P990053

SUMMARY OF SAFETY AND EFFECTIVENESS INFORMATION DATA

Mallinckrodt, Inc.
OxiFirst™ Fetal Oxygen Saturation Monitoring System

I. General Information

Device Generic Name: Fetal Pulse Oximeter

Device Trade Name: OxiFirst™ Fetal Oxygen Saturation Monitoring System

Applicant's Name and Address:

Mallinckrodt, Nellcor Perinatal Business
4280 Hacienda Drive
Pleasanton, CA 94588
USA

Premarket Approval (PMA) Application Number: P990053

Date of Panel Recommendation: January 24, 2000

Date of Notice of Approval to the Applicant: May 12, 2000

II. Indications for use

The OxiFirst™ Fetal Oxygen Saturation Monitoring System continuously monitors intrapartum fetal oxygen saturation ($FSpO_2$). Use of the OxiFirst™ System is indicated **as an adjunct** to fetal heart rate monitoring in the presence of a nonreassuring fetal heart rate pattern. It should only be used after maternal membranes have ruptured and on a singleton fetus in vertex presentation with a gestational age greater than or equal to 36 weeks.

III. Contraindications

Use of the OxiFirst™ Fetal Oxygen Saturation Monitoring System is contraindicated in patients with the following conditions:

- Documented or suspected placenta previa
- Ominous FHR pattern requiring immediate intervention
- Need for immediate delivery (unrelated to FHR pattern), such as active uterine bleeding.

IV. Warnings and Precaution

A listing of Warnings and Precautions can be found in the device labeling.

V. Device Description

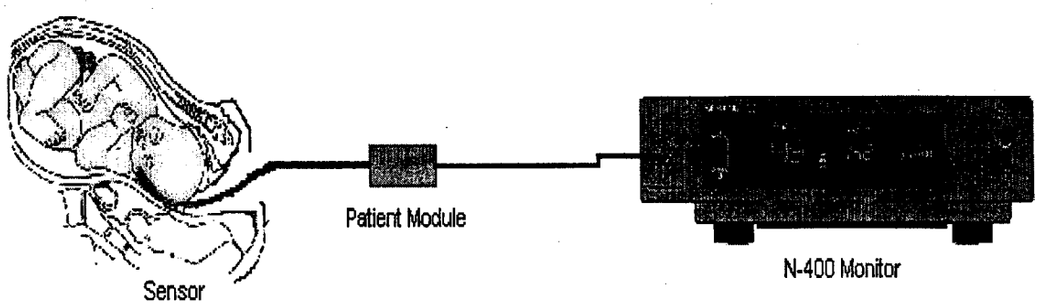
Functional Components: The OxiFirst™ Fetal Oxygen Saturation Monitoring System is a pulse oximetry system used during labor and delivery to measure fetal oxygen saturation ($FSpO_2$). The system consists of a sensor, a patient module, and a microprocessor-controlled monitor. The sensor is inserted transcervically into the mother's uterus and is positioned against the cheek or temple of the fetus. Two light emitting diodes (LEDs) located within the sensor shine light into fetal tissue and back-scattered light is received by an adjacent photodetector. Hardware and software within the monitor process this signal to determine the oxygen saturation and pulse rate of the fetus and assess the quality of the optical signals. The values of fetal oxygen saturation and optical pulse rate are displayed on the monitor's front panel (along with other indicators) and communicated to external equipment via serial and/or analog ports.

The OxiFirst™ Fetal Oxygen Saturation Monitoring System consists of three components:

- OxiFirst™ Fetal Oxygen Sensor, Series FS14,
- Nellcor® Fetal Patient Module, Model $FSpO_2$-PM, and
- Nellcor® Fetal Oxygen Saturation Monitor, Model N-400.

A diagram of the OxiFirst™ System in context is shown below.

Figure 1: Diagram of the OxiFirst™ System components.



Device Properties: Properties of the device such as materials, colors, sizes, shapes, displays, icons, indicators, and packaging have been selected and designed to be relevant to the clinical use of the device, the optimization of the acquired signal, and the determination of fetal oxygen saturation.

Theory and Principles of Operation: The technology used in the OxiFirst™ Fetal Oxygen Saturation Monitoring System, like that of other pulse oximetry

monitors, is based upon two basic principles. The first is that oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) differ in their ability to absorb light according to wavelength. The second is that the volume of arterial blood in tissue (and hence, the light absorption by that blood) changes during the pulsatile flow produced by each cardiac cycle.

Software: In the OxiFirst™ System, software responsibilities are divided between two microprocessors, the Oximetry Processor (OP) and the Communications Processor (CP). The OP is responsible for digitizing the sensor photodetector signal, determining if the sensor is in contact with the fetus, detecting pulsatile activity from the IR and Red plethysmographic waveforms, and computing and displaying saturation, pulse rate and signal quality. The CP is responsible for all serial and analog communication with external devices as well as communicating status information between itself and the OP. In accordance with FDA policy, the highest level of concern in the OxiFirst™ System software was determined to be "Moderate".[1]

Design verification consisted of audits, design reviews, code reviews, and testing at multiple levels to assure that design output matched design input. Design validation consisted primarily of testing to assure that the software is consistent with the intended use of the device.

VI. Alternative Practices and Procedures

Electronic fetal heart rate monitoring is currently the most commonly used method for assessing fetal intrapartum wellbeing during labor. Clinical palpation and auscultation are also used to assess the fetus during labor.

Fetal scalp pH and fetal scalp stimulation are also used as an indirect measure of fetal oxygen levels.

VII. Marketing History

Commercial sale of the Nellcor N-400 Fetal Oxygen Saturation Monitor first occurred in December 1994. Export countries for both revenue and non-revenue products have included the European countries, Canada, Japan, Chile, Egypt, Singapore, Australia, Israel, Saudi Arabia, and South Africa.

OxiFirst™ technology has also been commercially available in a limited number of countries outside of the United States since February 1997 from Corometrics Medical Systems, an OEM customer/partner, and since September 1998 from Agilent, a technology licensee. OxiFirst™ technology is available in the

---

[1] Center for Devices and Radiological Health, Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 29, 1998).

Monitors as a factory configured option or upgrade sold by these partner companies. All multi-parameter monitors sold with integrated OxiFirst™ technology use the FS-14 Series sensors manufactured and sold by Mallinckrodt, Inc.

VIII. Potential Adverse Effects of the Device on Health

Fetal outcomes: The overall incidence of adverse events during the pivotal clinical study in the neonatal control population was 64% and in the test population 70% (p=0.029; controlled for site). When the adverse events are evaluated individually, there was no statistical difference for the most common adverse events. These included respiratory distress, jaundice, hypoglycemia, sepsis, and injury from scalp electrodes, forceps, and vacuum applications. In the test group, there was a statistically significant increase in the incidence of ecchymoses (bruising), 80 patients in the control group and 121 in the test group (p=0.040), with the majority of ecchymoses located on the head. Eleven patients (of the 121) in the test group had bruises or marks that the clinician considered to be probably associated with device use. Almost all of these marks resolved before discharge.

Maternal outcomes: There were no maternal adverse events during the study that were identified as being absolutely associated with device use in the clinical study. Fever was the most common adverse event considered as possibly related to device use, but its onset or any causal relationship to the device could not be explained by the data.

For additional details regarding adverse events observed in the clinical study see Section X, Page 20 of this document.

IX. Summary of Published Literature, Pre-clinical and Clinical Feasibility Studies

Published literature on the fetal pulse oximeter:

Articles on fetal oxygen saturation monitoring, English language Congress abstracts, English abstracts of foreign language articles, and unpublished material submitted to the company has been reviewed and summarized for the period from 1987 through May 26, 1999.

The review of animal studies included: demonstration of the optical equivalence of human and other mammalian hemoglobins at the wavelengths of light used by pulse oximetry, spectral differences between human and other mammalian hemoglobins when using co-oximetry, fetal transmission and reflectance pulse oximetry, defining a critical SaO_2 value (O_2 saturation determined from arterial source), and calibration issues and potential factors affecting fetal pulse oximetry.

The review of human studies included: discussion of the potential effect of fetal hemoglobin, hemoglobin concentration and content, and blood content of tissue; feasibility of fetal pulse oximetry use in the antenatal period and during labor; history of the development of fetal pulse oximetry; determination of the "normal" range of fetal SpO_2 values during labor (O_2 saturation determined from pulse oximeter); examination of the agreement between two identical reflectance sensors on the same fetus; and mothers' experiences of being monitored with fetal pulse oximetry during labor.

Technical issues examined in the literature include the effect of pressure, sensor location, sensor design, and mathematical modeling of wavelength selection. Review articles covering the history of fetal pulse oximetry development were also presented.

Clinical issues included: an examination of fetal pulse oximetry and fetal heart rate monitoring, Doppler velocimetry and near infrared spectroscopy, maternal oxygen administration and maternal positioning, umbilical and scalp blood analysis, the effect of labor (first and second stages), meconium, pulsating arteries, caput succedaneum, various common obstetrical procedures and clinical conditions.

Pre-clinical Testing

Safety Studies: The potential safety issues of optical radiation emitted by the fetal oxygen sensor, temperature rise in fetal tissue induced by contact with the fetal oxygen sensor, and electrical shock hazards were specifically addressed since these hazards could be considered unique to fetal pulse oximetry.

