STUDY TITLE:

Trans-abdominal fetal pulse oximetry: PILOT 1

STUDY SPONSOR:

Raydiant Oximetry, Inc.
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Version No.	Version Date	Modifications
V1	3/15/21	N/A- Original Release
V2	4/9/21	Added exclusion criteria to correspond with Nellcor IFU
V3	6/7/21	Clarification of inclusion induction/active labor enrollment, timing& removal device, Amazon card replaced with UTMB Clincard, defined health provider (physician, midwife, nurse practitioner, nurse)
V4	7/14/21	Additional clarifications added in the Background, Procedures, and Risks Sections. Added that internal sensor previously manufactured by Nellcor, is now manufactured by Axcesor. Clarification on enrollment and sensor comparison statistics.
V5	9/8/21	Remove reference to sterile sleeve, replace words to indicate internal sensor is sterilized.

Study Synopsis

Title: Trans-abdominal fetal pulse oximetry; PILOT 1

Study Design: Prospective, observational, investigator-blinded study.

Study Device: The Raydiant Oximetry Sensing System (LUMERAH)

Objectives: 1) Assess safety and performance of the LUMERAH device as an adjunct to cardiotocography; 2) Assess human factors, device usability factors, and signal capture; and 3) Compare device output to "ground truth" technology (Nellcor N-400 with internal sensors manufactured by Axcesor).

Safety Endpoints	Rate of device-related adverse events such as erythema or rash on the maternal abdomen at the location of the sensor. Note: In this study, use of the device provides additional clinical information, but clinical judgement is based on standard fetal monitoring, including cardiotocography, and investigators are blinded to oximetry readings. The maternal skin at the sensor site will be examined intra and postpartum.
Effectiveness Endpoints	Primary efficacy endpoint is concurrence of oximetry readings compared to those of the Nellcor N400 System ("ground truth").
Study Populations:	Up to 60 pregnant women. who are/have: 1) Willing and capable to provide informed consent 2) Age $\geq$ 18 years 3) BMI $\leq$ 50 (with no more than 4 cm between maternal skin and fetal skin) 4) Gestational age $\geq$ 36 weeks 5) Singleton pregnancy 6) Vertex presentation 7) Active labor 8) Category I or Category II tracings 9) Ruptured amniotic sac with cervical dilation of $\geq$2 cm and a station of -2 or lower
Exclusion Criteria	1) Age <18 years 2) BMI > 50 third trimester 3) Gestational age < 36 weeks 4) Multiple gestation 5) Nonvertex fetal presentation 6) Suspected vasa previa 7) Latent labor 8) Category III CTG tracing (i.e., need for immediate delivery) 9) Fetal anomalies and/or chromosomal disorders 10) Chorioamnionitis 11) Placenta Previa

12) History of HIV, Genital Herpes, or other infection precluding internal monitoring
13) Unable to provide informed consent (e.g., cognitively impaired)

Description of Device and Study Intervention Including Non-Significant Risk Determination:

The Raydiant Oximetry Sensing System (LUMERAH) is a non-invasive fetal pulse oximeter that measures fetal arterial oxygen saturation using safe, non-invasive, transabdominal near-infrared spectroscopy. The LUMERAH device is intended as an adjunct to cardiotocography by detecting decreases in fetal oxygenation. In this study, women in labor will be simultaneously monitored with proven (previously FDA-approved) technology as a "ground truth". These women will be simultaneously monitored with the LUMERAH device and the Nellcor N-400 device. Obstetric health-care providers are blinded to oximetry data presented by both devices; therefore, clinical decisions regarding interventions are made based on the standard factors, including cardiotocography. The primary efficacy analysis will be performed retrospectively by comparing data of fetal oxygenation displayed and recorded by both devices. It is the opinion of the Sponsor that this device and study design, including the placement of the sterile internal sensor *after* membrane rupture, pose no significant risk to the mother or fetus. Further, to mitigate any chance of dystocia, the internal sensor will be placed for 6 hours or less. There is no change to standard of care procedures for fetal heart rate monitoring. The fetal heart rate that will be monitored with the Investigational device will be used for research purposes only. Results of either the LUMERAH sensor or the internal sensor will not be used to guide or alter patient management.

