2.

The sensitivity for monitoring contractions in subjects without an IUPC placed, modified S, will be analyzed as described for run-in subjects described in Objective 2, endpoint 2.4a. Objective 2. To determine the efficacy of PreTel's fetal monitor against the external standard of care and internal gold standard of fetal monitoring.

**Fetal Heart Rate analysis**
Fetal heart rate tracings will be analyzed in 1 second epochs.

Endpoint 2.1 – FHR interpretability. "PPA" is positive percent agreement for ECG or Doppler vs gold standard (GS). 2x2 tables for interpretable and uninterpretable data using ECG or Doppler versus FSE will be created. The presence of a "valid" FHR using ECG or Doppler will be tested against a valid FSE (as GS) in each epoch. PPA = percent of epochs with "valid GS reading" that also has a valid reading by ECG or Doppler.

Endpoint 2.2 – FHR accuracy. Bland-Altman difference plots (using epoch values) of test vs gold standard will be created for each subject (hence two plots for each subject). RMS error will be calculated from data for each device. RMS = [average(delta^2)]^0.5. This yields an RMS for each subject for each device, then mean RMS errors will be reported for ECG and Doppler.

**Contraction analysis**
Endpoint 2.3. Uterine contraction interpretability. A 2x2 table of interpretable/uninterpretable data of EMG vs IUPC will be constructed using 10 second epochs and the PPA determined in the same manner as described in endpoint 2.1 for FHR.

14.3. **Data and Safety Monitoring**
This study entails no more than minimal risk to the patient and fetus. As such, the study does not need a Data and Safety Monitoring committee. Oversight and monitoring of the conduct of the progress of the study will be the responsibility of the local investigators. Concern for the safety and wellbeing of the patients will be reported to the local investigators who will in turn contact the study Sponsor. Data validity and integrity will be handled by Dr. Roger Young following transfer of the de-identified uEMG data.

Endpoint 2.4a – Uterine contraction sensitivity and accuracy. A table of individual contractions identified by EMG, Toco and IUPC will be generated. Contractions detected by EMG or Toco within +/- 30 seconds of IUPC will be defined as True Positive (TP) detections. False Negative (FN) detections are defined as those contractions not detected by EMG or Toco, but detected by IUPC.

Sensitivity, S, for both EMG and Toco, will be calculated as

$$S\ (\text{EMG or Toco}) = \frac{TP}{TP + FN}$$

For training purposes, the data on laboring patients using non-invasive methods (i.e., not using IUPC) will be analyzed using a modified calculation for S where Toco positive will be used as a proxy gold standard.

$$\text{Modified S (EMG)} = \frac{\text{EMG positive}}{\text{Toco positive + apparent FN}}$$

Endpoint 2.4b – Contraction timing accuracy.
$\Delta t$ is a measure the capability of each method to detect the timing of each contraction compared to gold standard. $\Delta t$ is defined as the time the contraction peak is detected by EMG or Toco minus the time the peak is detected by IUPC in the corresponding contraction.

**Maternal Heart Rate analysis**
Maternal heart rate will be calculated from the maternal ECG as recorded by the PreTel Monitor. These maternal heart rates will be compared with the corresponding maternal heart rates obtained from the gold standard pulse oximeter. Interpretability and accuracy of maternal heart rate will be analyzed in a manner similar to the fetal heart rate endpoints 2.1 and 2.2.

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