- The fetal sensor utilizes diodes that emit optical radiation. Under double fault conditions, the diodes irradiance at the retina (highly susceptible tissue) are several orders of magnitude below levels shown to cause retinal damage and an order of magnitude below safety guidelines for the adult human. There is also overcurrent circuit protection that limits the current to the diodes and, therefore, the optical radiation output. It was determined through this evaluation, a review of the literature on optical radiation, the experience during the pivotal study and abroad with more than 35,000 uses of the sensor with no reported events, that the device does not present a significant optical radiation risk of injury to fetal tissues.

- Under both normal operating conditions and in an N-400 double-fault condition, the maximum temperature increase at the surface of the FS14 Fetal Sensor complies with the requirements for patient contact surface temperature to be no greater than 41°C, a commonly accepted limit for

thermal safety. This information was supported by theoretical discussions regarding the application of this limit to fetal corneal tissue. It was determined that the device does not pose a significant risk of tissue injury from thermal energy.

- Electrical shock mitigations were incorporated into the N-400 Fetal Oxygen Saturation Monitor. Both the N-400 and the contact electrodes in the FS14 Fetal Sensor were designed to meet current medical/electrical safety standards including high potential test, patient leakage current, and patient auxiliary leakage current. All patient related circuitry is isolated from the Mains Power and every N-400 system is tested in production to applicable safety requirements.

Testing pertinent to Electromagnetic Compatibility (EMC) was conducted in accordance with IEC 60601-1-2 (1993-04). The N-400 Fetal Oxygen Saturation Monitor has been evaluated to the applicable ANSI/UL and CSA Standards.

Biocompatibility Studies: Biocompatibility testing was performed using NAmSA standard protocols under Good Laboratory Practices and in accordance with ISO 10993-1. All exposed materials in the FS14 Fetal Sensor were subjected to in vitro tests for cytotoxicity, hemolysis, and mutagenicity (Ames), and in vivo tests for acute systemic toxicity, sensitization, pyrogenicity, and dermal, vaginal, ocular, and intracutaneous irritation. Subchronic toxicity and hematology and 7-day implantation tests were also conducted, as well as ethylene oxide (EO) residual testing. All testing showed acceptable results per ISO 10993.

The body of the Fetal Sensor is constructed primarily of a polypropylene-based material containing a coloring agent utilizing carbon black. All biocompatibility testing gave negative results. The total amount of carbon black present in the device is below the threshold for risk of cancer to either mother or fetus. Information relating to the colorant material (blue) used in the cable jacket portion of the Fetal Sensor was reviewed and does not contain any material likely to pose a health risk to patients.

Feasibility Studies – Animal and non-IDE Human Studies

Calibration, Verification and Validation Studies: Preliminary studies were performed on fetal sheep to calibrate prototype systems that used standard oximeter sensor LED wavelengths (660 & 940nm) and 10-mm LED-Detector separation. These studies uncovered two key problems with early prototype N-400 systems - at low oxygen saturation (<50%), the calculated SpO_2 value varied with both the anatomical location of the sensor and the force applied to the sensor. Subsequent experiments on lambs studied various prototype sensors and were successful in identifying design features that reduced the force and site sensitivity of the system. These features were incorporated into the FS14B design.

A piglet model was used for final calibration. Table 1 summarizes the System accuracy from this calibration.

Table 1: System accuracy calibration using piglet model.

Source of Data	Oxygen **Saturation Range** ($\%SpO_2$)	Mean Bias (Δ) Of Difference § (SaO_2-SpO_2)	Standard Deviation (σ) Of Difference¶ (SaO_2-SpO_2)
Calibration Study 7 piglets, aged 9 days-6 weeks, weighing 3-20 kg n= 348 data pairs, $r^2 = 0.96$	7% - 100%	0.0%	4.9%
	15% - 40%	+0.6%	4.8%
	41% - 80%	-1.8%	4.5%

An independent laboratory subsequently verified the piglet calibration, confirming Nellcor's calibration. Results from this study were published in a peer-reviewed journal[2]. Table 2. summarizes the results.

Table 2: System accuracy calibration confirmation studies using piglet model.

Source of Data	Oxygen Saturation Range ($\%SpO_2$)	Mean Bias (Δ) Of Difference § (SaO_2-SpO_2)	Standard Deviation (σ) Of Difference ¶ (SaO_2-SpO_2)
Verification Study 4 piglets, aged 6-14 weeks, weighing 7-26 kg n= 247 data pairs	6% - 100	+1.8	5.3
	15% - 40	+4.4	4.4
	41% - 80%	+0.9%	5.1%

To validate that the pig model calibration was appropriate for human use, data from sick infants and children with low oxygen saturation resulting from cyanotic heart disease or severe pulmonary dysfunction were collected. This data was to quantify any differences between the observed N-400 values and concurrent arterial blood SaO_2 values from arterial blood samples obtained as part of routine care.

These results, (Table 3) confirmed that the piglet was an appropriate model, thus creating a link from the animal model to humans.

---

§ Units used in the table are given as saturation percentage points.

¶ Standard deviation is defined as the standard deviation of the differences (SaO_2-SpO_2).

2 Nijland et al (1997): Validation of reflectance pulse oximetry: An evaluation of a new sensor in piglets. J. Clinical Monitoring 13: 43-49.

14

Table 3: System accuracy calibration confirming the piglet model.

Source of Data	Oxygen Saturation Range ($\%SpO_2$)	Mean Bias (Δ) Of Difference § (SaO_2-SpO_2)	Standard Deviation (σ) Of Difference ¶ (SaO_2-SpO_2)
Human Infants & Children 27 infants & children, aged 6 days-22 months, weighing 1.2-14.6 kg n= 72 data pairs	34% - 95%	+1.9% (signed) +4.3 (absolute)	5.4%

System precision was evaluated in the environment of use by a series of human "dual sensor" studies. Two fetal sensors were placed *in utero* on opposite sides of the fetal face. $FSpO_2$ data from both sensors, each connected to separate monitors was collected simultaneously and analyzed to determine the differences between readings from the two sensors. The most common value of the difference between the two sensors was 1%, with slightly more than 75% of all reading differences being less than or equal to 6%. Reproducibility results are shown in Table 4.

Table 4: Reproducibility results for precision.

Source of Data	Oxygen Saturation Range ($\%SpO_2$)	Mean Absolute Difference($\|\Delta\|$) ($\|SpO_{2A}$-$SpO_{2B}\|$)	Standard Deviation (σ)
Intrapartum Reproducibility. 13 human fetuses monitored during labor with two sensors placed on each fetus. Study duration ⇒ 75-470 minutes Total study time >58 hours	20% - 75%	4.8%	4.7%†

From the calibration and dual-sensor precision studies described above, the following clinically relevant conclusions about the accuracy of the N-400 system can be made:

1. In a piglet model with SaO_2 between 15% and 40%, the observed average bias of the N-400 SpO_2 readings was -0.6% (i.e., the SpO_2 readings were on average 0.6% lower than the SaO_2 values in this saturation range). The

§ Units used in the table are given as saturation percentage points.

¶ Standard deviation is defined as the standard deviation of the differences (SaO_2-SpO_2).

† When the readings from two sensors are independent of one another, the standard deviation of a single sensor is given by the product of $1/\sqrt{2}$ and the standard deviation of the difference in readings between the two sensors. The standard deviation of the difference in readings between the two sensors observed in this study was 6.6%, thus the resulting standard deviation that can be expected from a single sensor is $6.6\%/\sqrt{2}$, or 4.7%.

standard deviation of the differences between SaO_2 and SpO_2 in this experiment was 4.8%. (Approximately 67% of all observations can be expected to fall within plus or minus one standard deviation from the mean, and 95 % of all observations can be expected to fall within plus or minus two standard deviations.)

2. In sick infants and children with SaO_2 between 34%-95%, the observed average bias of the N-400 SpO_2 was -1.9% (again, average SpO_2 < average SaO_2). The standard deviation of the differences between SaO_2 and SpO_2 was 5.4%. This series of experiments confirms that the calibration initially performed on animals is appropriate for use on humans.

3. When simultaneously monitoring $FSpO_2$ in utero with two N-400 systems on a single fetus, the standard deviation of the differences between two sensors was observed to be 6.6%; the precision of a single N-400 system may therefore be estimated to be $6.6\%/\sqrt{2} = 4.7\%$.

The implications of these findings for clinical use are as follows:

- $FSpO_2$ values at a single point in time may not provide an exact measure of fetal arterial oxygen saturation. Approximately 95% of the observations can be expected to fall within $\pm$ 10% of the true value.

- When the $FSpO_2$ value is observed through several contractions, the system more accurately reflects the true oxygenation status of the fetus (-0.6% difference between SaO_2 and SpO_2 when tested in animal models).

Nellcor also investigated the impact on device performance from materials commonly found in utero. These materials, which include vernix, hair and blood, could be present at the interface of the sensor optics and fetal skin. Perturbing materials, in various amounts, were placed between the sensor and the skin of a piglet. The only perturbation with a clear impact was a large amount of blond hair. Since it is intended that the sensor be placed on the temple-cheek area of the fetus (below the hairline) the performance of the N-400 should not be affected.