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1. Introduction, Background and Rationale

Newborn metabolic acidosis is a condition that can result in debilitating sequelaesuch as brain injury, renal insufficiency, pulmonary hypertension, necrotizing enterocolitis ,hypoxic–ischemic encephalopathy, and cerebral palsy, [2]. During gestation, labor and delivery, fetal oxygenation is dependent on placental oxygen transfer to the fetus. The rate and effectiveness of this oxygen delivery process is affected by numerous factors, including maternal partial pressure of oxygen, maternal blood oxygen content, blood flow in the uterine circulation, fetal blood oxygen content and umbilical blood flow, the relative affinities of fetal and maternal hemoglobin for oxygen, permeability and surface area of the placental barrier, and placental oxygen consumption.[3] Initially, compromised oxygen delivery to the fetus can be tolerated and compensated for by increased oxygen extraction and reduction of blood flow to non-essential organs. However, the fetus has limited ability to increase placental blood flow[3]. When the fetal oxygen saturation falls below 30% for 10 minutes, the fetus begins suffering hypoxia-ischemia and anaerobic metabolism results in the formation of lactic acid, decreasing blood pH. Newborn metabolic acidosis is the clinical presentation of prolonged fetal hypoxia-ischemia (i.e., insufficient oxygenation of the fetus).[4] This decrease in blood pH due to oxygen deprivation has been described as fetal blood oxygen saturation percentage of <30%[5] (hemoglobin that is bound to oxygen divided by total hemoglobin). Prolonged oxygen deprivation then results in the development of a metabolic (lactic) acidosis. When insufficient oxygenation is prolonged and further acid is formed, the fetus is at increased risk of morbidity.[6]

Intrapartum, the fetus presents with abnormalities in a cardiotocography (CTG), the assessment of fetal heart rate patterns in temporal relation to uterine contractions (e.g., Philips Avalon Maternal/Fetal Monitors). CTG is used by obstetric healthcare clinicians for detecting and predicting inadequate fetal oxygenation to help decide whether or not to intervene in the birth process, with the goal of avoiding fetal hypoxic injury and newborn metabolic acidosis (pH <7.1 and/or a base deficit of ≥12mmol/L[7]). As hypoxic injuries result from oxygen deprivation and CTG presentation of potential fetal injury is very nonspecific, only rarely do clinicians translate CTG abnormalities to fetal hypoxia or ischemia.[8] Thus, monitoring fetal oxygenation directly will provide a more precise modality for fetal surveillance during labor and allow clinicians to more rationally decide when to intervene in the presence of nonspecific CTG abnormalities.

In developed countries, the prevalence of fetal asphyxia at delivery is around 25/1000 live births,[9] of which 2.5/1000 live births at term will develop early onset hypoxic-ischemic encephalopathy (HIE)[6]. A recent large cohort study of 115,502 deliveries in the USA between 2008 and 2011 reported that hypoxia-ischemia in preterm birth may be significantly higher with 37.3/1000 babies born before 37 weeks of gestation reported as having moderate to severe HIE.[10] Hypoxia can be fatal either in fetal or newborn stage, and it is estimated that the mortality is approximately 6% in infants presenting with newborn metabolic acidosis.[3]

CTG-based fetal heart rate monitors are currently used during labor and delivery to identify fetuses that are inadequately oxygenated during labor, allow timely medical intervention, and thus avoid the detrimental effects of newborn hypoxia-ischemia with metabolic acidosis. However, these fetal heart rate monitoring technologies have significant limitations for detecting fetal hypoxia.

Fetal heart rate tracings, which are generated by fetal heart rate monitoring technology, are classified into 3 categories, Category I, II, and III. Category I and III provide certain information for clinician action, whereas category II includes uncertainty in the state of the fetus, and are presented in this order, as follows:

- Category I fetal heart rate tracings are considered normal and occur exclusively in about 15% of the all pregnancies in the United States.[11] When the clinician identifies Category I, no intervention is needed to address concern to the fetus. Category I FHR tracings are *normal*. Category I FHR

tracings are strongly predictive of normal fetal acid-base at the time of observation and may be followed in a routine manner with no specific action required.

- Category III fetal heart rate tracings are considered ominous and occur in less than 5% of pregnancies in the United States.[12] Category III fetal heart rate tracings typically require immediate intervention to protect the fetus. The National Institute of Child Health and Human Development (NICHD) states, "Category III FHR tracings are *abnormal*. Category III tracings are predictive of abnormal fetal acid-base status at the time of observation. Category III FHR tracings require prompt evaluation. Depending on the clinical situation, efforts to expeditiously resolve the abnormal FHR patter may include, but are not limited to, provision of maternal oxygen, change in maternal position, discontinuation of labor stimulation, and treatment of maternal hypotension." [13] In this study, Category III tracings are excluded.
- Category II fetal heart rate tracings are considered indeterminate and occur in about 80% of pregnancies in the United States.[14] However, it is often challenging for obstetric clinicians to determine whether a Category II fetal heart rate tracing truly represents a situation of concern to the fetus and consequently has resulted in the overuse of intervention, including a high rate of medically unnecessary cesarean delivery.[14] Application of the standard algorithm may be initially delayed for up to 30 minutes while attempts are made to alleviate category II pattern with conservative therapeutic interventions (e.g., correction of hypotension, position change, amnioinfusion, tocolysis, reduction or discontinuation of oxytocin). It has been well demonstrated that Category II CTG tracings have poor agreement with newborn metabolic acidosis[15]. This is the target population for this study.