X. Summary Of Pivotal Clinical Studies

The multi-center Randomized Controlled Trial of fetal pulse oximetry was designed to test the hypothesis that:

> In laboring women with ruptured membranes and a fetal heart rate pattern considered non-reassuring in common clinical practice, the use of Nellcor $FSpO_2$ monitoring together with conventional FHR monitoring reduces the rate of Cesarean deliveries performed for non-reassuring fetal status by a clinically meaningful amount while maintaining an acceptable balance between risk and benefit for the mother and fetus.

Objectives: The objectives of the study were:

- To assess whether the addition of the OxiFirst™ System to standard fetal heart rate (FHR) monitoring, within a defined treatment protocol, results in a clinically meaningful reduction of the rate of cesarean deliveries performed for the indication of non-reassuring fetal status (NRFS).

- To assess whether using the OxiFirst™ System as an adjunct to FHR monitoring permits the safe continuation of labor during periods of nonreassuring fetal status and reassuring $FSpO_2$. Use of the system is intended to continue labor during periods of non-reassuring FHR when the $FSpO_2$ is >=30% between contractions. The system is not intended to determine when to interrupt labor.

- To assess the safety of placement, presence and removal of the fetal oxygen sensor.

The study objectives focused on reducing Cesarean deliveries performed for the indication of nonreassuring fetal status, as a surrogate for the specificity of diagnosis for NRFS, without causing injury to mother or baby. The study was not designed to determine the sensitivity of the OxiFirst™ System at detecting fetal acidosis, or to examine other indications and modes of delivery such as assisted vaginal or Cesarean deliveries performed for reasons other than nonreassuring fetal status. In particular, there is no physiologic reason to believe that better intrapartum diagnosis of fetal oxygenation would have any impact on Cesarean delivery for dystocia or other reasons unrelated to fetal oxygenation.

Study Design: A multi-center, three-phase study was conducted to evaluate the safety, effectiveness, and clinical utility of the OxiFirst™ System in women in labor who had fetal heart rate tracings considered non-reassuring (Table 5).

- The first phase (baseline) was an observational study designed to prospectively document the baseline incidence of Cesarean deliveries associated with non-reassuring fetal status at the investigational sites using their standard procedures. No investigational devices were used during the Baseline Phase.

- The second phase was a "Pilot" Study designed to provide instruction and proficiency in the use of the OxiFirst™ System, the clinical management protocol, and the randomization system by investigators and sub-investigators at all study sites.

- The third phase was a Randomized, Controlled Clinical Trial (RCT), designed to test the stated hypothesis. The major maternal outcome measures were the rate of Cesarean deliveries associated with nonreassuring fetal status and maternal safety measures. The major fetal outcome measures were neonatal status at birth and events of the immediate postpartum period.

Table 5: Clinical trial summary

Study Phase	Description
1. Baseline	Observational with no use of the pulse oximeter, and no interventional protocol. Purpose was to obtain an estimate of baseline clinical practice and, screen for sites willing an able to participate, recruit study subjects, agree to the study and management protocols, and produce high quality data
2. Pilot	Interventional, randomized, controlled study to practice and learn the randomization process, the placement and use of the pulse oximeter sensor, and the use of the clinical management protocol
3. Randomized Controlled Trial	Interventional, 2-arm, open (not blinded) controlled trial in which eligible patients were randomized to receive monitoring either with conventional FHR monitoring alone (Control) or with FHR plus $FSpO_2$ (Test). Both groups were managed using the same protocol, with the only difference between the Control and Test patients being the addition of $FSpO_2$ monitoring in the Test group.

The RCT Exclusion Criteria included the following:

- Unwilling or unable to give informed consent according to applicable state laws;
- Participation in other conflicting clinical studies;
- Elective cesarean delivery;
- Gestation < 36 weeks, 0 days;
- Multiple gestation;
- Documented placenta previa;
- Non-vertex fetal presentation;
- Need for immediate delivery (unrelated to FHR pattern), such as active uterine bleeding;
- Ominous FHR pattern which requires immediate intervention; and,
- Active genital herpes or other infection precluding internal monitoring (Maternal fever and group β strep were not exclusions).

Sensor placement criteria for inclusion in the RCT included women in:

Active labor (dilation ≥ 2 cm, vertex -2 station or lower) with ruptured membranes,

AND

A fetus that exhibited fetal heart rate tracings considered nonreassuring as defined by the following Sensor Placement (Inclusion) Criteria:

- Baseline FHR between 100-110 with no accelerations > 15 bpm for more than 15 seconds;
- Baseline FHR < 100 bpm with accelerations;
- Increased variability > 25 bpm for > 30 minutes;

- Mild or moderate variable decelerations for > 30 minutes;
- Late decelerations (at least 1 per 30 minutes);
- Decreased variability < 5 bpm for > 30 minutes;
- Persistent late decelerations (> 50% of contractions) for > 15 minutes;
- Tachycardia > 160 bpm with long term variability < 5 bpm;
- Sinusoidal pattern;
- Variable decelerations with any of the following:
  - a relative drop of ≥ 70 bpm or an absolute drop to ≤ 70 bpm for 60 seconds;
  - persistent slow return to baseline;
  - long term variability < 5 bpm; and,
  - tachycardia > 160 bpm.
- Recurrent prolonged decelerations (2 or more below 70 bpm for > 90 seconds in 15 minutes).

Results from the Pilot Study and RCT were used to assess neonatal and maternal outcomes for FHR monitoring alone or in combination with the use of the OxiFirst™ System. All results were calculated on an intent-to-treat basis with no patients excluded.

Methods: Patients who met the inclusion/exclusion criteria were randomized into either the Test or Control group of the RCT. Control patients were managed with conventional electronic FHR monitoring (FHR Alone) and Test patients were managed with conventional FHR monitoring and the OxiFirst™ System.

During labor, the fetal heart rate tracing was classified as outlined in Table 6. The patterns designated as Class II (a subset of those used as criteria for sensor placement) are those typically associated with increased concern for fetal status. During the RCT, 67% of patients meeting Sensor Placement Criteria developed a Class II pattern.

Table 6: Fetal Heart Rate Classification

FHR Classification	FHR Criteria
I	**Reassuring Group** - Any FHR pattern that did not meet criteria for groups II or III.
II	**Nonreassuring Group**: (Any one of the following for > 15 minutes) 1. Persistent late decelerations (> 50% of contractions) 2. Sinusoidal pattern* 3. Variable decelerations with one or more of the following: • A relative drop of ≥ 70 bpm or an absolute drop to ≤ 70 bpm for > 60 sec.** • Persistent slow return to baseline • Long term variability < 5 bpm*** • Tachycardia > 160 bpm 4. Recurrent prolonged decelerations (2 or more below 70 bpm for > 90 seconds) (Any one of the following for > 60 minutes) 1. Tachycardia > 160 bpm with long term variability < 5 bpm 2. Persistent decreased variability (≤ 5 bpm for > 60 minutes)***
III	**Ominous Group** – Prolonged deceleration to < 70 bpm for > 7 min.

* Sinusoidal pattern were defined as regular oscillations about the baseline, 5–15 bpm in magnitude, with 2 to 5 cycles per minute on an otherwise normal baseline with absent short-term variability.

** Variable decelerations were to be timed from the beginning of the deceleration to the end of the deceleration (i.e., >60-sec. in duration).

*** Decreased variability not otherwise explained by the clinical situation (i.e., narcotic administration)

Patients were managed according to a clinical management protocol that was guided by the FHR Classification alone in the Control group and a combination of the FHR Classification and oxygen saturation data in the Test group. The clinical management protocols for both study groups of the study are described in Table 7.

Table 7: Clinical Management Protocol (Matrix)

FHR Alone	FHR PATTERN GROUP	FHR and Oximeter	
		$FSpO_2$ Not Reassuring*	$FSpO_2$ Reassuring**
Continue labor unless otherwise indicated ***	**CLASS I – REASSURING FHR**	Continue labor unless otherwise indicated ***	Continue labor unless otherwise indicated ***
Evaluate and manage non-reassuring FHR	**Class II - Nonreassuring FHR**	Evaluate and manage non-reassuring FHR	Continue labor unless otherwise indicated ***
Deliver for fetal distress	**Class III - Ominous FHR**	Deliver for fetal distress	Deliver for fetal distress

* $FSpO_2$ Not Reassuring = $FSpO_2$ remains < 30% between contractions, or no value available despite sensor adjustment.

** $FSpO_2$ Reassuring = $FSpO_2$ returns to a value of ≥ 30% between contractions

*** All corrective non-operative measures are allowed as in protocol text (5.3.5.6)

During the RCT, when the action called for in Table 7, was "Evaluate and manage nonreassuring FHR", the clinician was instructed to execute a series of escalating maneuvers intended to improve fetal oxygenation in an attempt to correct the condition(s) which triggered the abnormal state. These maneuvers included:

- Maternal repositioning to achieve uterine displacement
- Hydration
- Correction of hypotension, (causes other then dehydration)
- Tocolytic for hypertonic contractions
- Maternal oxygen
- Amnio-infusion
- Assessment and correction of oxytocin drug dose

In addition, if the fetus was being monitored with the OxiFirst™ System and no $FSpO_2$ value was being displayed, the clinician adjusted the sensor in an attempt to optimize placement.

If these maneuvers corrected the indication for an intervention, the action listed corresponding to the corrected conditions determined the intervention level. Thus, if the protocol matrix (Table 7) indicated "Deliver for fetal distress", but the maneuvers taken by the bedside clinician corrected the FHR and/or $FSpO_2$ such that the indicated action changed to "Continue labor unless otherwise indicated", the appropriate action became to "Continue labor unless otherwise indicated". If the protocol matrix following the corrective maneuvers still indicated "Deliver for Fetal Distress", the fetus was to be delivered as soon as practical by whatever means was judged appropriate by the clinician.

If the protocol matrix following the corrective maneuvers indicated "Evaluate and manage nonreassuring FHR", the clinician used the Evaluation protocol described In Figure 2: Fetal Evaluation Protocol to obtain additional information regarding the fetal well being. In addition, any of the above non-operative measures were allowed when the status was "Continue labor unless otherwise indicated."

Results

Patient Population/Disposition: Four hundred seventy-two women were enrolled in the Baseline Phase of this study at 11 centers. A total of 179 women were enrolled in the Pilot Study at ten centers and the Randomized Controlled Clinical Trial enrolled 1011 women at 9 centers. Patients were followed for three days after delivery, or until hospital discharge.

During the Pilot Study and Randomized Controlled Clinical Trial, 36 patients did not complete the study. Reasons for withdrawal included discovery of pre-existing exclusionary conditions (15 patients), adverse event (reversible fetal bradycardia in one patient), patient request to be withdrawn (14 patients) and

other miscellaneous reasons (six patients). Data from all these patients was included in the analysis.

Figure 2: Fetal Evaluation Protocol

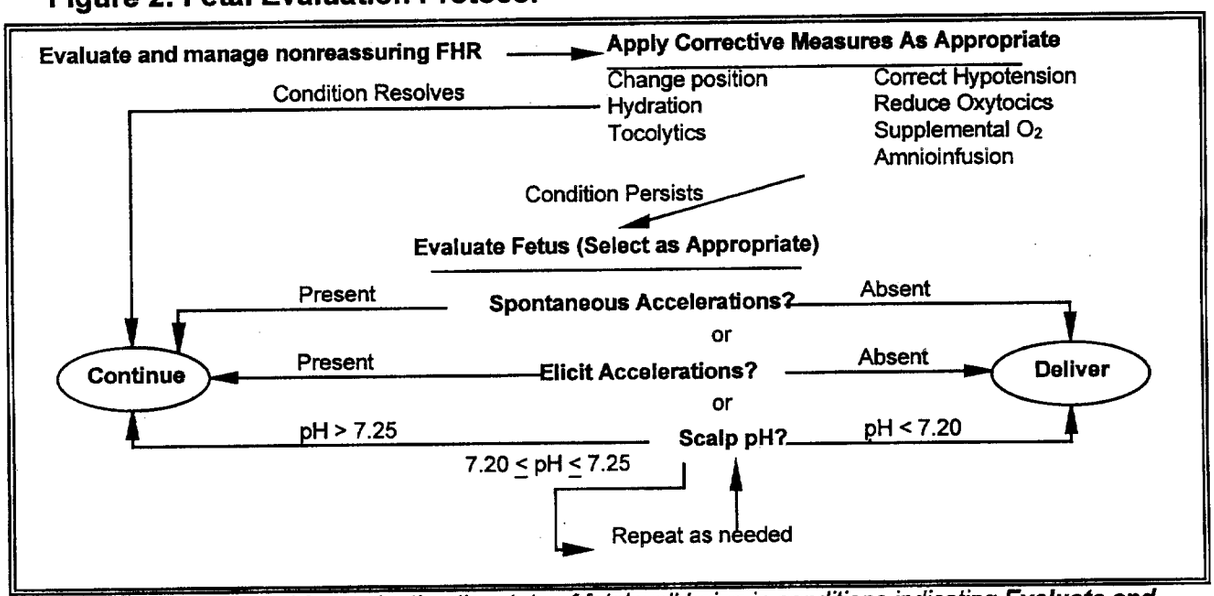


*Figure 2. Protocol for evaluating the state of fetal well being in conditions indicating **Evaluate and Manage Nonreassuring FHR** after steps taken to correct the condition.*

Demographic and Obstetrical History Characteristics: The mean age of the women in the Randomized Study was 27.0 years with no significant differences between the FHR and FHR+FSpO_2 groups. While differences between the overall distribution of maternal race do not reach significance, there were proportionately more Caucasian women in the FHR + FSpO_2 group (65%) than in the FHR alone group (60%), and more African American women in the FHR alone group (14%) than in the FHR + FSpO_2 group (10%). Insurance status, gravidity, parity and number of previous Cesarean deliveries were well matched in the Randomized Phase.

At enrollment for the Baseline, Pilot, and Randomized studies, approximately two-thirds of the women had one or more risk factors for a Cesarean delivery. Similarly, approximately one-third of the fetuses had one or more risk factors. There were no overall statistically significant differences between the treatment groups in maternal or fetal risk factors.

Labor Summary: Variables assessed during labor in the Baseline Phase of the study included spontaneous or artificial rupture of membranes, the status of amniotic fluid, external and/or internal FHR and uterine activity monitoring, cervical dilation at study entry, the number of vaginal examinations during labor, and cervical dilation and station of vertex prior to cesarean delivery.

During the pilot study and randomized controlled trial, all of the labor variables recorded for the baseline study were collected. In addition, cervical dilation at admission, at the time of prostaglandin ripening, at the time of oxytocin administration and at the time of epidural placement were determined retrospectively by chart review. Investigators also recorded results of vaginal examinations after randomization, intrapartum risk factors, type of labor, labor interventions or maneuvers, and whether or not a research nurse was present.

Of the labor summary variables recorded during all three phases of the study, a statistically significant difference (controlled for site) was observed for only one variable. The mean number of vaginal examinations performed during labor was significantly greater during the Randomized Controlled Trial ($p<0.001$) for the FHR-plus-$FSpO_2$ group (9.3) compared to the FHR-only group (8.2). Of the labor summary variables recorded, a statistically significant difference (controlled for site) was observed only during the Randomized Phase. The statistically significant difference was between the FHR-plus-$FSpO_2$ group and the FHR-only group for the mean number of vaginal examinations after randomization ($p<0.001$; 5.4 and 4.4, respectively) and the mean cervical dilation at prostaglandin ripening ($p=0.003$; 0.9 cm and 1.1 cm, respectively).

Device Exposure: Device exposure was determined from the 430 RCT cases in which the sensor was successfully placed and an electronic data recording was available. The total device exposure for these patients was 1371 hours, with a median exposure time of 2-hr 30-min, a minimum exposure of 1 min and a maximum exposure of 16-hr 45-min.

Device Performance: An $FSpO_2$ signal was obtained in 95% of the test subjects where sensor placement was attempted. When a sensor adjustment or replacement was made during a period of no $FSpO_2$ display, the signal was restored in 88% of cases. The median time between the adjustment and re-display was 3 minutes. In 39 cases (8%) an $FSpO_2$ sensor was not placed in women assigned to the FHR+$FSpO_2$ group. Reasons for non-placement of sensors are given in Table 8.

Table 8: Summary of reasons device placement not attempted

OxiFirst™ Fetal Oxygen Saturation Monitoring System Randomized Controlled Trial	
Reasons device placement not attempted*	**FHR+$FSpO_2$ Group N=509**
Imminent delivery	15
Decision to C/S made prior to placement	7
Patient withdrew	7
Not eligible (discovered after patient was enrolled)	4
Physician withdrew	3
Research nurse not available	2
Heart rate ominous	1
Equipment failure	1

*More than one reason was reported in two patients

In the 469 patients in whom an attempt was made to place the sensor, placement was successful in 446 (95%), and unsuccessful in 23 (5%) (Table 9). Data from all women in whom sensor placement was either not attempted or was unsuccessful are included in the analysis.

Table 9: Summary of reasons for unsuccessful sensor placement

OxiFirst™ Fetal Oxygen Saturation Monitoring System Pilot Study +Randomized Controlled Trial	
Reasons for unsuccessful sensor placement	**FHR + $FSpO_2$ N=509**
Difficult / other	10
Imminent delivery	5
Advanced Dilation	4
Bradycardia	1
High station / not eligible	1
Vernix	1
Decision to deliver by Cesarean prior to sensor readings available	1

Safety

Safety analyses included the status of the mother (postpartum maternal fever, postpartum hemorrhage, uterine injury, placental trauma, and length of stay), and newborn at birth, (Apgar scores, neonatal death, the need for transfer to the NICU, arterial and venous cord blood gases, injury to the newborn, and neonatal neurological sequelae). For all variables, comparisons were made between patients in the baseline phase and patients in both **randomized phases** (pilot and pivotal randomized controlled trials combined) whose labor was managed by FHR alone and patients whose labor was managed with FHR combined with the N-400.