In the case of Category II heart tracings, which represent the majority (80%) of all fetal heart rate tracings during labor, as indicated above, standard care CTG technology, even under ideal circumstances, has been demonstrated to have poor ability to identify infants born with metabolic acidosis[16]. CTG further exhibited a staggering 99% false positive rate for prediction of cerebral palsy, a severe potential consequence of fetal hypoxia that remains untreated.[17] Further, CTG has been and prior studies reported as high as 89% false positive rate for predicting newborn metabolic acidosis.[18] Umstad et al. reported that fetal heart rate monitoring has a 6.2% positive predictive value and 24.1% sensitivity for detecting newborn metabolic acidosis (defined by a pH <7.12).[19]

In addition to the widely-used CTG, there are a few alternative technologies for assessment of the fetus at risk for metabolic acidosis, such as analyses of the ST segment of the fetal electrocardiogram, fetal scalp stimulation and fetal scalp blood sampling for lactate and/or pH determination. However, overall these ancillary tests have not proved reliable. Fetal scalp sampling is invasive, requires transvaginal placement of a probe or similar tool to access the fetal scalp, and once accessed, the device penetrates the fetal scalp and is thus associated with risks such as bleeding and infection. It may require repeating. All the while, none of these technologies directly assess fetal oxygen saturation.

Pulse oximetry exists in virtually every other clinical setting as a means to diagnose and treat dangerously low oxygen levels that can lead to organ and brain injury in extreme cases. Yet no such technology exists for fetuses, even during the physiologically stressful stages of labor. However, fetal pulse oximeters had been available in the U.S. (Nellcor, Pleasanton), and clinical research demonstrated that fetal pulse oximetry values provide 54.2% positive predicative value and 92.9% sensitivity for detecting newborn metabolic acidosis (defined by pH<7.15).[20] This provided a significant aid to clinicians for diagnosing endangering states of fetal hypoxia. These Class III devices are no longer in commercial distribution after 1) the company was sold to Tyco Inc. and a business decision was made to no longer manufacture the product and 2) one study indicated that intrauterine placement was associated with a higher risk of labor dystocia.[21] This was an observation that turned out to be statistically significant but providers do not believe that it was caused by the device. The most likely explanation is

that it is statistical finding due to multiple comparisons. Although the rate of cesarean delivery for the indication of dystocia in the oximetry group more than doubled in the largest RCT reported (Bloom, 2006)[25], it was subsequently suggested that nonreassuring fetal heart rate patterns herald the occurrence of fetal vertex malposition, and when fetal well-being was assured by normal pulse oximetry, these evolve to abnormal progress of labor and ultimately result in cesarean delivery for dystocia. (Porreco, 2004)[26] Use of the Nellcor sensor did not cause dystocia, rather it provided reassurance of fetal well-being in the presence of a nonreassuring fetal heart rate pattern that heralds fetal vertex malposition.

Raydiant Oximetry, Inc. is developing a novel and non-invasive fetal pulse oximetry device to fundamentally improve how fetuses are monitored during labor. The Raydiant Oximetry Sensing System (LUMERAH) is a fetal pulse oximeter that measures fetal arterial oxygen saturation using safe, non-invasive, transabdominal near-infrared spectroscopy. The LUMERAH device performs its measurements without the requirement for transvaginal placement and its associated risks. The LUMERAH is intended as an adjunct to cardiotocography by detecting fetal oxygen deprivation which is both life-threatening to the fetus and can lead to the irreversibly debilitating consequences of newborn metabolic acidosis. The severe consequences associated with newborn metabolic acidosis and the lack of availability of an effective tool to support its early diagnosis led to the development of the LUMERAH device.

The LUMERAH device has undergone accuracy testing using pregnant sheep whereby the oxygenation of the sheep fetus can be manipulated and measured by taking periodic fetal blood samples. This cannot be done in the human model as it carries too much risk to both the mother and the baby; therefore, the Sponsor used the previously approved fetal oxygen sensor made by Nellcor to manufacture new sensors, the new sensors are now being manufactured by Axcesor. The Nellcor sensor was considered to be very accurate and underwent a great deal of scientific rigor before submitting all of the clinical and regulatory documents to the FDA. There were over 50 scientific papers published on the utility of the device. After the company was sold to Tyco, it was then sold to Covidien, then to Medtronic and during that time, they let the approval with the FDA lapse in 2017. The device was not as user-friendly as the proposed investigational device but because of its accuracy, the Nellcor device is necessary to use as the "ground truth" during this study. In other words, before we train the algorithm of the less-invasive LUMERAH device, we want to be sure that it is as accurate as possible and the only way to do that is by using internal sensors. To obtain these devices, Raydiant Oximetry (made up of mostly ex-Nellcor employees) either had devices or contacted prior investigators from the Nellcor studies. These older Nellcor sensors will be used as samples, the new single-use internal sensors are now being manufactured by Axcesor. The benefit/risk analysis supports using a prior FDA approved product (Nellcor System) that is no longer marketed with new manufactured internal sensors vs invasive blood sampling of a fetus in-utero.

2. Objectives

The objectives of this study are as follows: 1) Assess the LUMERAH device specificity in the prediction of newborn metabolic acidosis as an adjunct to cardiotocography; 2) Assess human factors, device usability factors, and signal capture relative to subject factors (e.g., BMI, device position, maternal movement, etc.); and 3) Compare Nellcor N-400 device output to the LUMERAH output.

3. Study Design, Recruitment Methods, Investigator/Team Training and Timeline

This is a prospective, observational, investigator-blinded study. One to two sites in the United States will participate in this study. IRB approval will be obtained prior to entering data in the screening and enrollment logs. The Principal Investigator or research team member may consult a list of eligible patients based on predicted delivery dates and scheduled inductions. Women who are planning to undergo labor

will be approached regarding this study. The enrollment log will be a separate log which will contain the key linking subject information with the study ID. Study ID will be assigned to subjects in a sequential order (e.g., 01-001, 01-002, 01-003….). Subject initials will not be included in the study ID. Logs will be stored on password protected desktops of the study team in a research folder accessible to the OBGYN/Pediatric study team only. The infants born of the subjects will be identified with an "n" following the subject number (e.g., 01-001n).

During this study, women will also undergo sonographic evaluation to assess distance from maternal skin to fetal tissue and to confirm fetal presentation and position. Although sonography is performed routinely during pregnancy, these measurements and confirmation at or after 36 weeks is not routine. The internal sensor (manufactured by Axcesor) will be placed according to the Instructions for Use but only after membranes are ruptured. The LUMERAH device will be simultaneously positioned on the maternal abdomen in various locations depending on the sonographic evaluation. The LUMERAH sensor will obtain fetal pulse oximetry signals for a period of at least 10 minutes but no greater than 6 hours during active labor.

PROCEDURE / TEST	**Pre-partum**	**Peri-Partum**
Subject Medical / Clinical History	√	
Subject Informed Consent	√	
General Inclusion / Exclusion Criteria	√	
LUMERAH external and Nellcor/Axcesor internal data collection		√
Adverse Events (AEs)		√

The Sponsor anticipates that this study will require about 6 months to enroll up to 60 subjects and another month to complete the primary analyses.

4. Enrollment Criteria:

*This study will **include** pregnant and laboring women who are:*

1) Willing and capable to provide informed consent
2) Age ≥ 18 years
3) BMI ≤ 50 (with no more than 4 cm between maternal skin and fetal skin)
4) Gestational age ≥ 36 weeks
5) Singleton pregnancy
6) Vertex presentation
7) Active labor
8) Category I or Category II tracings
9) Ruptured amniotic sac with cervical dilation of ≥2 cm and a station of -2 or lower

Exclusion Criteria:

1) Age <18 years
2) BMI > 50 third trimester
3) Gestational age < 36 weeks
4) Multiple gestation
5) Nonvertex fetal presentation
6) Suspected vasa previa
7) Latent labor
8) Category III CTG tracing (i.e., need for immediate delivery)
9) Fetal anomalies and/or chromosomal disorders
10) Chorioamnionitis
11) Placenta Previa
12) History of HIV, Genital Herpes, or other infection precluding internal monitoring
13) Unable to provide informed consent (e.g., cognitively impaired)

5. Withdrawal of Subjects

Subjects will be withdrawn from the study if, after obtaining informed consent, the subject no longer meets the inclusion/exclusion criteria or if the pregnancy is no longer a normal pregnancy, e.g., if there are health risks to mother or fetus or both. If subjects self-withdraw from the study, any data abstracted from the investigational device up until that point will be used in data analysis. No further measurements or data will be collected after withdrawal. The study involves measurement of the fetal pulse signal with the investigational device during labor. The study does not involve any drugs or evaluative X-ray and no additional safety precautions or follow up will need to be taken if a subject withdraws from the study.