Deaths: There were no maternal deaths reported in the clinical trial. In the **baseline phase** there was one neonatal death diagnosed as asphyxia secondary to uterine rupture, hypoxic encephalopathy, and generalized seizures. There were 5 neonatal deaths during the **randomized phases** of the study, none within 24-hours of birth and none considered by the investigators to be related to the study device or the study protocols. Complex congenital heart defects accounted for the two deaths in the Control group and two deaths in the test group. The 3rd death in the FHR+$FSpO_2$ group was the result of post-birth asphyxia secondary to an unrecognized tension pneumothorax rather than any intrapartum event.

Maternal: In the **baseline phase** of the study, 394 women (86%) received routine postpartum care and 64 (14%) required non-routine care. Of the women in the FHR-alone group of the **randomized phases**, 495 women (90%) received routine postpartum care and 58 (10%) required non-routine care. Similarly, in the FHR+FSpO2 group of the **randomized phases**, 575 women (90%) received routine postpartum care and 62 (10%) required non-routine care

In the **baseline phase**, eight maternal patients (2%) required blood transfusions, four patients (1%) required surgical intervention (2 D&C's one cystotomy repair and 1 exploratory laparotomy), and 16 patients (3%) required a pharmacological agent (other than oxytocin) to control hemorrhage. Twenty-two patients (5%) experienced postpartum fever, and three patients (1%) experienced a uterine injury. In the FHR-alone group of the **randomized phases**, three patients (0.5%) required blood transfusions, one patient (0.2%) required a surgical intervention (D&C), and 17 patients (3%) required a pharmacological agent (other than oxytocin) to control hemorrhage. Sixteen patients (3%) experienced postpartum fever and one patient (0.1%) experienced a uterine injury. Similarly, in the FHR+FSpO2 group in the **randomized phases**, one patient (0.5%) required a blood transfusion, five patients (1.0%) required surgical intervention (2 D&C's, one vaginal repair, one cervical repair and one hemolytic anemia coded as a surgical intervention), and 14 patients (2%) required a pharmacological agent (other than oxytocin) to control hemorrhage. Twenty-two patients (3%) experienced postpartum fever and no patients (0%) experienced a uterine injury.

The mean length of stay for the mothers was 3.3 days in the **baseline phase** of the study, with a minimum stay of 2.0 days and a maximum stay of 9.0 days. Four hundred seventy-one of the mothers (99%) were discharged home, and one mother was transferred to another hospital. The mean length of stay for mothers in the FHR-alone group of the **randomized phases** was 3.5 days (range 1 to 13 days) and in the FHR+FSpO$_2$ group was 3.6 days (range: 2 to 19 days). All mothers were discharged home.

The various measures of the maternal partal conditions and interventions are presented in Table 10.

Table 10: Maternal Partal Conditions and Interventions.

Maternal Complications [counts (%) or values]	**Baseline N=472**	**Pilot/RCT FHR N=552**	**Pilot/RCT FHR+FSpO$_2$ N=638**	**Chi Square p-value**
Non-routine post-partum/post-cesarean care*:	64 14%	58 11%	62 10%	NS
Post-partum hemorrhage requiring:				
• Blood transfusion	8 2%	3 1%	1 0%	0.009
• Surgical intervention	4 1%	1 0%	5 1%	NS
• Pharmacologic agent other than oxytocin	16 3%	17 3%	14 2%	NS
Post-partum fever	22 5%	16 3%	22 3%	NS
Uterine injury	3 1%	1 0%	0 0%	NS
Maternal Length of Stay in days (mean)	3.3	3.5	3.6	NS

*More than one condition or intervention may be reported in patients.

Neonates: Apgar scores assessed neonates on heart rate, respiratory effort, muscle tone, reflex irritability, and color of the body and extremities on a scale of zero to 10. Median Apgar scores for the 472 neonates in the **baseline phase** were 8 and 9 at one and five minutes, respectively. As in the baseline phase, the median Apgar scores in both the FHR and the FHR+FSpO$_2$ groups in the **randomized phases** of the study were 8 and 9 at one and five minutes respectively. There were no statistically significant differences in the median one or five-minute Apgar scores between the **baseline and randomized phases** of the trial.

Table 11: One and five-minute Apgar scores.

1-Minute Apgar	Baseline		Pilot/RCT-FHR		Pilot/RCT-FSpO$_2$	
Score	Frequency	Percent	Frequency	Percent	Frequency	Percent
0	1	0.2%	0	0.0%	0	0.0%
1	3	0.6%	7	1.3%	9	1.4%
2	4	0.8%	10	1.8%	10	1.6%
3	9	1.9%	14	2.5%	13	2.0%
4	8	1.7%	7	1.3%	20	3.1%
5	10	2.1%	21	3.8%	23	3.6%
6	25	5.3%	25	4.5%	37	5.8%
7	47	10.0%	65	11.8%	89	13.9%
8	226	47.9%	243	44.0%	263	41.2%
9	138	29.2%	157	28.4%	172	27.0%
10	1	0.2%	2	0.4%	1	0.2%
Missing	0	0.0%	1	0.2%	1	0.2%
Total	472	100.0%	552	100.0%	638	100.0%

5-Minute Apgar	Baseline		Pilot/RCT-FHR		Pilot/RCT-FSpO$_2$	
Score	Frequency	Percent	Frequency	Percent	Frequency	Percent
0	1	0.2%	0	0.0%	0	0.0%
1	0	0.0%	0	0.0%	0	0.0%
2	0	0.0%	0	0.0%	0	0.0%
3	2	0.4%	0	0.0%	1	0.2%
4	1	0.2%	2	0.4%	2	0.3%
5	2	0.4%	4	0.7%	4	0.6%
6	3	0.6%	12	2.2%	7	1.1%
7	9	1.9%	7	1.3%	33	5.2%
8	52	11.0%	70	12.7%	77	12.1%
9	390	82.6%	446	80.8%	498	78.1%
10	11	2.3%	11	2.0%	16	2.5%
Missing	1	0.2%	0	0.0%	0	0.0%
Total	472	100.0%	552	100.0%	638	100.0%

Overall, 433 (92%) neonates in the **baseline phase** required some form of resuscitation, with oral or pharyngeal suctioning being the most prevalent (376 neonates, 80%). During the **randomized phases**, in the FHR group 529 neonates (96%) required some form of resuscitation, with oral and pharyngeal suctioning and supplemental oxygen administration being the most prevalent. Similarly, in the FHR+FSpO_2 group 619 neonates (97%) required some form of resuscitation with oral and pharyngeal suctioning and supplemental oxygen administration again being the most prevalent.

In the **baseline phase** of the study, a total of 49 neonates (10%) required transfer to the Neonatal Intensive Care Unit (NICU), 18 neonates (4%) experienced some physical injury, and three neonates (1%) exhibited neurological sequelae. During the **randomized phases** in the FHR-alone group, a total of 79 neonates (14%) required transfer to the NICU and 11 (2%) experienced some physical injury. Similarly, in the FHR+FSpO_2 group a total of 104 neonates (16%) required transfer to the NICU and 18 (3%) experienced some physical injury. In the FHR+FSpO_2 group two neonates (0.2%) exhibited neurological sequelae. In one case (transient facial paralysis secondary to forceps injury), the study investigator classified the event as having an uncertain relationship to the study device. In the other case (intraparenchymal cranial hemorrhage), the study investigator classified the event as having no relationship to the study device.

The mean length of stay for the neonates in the **baseline phase** of the study was 3.1 days, with a range of 1.0 to 22 days. Four hundred sixty-eight of the neonates (99%) were discharged home, three neonates (1%) were transferred to another hospital, and one neonate (0.2%) expired. The mean length of stay for neonates in the FHR-alone group in the **randomized phases** was 3.7 days (range 1 to 61 days) and in the FHR+FSpO_2 group was 3.6 days (range: 1 to 25 days). In FHR group of the **randomized phases**, 548 of the neonates (99%) were discharged home and four neonates (1%) were transferred to another hospital. In the FHR+FSpO_2 group, 631 of the neonates (99%) were discharged home, four neonates (0.6%) were transferred to another hospital, two neonates (0.3%) expired prior to hospital discharge and the disposition of one neonate is unknown.

Details of the various measures of immediate neonatal condition are presented in Table 12.

Table 12: Immediate Neonatal Condition.

Neonatal Condition (counts or value)		Baseline (n=472)		Pilot/RCT FHR (n=552)		Pilot/RCT $FSpO_2$ (n=638)		Chi Square p-value
Neonatal death (none within 24 hours of birth)		1	0%	2	0%	3	0%	NS
Apgar @ 1 minute	<4	17	4%	31	6%	32	5%	NS
Apgar @ 5 minute	<7	9	3%	18	3%	14	2%	NS
Cord arterial pH	<7.10	20	4%	27	5%	32	5%	NS
	<7.05	9	2%	11	2%	9	1%	NS
	<7.00	4	1%	4	1%	3	0%	NS
Cord arterial Base Excess	≤ -10 mEq/L	24	5%	34	6%	35	5%	NS
	≤ -12 mEq/L	12	3%	13	2%	13	2%	NS
	≤ -14 mEq/L	5	1%	8	1%	4	1%	NS
	≤ -16 mEq/L	4	1%	6	1%	0	0%	0.04
Resuscitation: bag & mask ventilation		53	11%	66	12%	91	14%	NS
Resuscitation: tracheal intubation & ventilation		12	3%	15	3%	13	2%	NS
NICU admission		49	10%	79	14%	104	16%	NS
Neonatal skin, eye, or ear injuries		0	0%	0	0%	0	0%	-
Transient skin marks - probably associated with sensor use		N/A		N/A		11	2%	
Neonatal Length of Stay in days (mean)		30.1		3.3		3.4		NS

Adverse events: All patients enrolled in all phases of the study and their neonates were included in the safety evaluations.