6. Consent process

Subjects will be consented upon admission to the labor and delivery unit in a private setting. Upon admission to labor and delivery, information will be delivered orally and in writing. If a patient agrees to participate at this time, consent will be obtained. It is assumed that at least 50% additional subjects (for a total of up to 90 subjects) will be initially consented compared to the number actually completing the study due to the inclusion/exclusion criteria that cannot be fully ascertained upon admission. In addition, a subject may originally consent to the study but change her mind once labor begins. The *i*nformed consent process will not be rushed and subjects will be informed that their participation is voluntary and there will be no change in their medical care if they choose not to participate. Investigators will describe the safe, noninvasive nature of this study, as well as the future benefit to women and their fetuses if measurement of fetal oxygenation can be performed. Subjects will be invited to ask questions, provide comments, or can choose to withdraw from participation at any time. A copy of the signed Informed Consent Form will be provided to each subject who chooses to participate.

Subjects who agree to participate and who complete participation (defined as device placement and monitoring) will receive a $150 UTMB Clincard.

7. Duration of Subject Participation

Following consent and baseline data collection, subjects are expected to actively participate in the study for up 6 hours (active labor stage). Subjects end their participation in the study after that time period.

8. Payment to Subjects/Cost of Participation

There is no expected cost of subject participation. Payment to the subjects who choose to participate will be set according to institutional standards.

9. Study Procedures/Device Use

Sonographic measurements of distances from maternal abdominal skin to fetus (skin-fetus) will be performed using standard ultrasound units that are available to the investigator. The images are taken to document fetal presentation and position using vertical angles of insonation from defined positions on the maternal abdomen. Sonography will also be employed to obtain detailed measurement (biometry) of intervening skin-fetus structures, including maternal abdominal wall, adipose tissue, uterus, amniotic fluid, placenta, and identification of underlying fetal anatomy at defined positions on the maternal abdomen. Correlation will be made of sonographic measurements with maternal characteristics, including age, height, weight, BMI, gestational age, placental location, and fetal characteristics, including presentation and position. The results of the sonographic measurements may influence the enrollment suitability of the subject as well as the placement of the Investigational device.

The LUMERAH device will be used to record fetal pulse signals during active labor and delivery. Measurements will be obtained using the investigational device along with a standard pulse oximeter. The location of the sensor will be marked on maternal abdomen with a pen; this can be easily wiped off. Simultaneously with recording the pulse signals, the fetal heart rate will be recorded using a standard Doppler-based fetal monitor that is already in clinical use. This consists of a base unit and a Doppler transducer that is positioned on the subject's abdomen, acoustically coupled with ultrasound gel, and secured with a soft flexible strap in accordance with standard clinical practice. The audio signal of the fetal heart will be obtained by placing a small microphone near to the speaker of the base unit or connecting to its headphone jack, if available. This will have no effect on the monitor's operation. Figure 1 below shows a diagram and position of the device components including the sensor ("A") and a combined transceiver/monitor ("C"). The off-the-shelf Doppler monitors for collection of fetal heart rate ("B") is also pictured.

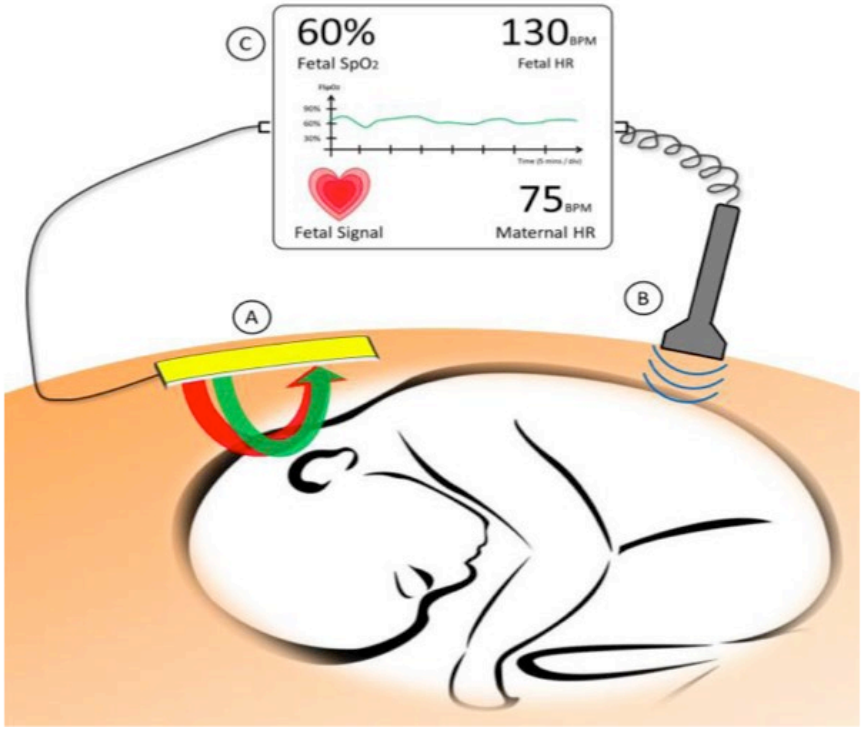

Figure 1: Position of device components

Simultaneously, the maternal pulse signal is normally recorded using a standard, FDA approved pulse oximeter via a data output port. This will aid in analyzing the data recorded by the investigational device.