Maternal: The most frequently reported maternal adverse events included fever, headache, mucus membrane disorder, anemia, and perinatal disorder. Although distributed between both the body-as-a-whole body system and the urogenital body system, the category of mucus membrane disorder included only the adverse events of amnionitis, chorionitis, endometritis and chorioamnionitis. For mothers, there were no statistically significant differences in the occurrence of any specific adverse event between the **baseline and randomized phases** or between the test and control groups.

Table 13: The incidence of adverse events reported from 3% or more of mothers.

	Baseline Phase	Pilot Study		Randomized Controlled Trial	
Body System N (%) Adverse event	**FHR N=472**	**FHR N=50**	**FHR + $FSpO_2$ N=129**	**FHR N=502**	**FHR + $FSpO_2$ N=509**
Body as a Whole					
Fever	34 (7.2)	6 (12.0)	8 (6.2)	40 (8.0)	48 (9.4)
Headache	0	4 (8.0)	0	4 (0.8)	5 (1.0)
Mucus membrane disorder	1 (0.2)	1 (2.0)	14 (10.9)	22 (4.4)	33 (6.5)
Abdominal pain	14 (3.0)	0	2 (1.6)	4 (0.8)	2 (0.4)
Neck pain	0	2 (4.0)	0	1 (0.2)	0
Pelvic pain	0	2 (4.0)	6 (4.7)	4 (0.8)	1 (0.2)
Perinatal disorder	1 (0.2)	3 (6.0)	3 (2.3)	5 (1.0)	5 (1.0)
Hemic/Lymphatic					
Anemia	8 (1.7)	2 (4.0)	9 (7.0)	12 (2.4)	7 (1.4)
Nervous System					
Paresthesia	15 (3.2)	0	1 (0.8)	2 (0.4)	0
Urogenital System					
Endometrial disorder	5 (1.1)	0	3 (2.3)	16 (3.2)	16 (3.1)
Postpartum hemorrhage	14 (3.0)	1 (2.0)	4 (3.1)	15 (3.0)	9 (1.8)
Mucus membrane disorder	16 (3.4)	0	0	0	0
Urinary retention	6 (1.3)	1 (2.0)	6 (4.7)	18 (3.6)	16 (3.1)
Urinary tract disorder	0	2 (4.0)	0	0	0

Neonates: The most frequently reported neonatal adverse events included ecchymosis, accidental injury, jaundice, perinatal disorder, and dyspnea. Included in the category of "perinatal disorder" were temperature instability and symptoms of respiratory distress.

For the neonatal population, there was no statistical difference in the adverse event rates of respiratory distress or sepsis. There was a significantly higher rate of ecchymoses (bruising) ($p=0.02$) observed in the FHR+$FSpO_2$ group of the **randomized phases** (121, 19%) compared to the **baseline phase** (63, 13%) and the FHR-alone groups of the **randomized phases** (80, 15%).

Overall the incidence of adverse events in the neonatal population was higher ($p=0.04$) in the FHR+$FSpO_2$ group of the **randomized phases** (450, 70%) compared to both **baseline** (311, 66%) and the FHR-alone groups of the **randomized phases** (352, 64%). This higher rate is due to the observed higher rate of ecchymoses. Excluding ecchymoses, there are no significant differences between adverse event rates in the baseline, FHR-alone and FHR+$FSpO_2$ groups of the pilot study and the randomized controlled clinical trial.

Table 14: The incidence of adverse events reported from 3% or more of neonates.

Body System N (%) Adverse event	Baseline Phase	Pilot Study		Randomized Controlled Trial	
	FHR N=472	FHR N=50	FHR + $FSpO_2$ N=129	FHR N=502	FHR + $FSpO_2$ N=509
Body as a Whole					
Congenital anomaly	7 (1.5)	1 (2.0)	4 (3.1)	5 (1.0)	2 (0.4)
Facial edema	8 (1.7)	0	4 (3.1)	8 (1.6)	8 (1.6)
Hematoma[1]	43 (9.1)	0	0	0	0
Hypothermia	7 (1.5)	1 (2.0)	4 (3.1)	21 (4.2)	11 (2.2)
Accidental injury	63 (13.3)	5 (10.0)	21 (16.3)	85 (16.9)	83 (16.3)
Perinatal disorder	103 (21.8)	9 (18.0)	24 (18.6)	55 (11.0)	50 (9.8)
Sepsis	13 (2.8)	3 (6.0)	12 (9.3)	21 (4.2)	26 (5.1)
Cardiovascular System					
Vascular anomaly	7 (1.5)	2 (4.0)	2 (1.6)	2 (0.4)	2 (0.4)
Cardiovascular disorder	21 (4.4)	2 (4.0)	10 (7.8)	20 (4.0)	28 (5.5)
Hematoma	2 (0.4)	2 (4.0)	12 (9.3)	31 (6.2)	35 (6.9)
Digestive System					
Jaundice	0	1 (2.0)	5 (3.8)	59 (11.8)	58 (11.4)
Hemic/Lymphatic					
Ecchymosis	63 (13.3)	6 (12.0)	21 (16.3)	74 (14.7)	100 (19.6)
Neonatal jaundice	54 (11.4)	5 (10.0)	10 (7.8)	18 (3.6)	21 (4.1)
Petechia	10 (2.1)	2 (4.0)	4 (3.1)	14 (2.8)	12 (2.4)
Metabolic/Nutritional					
Bilirubinemia	9 (1.9)	3 (6.0)	7 (5.4)	11 (2.2)	16 (3.1)
Cyanosis	1 (0.2)	0	6 (4.7)	11 (2.2)	14 (2.8)
Hypoglycemia	7 (1.5)	2 (4.0)	2 (1.6)	26 (5.2)	40 (7.9)
Musculoskeletal System					
Congenital anomaly	6 (1.3)	2 (4.0)	1 (0.8)	1 (0.2)	1 (0.2)
Respiratory System					
Dyspnea	16 (3.4)	2 (4.0)	8 (6.2)	45 (9.0)	54 (10.6)
Hyperventilation	15 (3.2)	0	3 (2.3)	7 (1.4)	17 (3.3)
Respiratory disorder	18 (3.8)	0	4 (3.1)	7 (1.4)	7 (1.4)
Skin/Appendages					
Rash	13 (2.8)	2 (4.0)	8 (6.2)	6 (1.2)	9 (1.8)
Skin disorder	6 (1.3)	0	4 (3.1)	1 (0.2)	1 (0.2)
Skin discoloration	18 (3.8)	3 (6.0)	7 (5.4)	1 (0.2)	2 (0.4)
Special Senses					
Conjunctivitis	3 (0.6)	2 (4.0)	3 (2.3)	7 (1.4)	9 (1.8)
Urogenital System					
Urogenital anomaly	0	2 (4.0)	4 (3.1)	7 (1.4)	3 (0.6)

Serious adverse events: For this study, a serious adverse event was defined as an adverse event that required major medical or surgical treatment outside the realm of routine obstetrical/neonatal care, such as: excessive hemorrhage, uterine perforation, or other serious injury to mother, fetus, or neonate.

Maternal: Thirteen mothers (2.8%) experienced serious adverse events in the **baseline phase**, while in the **randomized phases**, 37 mothers (3%)

experienced serious adverse events: 22 patients in the FHR-alone group (4%) and 15 in the FHR+FSpO$_2$ group (2%). The most frequently reported serious events were postpartum hemorrhage, endometrial disorder, and fever.