De-identified sonographic pictures will be obtained by a trained healthcare provider (physician, midwife, nurse practitioner, nurse) from the site for each test location of the optical sensor. The de-identified image will be uploaded to the database which is a secure web application for building and managing online surveys and databases. The study team will take every precaution to ensure that the image is completely free of identifiers.

A single de-identified photograph showing the position of the sensor for each test location on the maternal abdomen may be obtained on a stylized image. This image will be uploaded to the database which is a secure web application for building and managing online surveys and databases. The study team will take every precaution to ensure that the image does not capture any identifiable portion of the patient. All data will be de-identified prior to data entry in the database.

To verify accuracy of the LUMERAH algorithm for laboring women, as derived from experimental studies in the pregnant ovine model, Raydiant Oximetry will use a Nellcor N-400 system with a sterile internal sensor (manufactured by Axcesor) in all subjects. The internal sensor will be placed *after* rupture of membranes (amniotic sac) and the fetus has descended to at least a -2 station. The sensor will be placed by a trained healthcare provider (physician, midwife, nurse practitioner, nurse) and the placement confirmed before initiation of LUMERAH data collection. The data collection plan is to obtain approximately 40 data sets on each of the laboring patients. Each data set takes 90-120 seconds to gather (~ 2-3 hours in total), and a pre/post ground truth assessment will be obtained for each data set. It is anticipated that subjects will participate for a minimum of 10 minutes (where only a few data sets are obtained) but for no more than 6 hours. <u>The obstetric provider will be blinded to both the LUMERAH data and the internal sensor data.</u>

The device shipments/delivery and request for return will be the responsibility of the Sponsor. The device is not delivered to the site until IRB approval has been obtained. The Investigational device is pre-commercialization and will not be available to study subjects after participation in the study. Study subjects will not be restricted from use of any medication or other substance while participating in the study. In addition to the PI and co-investigators, members of the Raydiant Oximetry team may transport and be accountable for the investigational device.

10. Data Collection

In addition to specific LUMERAH device and cardiotocography data, the following data is the minimum subject data set to be collected during this study:

- Maternal demographics such as race, ethnicity, age, parity, prior perinatal outcomes, height, weight (to calculate BMI), number and date of prior cesarean deliveries, Maternal Vital Signs such as the maternal heart rate and maternal oxygen saturation.
- CTG Tracings to be downloaded from the EMR
- Location on maternal abdomen for best signal quality
- Safety data (see "Adverse Event Reporting" below)

In addition, the internal sensor data will be analyzed and compared to the LUMERAH device data. We will report the mean error, standard deviation of difference and root-mean square error from the study results. In addition, we will present a scatter plot (with the identity line and Deming regression line), a Bland-Altman plot [with the 95% limits of agreement (LoA)] and report the repeatability and reproducibility by providing a population mean bias ($\mu 0$), between-subject variance ($\sigma\mu 2$) and within-subject variance ($\sigma 2$) with our final statistical analyses.

Neonatal outcomes will not be collected during this study.

11. Risks to Subjects/NSR Determination

A significant-risk (SR) device study is defined by the United States Food and Drug Administration (https://www.fda.gov/media/75459/download) as one that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject;
- or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A Non-Significant Risk (NSR) device study is one that does not meet the definition for an SR device study. This study poses no significant risks to subjects or the fetus related to participation in the research. The proposed study uses noninvasive devices to measure fetal depth and fetal pulse. The following risks and mitigations explain the justification for the NSR determination:

- *Physical size and construction* -The Investigational device weighs less than 8 ounces. Therefore, incidental bumping or dropping will not pose a maternal or fetal threat, and there are no sharp edges on the device.

- *Electrical safety* - The patient-applied portion of device will be isolated electrically through a USB isolation device. This reduces any possibility of electrical leakage or shock. The patient-applied part of the device is USB powered only, which can provide only 12 Volts.
- *Temperature* - The device poses no thermal risk since any significant heat generated will be by the LEDs. Current has been limited and testing has verified that temperatures to not rise above acceptable limits.
- *Illumination* - The levels of illumination are below the safety thresholds set by IEC 62471 for IR LEDs. This assumes *direct* irradiance into an eye. Since the device will shine the illumination through maternal tissue, which will scatter, absorb, and diffuse the light significantly, the light a fetus's eye will be exposed to is greatly reduced.
- The internal sensor (manufactured by Axcesor)will be provided sterilized..
- Investigators are blinded to study device outputs. No medical decisions are made as a result of the devices placed during this study.

For these reasons, it is the opinion of the Sponsor that this device and study design, including the placement of the sterile internal sensor *after* membrane rupture, pose no significant risk to the mother or fetus. Further, to mitigate any chance of dystocia, the internal sensor will be placed and removed within 6 hours. There is no change to standard of care procedures for fetal heart rate monitoring. The fetal heart rate that will be monitored with the Investigational device will be used for research purposes only. **Results of either the LUMERAH sensor or the internal sensor will not be used to guide or alter patient management.**

Subjects may experience some minor inconveniences and discomfort associated with using the internal sensor (now manufactured by Axcesor) but there are no foreseeable medical risks, discomforts, or hazards associated with its use other than the potential for infection. To mitigate this risk, the Sponsor has planned to use a newly manufactured, sterile internal sensor. Due to the placement of the internal sensor on the cheek of the fetus, it is possible that the baby has a noticeable red mark or bruise on the cheek after birth. The LUMERAH device may cause a temporary warmth and redness on the abdomen where the sensor is placed. Although unlikely, women with extremely sensitive skin could potentially develop a rash at the location of the sensor. There is a small risk of unintentional loss of confidentiality. All efforts will be made to minimize this risk. There are no anticipated emotional, psychological, economic, legal, or social risks to the subjects associated with this study.

12. Potential Benefits to Subjects

There is no direct potential benefit to subjects. However, the study results may provide data necessary to refine the plans for future studies and device development, satisfy the requirements imposed by the U.S. Food and Drug Administration, and provide "ground truth" knowledge of the LUMERAH device. Overall, this study may lead to greater diagnostic capability during gestation to diagnose intrapartum fetal hypoxia and monitor fetal well-being that would benefit the population from which the subjects are recruited, benefit science and humanity in general.

13. Alternatives to Participation

Subjects will receive the standard care per clinical indication regardless of participation in the study. Declining to participate will not affect their clinical care. This is an observational study only, with no impact on standard care. This research device testing will be conducted only in a clinical research setting.

14. Confidentiality

The principal risk of a signed consent document would be the potential harm resulting from a breach of confidentiality. Every precaution will be taken to minimize this. The original signed consent documents will be stored in the research office which will be locked when not attended. Electronic logs will be stored in password protected desktop computers, accessible only to the research team. Data will be stored for 7 years after study is closed out with the IRB office(s).

At any given time, there will be 1 to 3 people from the Sponsor and/or site's research team present to abstract data with the Investigational device. De-identified data will be collected in the database which will be accessible to outside institution team members. Data transferred out of the site will be de-identified data with the study ID number. The key containing the study ID number with the subject information will be accessible to the study team only and will be stored securely on password protected computers. No genetic information will be collected for this study.

15. Adverse Event Reporting

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether considered related or not related to the study treatment.

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongs the post treatment hospitalization
- Results in persistent or significant disability or incapacity
- Causes a congenital anomaly in the offspring of the subject, or
- Is considered an important medical event that jeopardizes the health of the subject or requires surgical intervention to prevent one of the outcomes listed above.

No adverse or serious adverse events are anticipated as this study poses no additional known risks to subjects. Nevertheless, any serious adverse events associated with use of the Investigational device will be submitted to the IRB in writing within 24 hours of learning about the SAE. Reportable new information will be reported to the IRB per the institutional policy.

16. Statistical Considerations

This is an observational, noninvasive study with primary endpoints related to the LUMERAH device correlation with the Nellcor device and internal sensor (manufactured by Axcesor). Raydiant Oximetry met with the FDA on Feb 11, 2020 and suggested that we power our pilot and pivotal studies for specificity, and not sensitivity, because poor specificity of CTG technology is the unmet clinical need in obstetrics. CTG technology has a 29% specificity and the FDA agreed with this approach. Seelbach-Gobel[23] demonstrated that the Nellcor fetal pulse oximetry device had a specificity of 65% for the detection of newborn metabolic acidosis. The incidence of newborn metabolic acidosis has been reported to be 2-4% and the incidence of hypoxic fetuses is 3-4%. Our sample size calculations are based on a significance level of 0.05 (i.e. type 1 error=0.05) with the goal to achieve power of 0.8 and a lower confidence level of 80% to establish a clinical proof of concept. The sample size calculation, under these assumptions, is 48 subjects for this pilot study.

To compare the Nellcor N-400 device output to the LUMERAH output, we are following the FDA guidance document (dated March 4, 2013) for pulse oximeters, where the in-vivo validation set should include at least 200 data points from 10 or more human subjects. Per the FDA recommendation, we will report the root mean square (RMS) error and produce a scatter plot with the identity line and a Deming regression line. In addition, we will report a Bland-Altman plot with the 95% limits of agreement as well as the 95% confidence intervals for the limits of agreement.