Table 15: Incidence of Maternal Serious Adverse Events

	Baseline Phase	Pilot Study		Randomized Controlled Trial	
Body System N (%) Adverse event	FHR N=472	FHR N=50	FHR + FSpO$_2$ N=129	FHR N=502	FHR + FSpO$_2$ N=509
Body as a Whole					
Cellulitis	0	0	0	1 (0.2)	1 (0.2)
Fever	3 (0.6)	0	0	1 (0.2)	3 (0.6)
Headache	0	0	0	1 (0.2)	1 (0.2)
Infection	0	0	0	1 (0.2)	0
Abdominal pain	0	0	0	1 (0.2)	0
Back pain	0	0	0	1 (0.2)	0
Perinatal disorder	0	1 (2.0)	0	0	0
Sepsis	1 (0.2)	0	0	0	0
Cardiovascular System					
Hemorrhage	1 (0.2)	0	0	0	0
Syncope	0	1 (2.0)	0	0	0
Thrombophlebitis	0	0	0	1 (0.2)	1 (0.2)
Digestive System					
Colitis	1 (0.2)	0	0	0	0
Hemic/Lymphatic					
Anemia	1 (0.2)	0	0	1 (0.2)	0
Leukocytosis	1 (0.2)	0	0	0	0
Thrombocytopenia	1 (0.2)	0	0	0	0
Metabolic/Nutritional					
Healing abnormal	0	0	1 (0.8)	0	1 (0.2)
Nervous System					
Paresthesia	1 (0.2)	0	0	0	0
Respiratory System					
Pneumonia	0	0	0	0	1 (0.2)
Urogenital System					
Endometrial disorder	0	0	0	6 (1.2)	6 (1.2)
Hemorrhage	1 (0.2)	0	0	0	0
Vaginal hemorrhage	1 (0.2)	0	0	0	0
Hemorrhage of pregnancy	0	0	0	0	1 (0.2)
Mucus membrane disorder	1 (0.2)	0	0	0	0
Postpartum hemorrhage	4 (0.8)	0	1 (0.8)	3 (0.6)	2 (0.4)
Placental disorder	0	0	0	2 (0.4)	0
Accidental injury	1 (0.2)	0	0	0	0
Urinary tract disorder	0	1 (2.0)	0	0	0
Urinary tract infection	0	0	0	1 (0.2)	0
Ruptured uterus	2 (0.4)	0	0	2 (0.4)	1 (0.2)

Neonates: Thirty neonates (6%) experienced at least one serious adverse event during the **baseline phase**, while in the **randomized phases**, 163 neonates (14%) experienced serious adverse events: 71 patients in the FHR-alone group (13%) and 92 in the FHR+FSpO$_2$ group (14%). The most frequently reported neonatal serious adverse events included dyspnea, sepsis, hypoglycemia, and

perinatal disorder. Details of the incidences of neonatal serious adverse events are presented table in Table 16.

Table 16: Incidence of Neonatal Serious Adverse Events

	Baseline Phase	Pilot Study		Randomized Controlled Trial	
Body System N (%) Adverse event	**FHR** **N=472**	**FHR** **N=50**	**FHR + $FSpO_2$** **N=129**	**FHR** **N=502**	**FHR + $FSpO_2$** **N=509**
Body as a Whole					
Congenital anomaly	0	0	0	0	1 (0.2)
Fetal disorder	1 (0.2)	1 (2.0)	0	2 (0.4)	0
Fever	0	0	0	1 (0.2)	3 (0.6)
Hypothermia	0	0	0	1 (0.2)	0
Infection	2 (0.4)	0	0	1 (0.2)	0
Accidental injury	1 (0.2)	0	0	0	1 (0.2)
Mucus membrane disorder	0	0	0	1 (0.2)	0
Perinatal disorder	4 (0.8)	0	0	5 (1.0)	9 (1.8)
Sepsis	5 (1.1)	1 (2.0)	3 (2.3)	14 (2.8)	16 (3.1)
Withdrawal syndrome	0	0	0	0	1 (0.2)
Cardiovascular System					
Heart malformation	2 (0.4)	0	1 (0.8)	1 (0.2)	2 (0.4)
Bradycardia	1 (0.2)	0	0	1 (0.2)	2 (0.4)
Cardiovascular disorder	1 (0.2)	0	0	3 (0.6)	2 (0.4)
Hemorrhage	0	0	0	1 (0.2)	1 (0.2)
Pallor	1 (0.2)	0	1 (0.8)	2 (0.4)	0
Shock	1 (0.2)	0	0	0	0
Aortic stenosis	0	0	0	1 (0.2)	1 (0.2)
Tetralogy of Fallot	0	0	0	0	1 (0.2)
Vascular disorder	0	0	0	1 (0.2)	0
Digestive System					
Gastrointestinal disorder	0	0	1 (0.8)	0	0
Jaundice	0	0	0	0	1 (0.2)
Hemic/Lymphatic					
Anemia	0	0	0	2 (0.4)	1 (0.2)
Cyanosis	1 (0.2)	0	0	0	0
Hypovolemia	0	0	0	2 (0.4)	3 (0.6)
Neonatal jaundice	2 (0.4)	0	0	0	0
Polycythemia	0	0	0	0	2 (0.4)
Thrombocytopenia	0	0	0	0	1 (0.2)
Metabolic/Nutritional					
Acidosis	0	0	0	2 (0.4)	1 (0.2)
Bilirubinemia	1 (0.2)	0	0	2 (0.4)	2 (0.4)
Cyanosis	0	0	2 (1.6)	1 (0.2)	1 (0.2)
Electrolyte abnormality	1 (0.2)	0	0	0	0
Hypoglycemia	1 (0.2)	0	0	9 (1.8)	8 (1.6)
Musculoskeletal System					
Myopathy	0	0	0	0	1 (0.2)
Nervous System					
Convulsion	2 (0.4)	0	0	1 (0.2)	0
Hypotonia	0	0	0	3 (0.6)	1 (0.2)
Meningitis	1 (0.2)	0	0	0	2 (0.4)
Paralysis	1 (0.2)	0	0	2 (0.4)	0
Facial paralysis	0	0	0	0	1 (0.2)

Table 16: Incidence of Neonatal Serious Adverse Events continues on the next page.

Table 16: Incidence of Neonatal Serious Adverse Events (continued).

Body System N (%) Adverse event	Baseline Phase	Pilot Study		Randomized Controlled Trial	
	FHR N=472	FHR N=50	FHR + $FSpO_2$ N=129	FHR N=502	FHR + $FSpO_2$ N=509
Respiratory System					
Apnea	1 (0.2)	0	0	3 (0.6)	1 (0.2)
Asphyxia	1 (0.2)	0	0	0	0
Bronchitis	0	0	0	0	1 (0.2)
Dyspnea	6 (1.3)	1 (2.0)	2 (1.6)	20 (4.0)	24 (4.7)
Hyperventilation	2 (0.4)	0	0	0	6 (1.2)
Hypoventilation	2 (0.4)	0	0	3 (0.6)	1 (0.2)
Hypoxia	0	0	0	2 (0.4)	0
Lung disorder	0	0	0	1 (0.2)	0
Pneumonia	0	0	0	3 (0.6)	1 (0.2)
Pneumothorax	0	0	1 (0.8)	2 (0.4)	3 (0.6)
Respiratory disorder	3 (0.6)	0	3 (2.3)	7 (1.4)	2 (0.4)
Skin and Appendages					
Skin Disorder	0	0	0	0	1 (0.2)
Urogenital System					
Premature birth	0	0	0	1 (0.2)	0
Kidney failure	1 (0.2)	0	0	0	0
Penis disorder	1 (0.2)	0	0	0	0

Effectiveness

The RCT yielded the distribution of delivery routes in the FHR Alone (Control) and FHR+$FSpO_2$ (Test) groups shown in Table 17.

Table 17. Distribution of delivery routes in Control and Test groups in RCT.

Delivery Route: N (% of total in group)	FHR alone N=502	FHR+$FSpO_2$ N=509	Chi Square P
Spontaneous vaginal delivery (SVD)	255 (51%)	242 (48%)	0.50
Assisted vaginal delivery (AVD)	117 (23%)	120 (24%)	
Cesarean delivery, all indications (CD)	130 (26%)	147 (29%)	

The distribution of delivery mode (spontaneous vaginal, assisted vaginal, or cesarean section) was not significantly different between Test and Control groups (Chi-square P = 0.50). There was no statistically significant change in the overall rate of cesarean deliveries (26% *vs.* 29%).

77

Table 18. Distribution by indication for cesarean delivery in Test and Control groups.

Delivery Mode: N (% of total in Control and Test groups)	FHR alone N=502	FHR+FSpO$_2$ N=509	Fisher's exact p–value
Non-reassuring fetal status, single indication (NRFS)	51 (10%)	23 (5%)	0.0006
Fetal intolerance to labor with dystocia (FIL/DYS)	35 (7%)	27 (5%)	Not significant
Dystocia, single indication (DYS)	43 (9%)	94 (18%)	< 0.0001
Other	1 (0%)	3 (1%)	Not significant
Total cesarean deliveries	130	147	

The Chi-square p – value for this 4x2 table (Table 18) distribution is $p < 0.0001$. The cesarean delivery rate ascribed to NRFS was significantly reduced (51/502 vs. 23/509, Fisher's exact $p = 0.0006$) while the cesarean delivery rate ascribed to dystocia was significantly increased (43/502 vs. 94/509, Fisher's exact $p < 0.0001$). The cesarean delivery rate for the indication for cesarean delivery for FIL/DYS was unchanged. Thus, the overall cesarean delivery rate was unchanged, with the decrease in cesarean sections for NRFS offset by an increase in cesarean sections for dystocia.

Cesarean Delivery Rate for Dystocia: Since the increase in Cesarean deliveries for dystocia was an unexpected outcome, several post hoc analyses were performed in an attempt to identify possible causal mechanisms for the observation.

- An examination of the duration of labor in the Control and Test groups for evidence of slowing associated with sensor use or group assignment found that patients delivered by cesarean for dystocia, in both Control and Test groups, labored longer than patients delivered by cesarean for NRFS, as expected. In patients delivered by spontaneous vaginal delivery, assisted vaginal delivery, cesarean delivery for NRFS, cesarean for FIL/DYS, or cesarean for DYSTOCIA, there is no evidence of slowing of labor or delaying delivery attendant to the use of the FSpO$_2$ sensor or protocol management. It is therefore concluded that the sensor does not slow labor or cause dystocia.

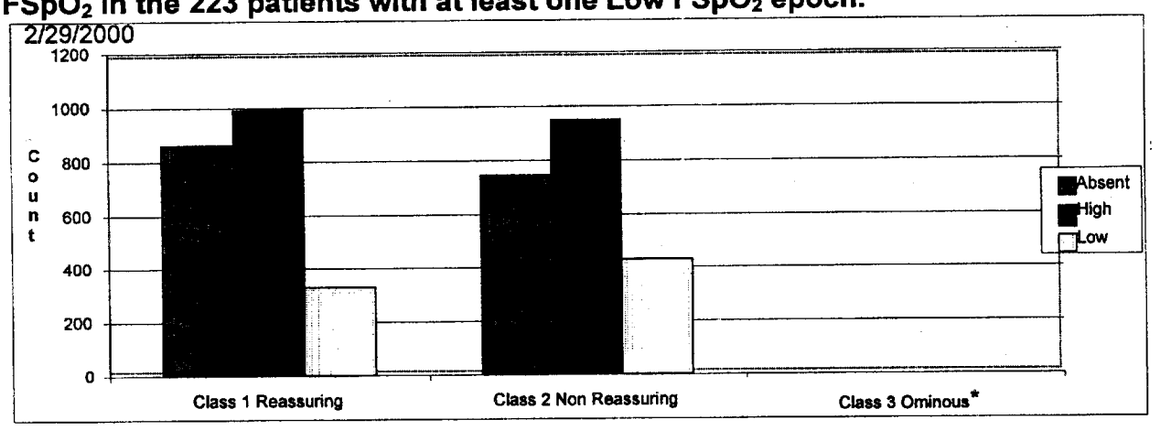
- Another possible explanation for the increase in Cesareans for dystocia is bias – either in patient selection or clinician behavior. Multiple analyses were performed looking for evidence that significant bias exists, but none was discovered. However, it must be acknowledged that this post hoc search for bias is limited by the available data and thus the question cannot be conclusively answered with the data at hand.

Post hoc observations of clinical behavior surrounding periods of $FSpO_2$ < 30%: This analysis was done to more fully understand the clinical study results, provide the clinician an interpretation for $FSpO_2$ values that fall below 30% and if possible, refine the clinical management matrix. In this analysis, the entire monitoring period was divided into sequential epochs; each defined as the time that the $FSpO_2$ value was either High (>=30%), Low (<30%) or Absent (no signal displayed) between contractions. The start of the first epoch was when the signal was initially obtained, reading High or Low. Subsequent epochs (High, Low or Absent) began when the $FSpO_2$ state between contractions changed. The following results and observations are from the 223 patients with at least one period of Low $FSpO_2$.

- The typical number of Low $FSpO_2$ epochs was one or two per patient. The typical (median) duration of Low $FSpO_2$ epochs was 5 minutes. The typical (median) duration of absent signal was also 8 minutes. In contrast, the typical (median) duration of high $FSpO_2$ epochs was 21 minutes. Thus, most of the time, the $FSpO_2$ is above 30% (reassuring) with relatively short signal absences. The majority of the Low $FSpO_2$ epochs (69%) recovered to a High $FSpO_2$ state, 27% were ended by a loss of signal, and 3% were followed by delivery of the fetus.

FHR patterns were not coupled to $FSpO_2$ status. Class 1 Reassuring FHR patterns and the various types of Class 2 Non-Reassuring FHR patterns were distributed across the Absent, High, and Low $FSpO_2$ epochs in roughly the same proportion as the number of Absent, High, and Low $FSpO_2$ epochs themselves, indicating that the two measurements are independent. This is to be expected since the FHR pattern has been demonstrated to be a non-specific method of assessing the fetal status. $FSpO_2$ directly measures the fetal oxygenation in real-time while FHR abnormalities may be an indication of actual current hypoxia, pre-existing brain injury, head and cord compression, or other disturbances.

Figure 3: Class 1, 2, and 3 FHR patterns during epochs of Absent, High, and Low $FSpO_2$ in the 223 patients with at least one Low $FSpO_2$ epoch.



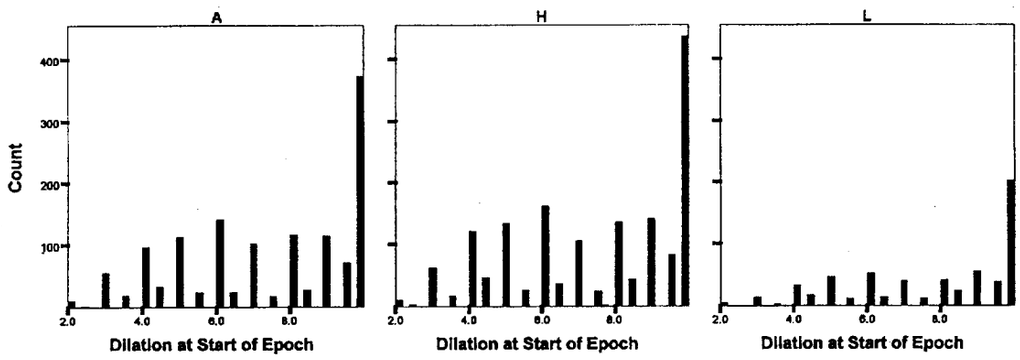
* No Class 3 Ominous FHR patterns were observed in patients with at least one Low $FSpO_2$ epoch.

35

During the 2nd stage of labor there were a significant number of Low $FSpO_2$ epochs as well as an increased number of intermittent signal dropouts.

The distribution of patients' cervical dilation at the start of Absent, High, and Low $FSpO_2$ epochs is shown below.

Figure 4: Cervical dilation of the patient at the start of Absent, High, and Low $FSpO_2$ epochs.



In patients exhibiting the presence of one or more epochs containing both Low $FSpO_2$ and non-reassuring FHR patterns in the same epoch, there was a higher incidence of delivery by Cesarean (34% vs. 27%) and AVD (36% vs. 20%). For Cesarean deliveries there was a higher incidence of delivery for NRFS (24% vs. 12%) and FIL/DYS (29% vs. 14%). This suggests increased clinician concern for those fetuses with both a non-reassuring FHR and $FSpO_2$ <30%.

XI. Conclusions Based on Study Objectives

The principal safety and effectiveness results demonstrated by the RCT are:

- The study showed no change in the overall Cesarean delivery rate. Cesarean sections for NRFS were reduced by 50% in the group monitored with FHR+$FSpO_2$. For reasons not explained by the available data, cesarean sections for dystocia in this same group increased .

- The continuation of labor during periods of non-reassuring fetal heart rate patterns and $FSpO_2$ ≥30% between contractions permitted by the use of Nellcor $FSpO_2$ monitoring does not result in any adverse impact on the neonate.

The safety profile associated with use of FHR+Nellcor $FSpO_2$ is similar to that of FHR alone for both mother and neonate.

XII. Panel Recommendations

The Obstetrics and Gynecology Devices Panel met on January 24, 2000 to discuss the Oxifirst™ Fetal Pulse Oximeter. After review of all the data and careful deliberation, the panel recommended that the device be considered approvable with conditions. One key condition to the Panel's approval recommendation was a postmarket study to track the following outcome measures:

1. cesarean sections, including indications (e.g., NRFS and dystocia);
2. reasons for sensor placement;
3. maternal infection rate;
4. impact of epidural drug use;
5. neonatal outcomes/cord gases.

The Panel recommended labeling changes. These included intended use statement (vertex presentation), as well as warnings (use of the device in women with HIV, herpes or hepatitis), precautions and contraindications (i.e., need for immediate delivery (unrelated to FHR pattern), such as active uterine bleeding). The Panel also recommended changes regarding discussion of device accuracy, patient labeling, proper instructions on how and when to place the device, and training.

XIII. FDA Decision

Based on a review of the data contained in the PMA, panel recommendations and additional analyses done by the company, CDRH determined that the Oxifirst™ System provides reasonable assurance of safety and effectiveness when used as indicated in the labeling. The applicant agreed to the post-approval requirement of a study to look at the effect of the use of the device on the Cesarean section rates in the general population and certain other outcome measures. Furthermore, the applicant agreed to conduct a second post approval study to assess human factors that may play a role in the use of the OxiFirst™ monitor as it is introduced to the U.S. market. The applicant will also ensure that physician education is available to new users pursuant to the training plan outlined in the PMA.

Where labeling materials describe the effects of monitoring with the OxiFirst™ System on Cesarean-section rates, FDA determined that the labeling must specify the following two essential elements:

- In a randomized clinical trial, use of the OxiFirst™ System as an adjunct to traditional FHR monitoring did not result in a reduction in the overall rate of Cesarean deliveries. Cesarean deliveries for nonreassuring fetal status (NRFS) were *reduced* in the test group (FHR + $FSpO_2$).

- For reasons not explained by the study data, Cesarean deliveries for dystocia were *increased* in the test group to offset the reduction in Cesarean deliveries for NRFS.

CDRH found the applicants manufacturing facilities to be in compliance with the device Quality System Regulation (21 CFR 820).

CDRH issued an approval order for the stated indication for the applicant's PMA for the OxiFirst™ Fetal Oxygen Saturation Monitoring System on May 12, 2000.

XIV. Approval Specifications

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.