Our preclinical data set for algorithm training required approximatively 300 data points from 20 sheep. We expect that a similar amount of human data sets will be required for algorithm training and then another 10 human subjects will be enrolled for prospective algorithm validation of the LUMERAH device. Therefore, the absolute *minimum* required sample size to compare Nellcor N-400 device output to the LUMERAH output is 30 subjects. However, we will calibrate and validate on up to 60 patients to ensure that we can identify hypoxic fetuses. East et al[24] reported that 3.9% of observations with the Nellcor N-400 technology displayed fetal oxygen saturations below 30%. Therefore, enrolling and following 60 subjects allows the opportunity to monitor and study approximately two hypoxic fetuses. We intend to collect up to 60 of these "ground truth" cases with varied oxygenation levels before proceeding to PILOT 2. With the expectation that we will have to consent an additional 50% who may not meet the inclusion/exclusion criteria, the total number consented will be a maximum of 90 subjects.

17. Data Management

Only individuals approved by the Sponsor and who have adequate training in the use of the Investigational device are given authorization of access to perform the measurement and record the data. The data collected will be marked with a study ID number to protect confidentiality of each subject.

Only the research staff will have access to the link between the study ID and the patient's identifying information. The key will be stored in a password-protected document on a restricted access folder on the hospital network. Only the PI/Co-I and research team will have access to this document.

A separate document listing only study ID numbers will be stored on a password-protected document on a restricted access folder on the hospital network. This will contain the subjects' de-identified obstetric and medical history as relevant for the project. Data will be submitted to the sponsor through an electronic, secure database.

18. Study Monitoring

This study will be monitored for data accuracy and adherence to the protocol by the Sponsor's representative and/or a 3rd party qualified monitor. It is expected that there will be frequent attendance of the Sponsor's representative at the study site. Major protocol deviations will be reported to the Sponsor immediately and the IRB at the required reporting intervals.

19. Regulatory Requirements

Due to the non-significant risk determination by the Sponsor, this study is subject to the abbreviated requirements set forth by CFR 21 Part 812.2(b), 21CFR Part 50 (Informed Consent), and 21CFR Part 56

(IRB Review). The manufacturer of the device developed a data collection unit that gathers light that is reflected from in-utero fetuses. It should be noted that as an experimental device, the Investigational device has not been tested at NRTL registered testing facilities. This is common practice during the early stages of medical device development.

20. Personnel Responsibilities

20.1 Principal investigator responsibilities

a) Permit Sponsor/Monitor inspection of facilities and records.
b) Permit inspection of facilities and records by government bodies.
c) Submit protocol and informed consent to IRB and await approval.
d) Submit proposed amendments to protocol and informed consent to IRB and await approval, unless the change reduces the risk to subjects.
e) Obtain informed consent of subjects.
f) Implement study in accordance with protocol.
g) Complete case report forms.
h) Explain deviations from protocol and report to monitor.
i) Submit annual progress reports, final reports, and adverse effect reports to IRB and Sponsor as required by law.
j) Record the receipt, disposition, and return of devices.
k) Retain records for a minimum of two years following study completion (refer to IRB rules).

20.2 Sponsor responsibilities

a) Assure IRB approval of protocol and informed consent is obtained
b) Select and train DSMB and study Monitors as needed
c) Select Sites and Investigators
d) Train Investigators in device use
e) Obtain curriculum vitae and proof of appropriate licensure of Investigators and study staff
f) Control shipment of devices
g) Investigate device-related adverse events
h) Maintain responsibility for data review and analysis
i) Obtain statement of financial disclosure for publication and presentation purposes

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Study Acknowledgement and Confidentiality Statement

The information in this document and future information which will be provided to you contains information that is confidential to Raydiant Oximetry, Inc. (hereinafter referred to as Raydiant) and may not be disclosed without prior written approval of Raydiant, unless such disclosure is required by federal or other laws or regulations. Information that is provided to you by Raydiant may be communicated by you to other persons who have a "need to know" the information in order to facilitate and implement the study in which you are participating. However, such persons must be informed that the information provided is confidential to Raydiant and may not be further disclosed by them.

The signatures of the investigator and the sponsor medical representative below constitute their approval of this protocol and agreement to the confidentiality statement above.

The investigator agrees to supervise all testing of the device and to ensure that requirements for obtaining informed consent are met.

The investigator and sponsor representative agree to:

- conduct the study according to the protocol and approved protocol amendments.
- conduct the study in accordance with the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, and/or the applicable local regulations, whichever provide the greater protection of the individual.

Signature of Investigator	Date
Investigator Name (Print)	
Signature of Sponsor Representative / Title	Date
Sponsor Representative Name (Print)	