

**OxiFirst® Fetal Oxygen Saturation  
Monitoring System  
PMA#990053**

APR 24 2001

**Summary of Post-Approval Clinical Studies Plans  
(For General Distribution)**

**Mallinckrodt Inc.  
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**Summary of Information Presented to  
FDA CDRH Obstetrics and Gynecology Devices  
Advisory Panel  
(May 21, 2001)**

**Sponsor:** Mallinckrodt Inc. (A Division of Tyco Healthcare Group LP)  
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**Subject:** Supplement #1 to PMA #P990053  
OxiFirst™ Fetal Oxygen Saturation Monitoring System  
Required Post-approval Study

**Date:** May 21, 2001

**Purpose:** Nellcor will present the information contained in its April 6, 2001 supplement to PMA #990053. This supplement is intended to fulfill the following requirements for the conduct of a post-approval clinical study, as set forth in the PMA Approval Order issued by FDA on May 12, 2000:

*"You must conduct a post approval study to assess how use of the OxiFirst™ Fetal Oxygen Saturation Monitoring System will impact C-section rates and other important variables within general clinical practice. The study will address the following parameters:*

1. *Indication(s) for OxiFirst™ sensor placement,*
2. *Cesarean-section rates,*
3. *Maternal infection rates,*
4. *Duration that fetal oxygen saturation can remain below 30% before risk of fetal injury,*
5. *Adequacy of Labor, and*
6. *Neonatal Outcomes (e.g., cord blood gases, Apgar scores, etc.)."*

The contents of this PMA supplement have been the subject of communications between representatives of Mallinckrodt, the FDA and the National Institutes of Health (NIH). As proposed, implementation of FDA's post-approval requirements would best be achieved through execution of three clinical studies, each of which is carefully designed to gather a particular set of data. We believe that implementation can be most successfully achieved in a "least burdensome" fashion utilizing this multi-faceted approach.

The Implementation Plan devised to meet FDA's post-approval requirements is summarized in tabular form in **Attachment A**. Please note the following:

- The study entitled, A MULTI-CENTER, OBSERVATIONAL STUDY OF FETAL OXYGEN SATURATION MONITORING: ("OxiFirst™ General Use Study") aims to address most of the study parameters of interest, as outlined in FDA's May 12, 2000 approval order. This prospective observational study is designed to gather information on the use of OxiFirst™ in a general obstetrical population. Additional information about this study is contained in **Attachment B**.
- Data gathered from the study entitled, DYSTOCIA IN NULLIPAROUS PATIENTS MONITORED WITH FETAL PULSE OXIMETRY ("Dystocia Study") is intended to address those parameters that cannot be fully addressed by the "General Use Study." Most importantly, this study will evaluate "adequacy of labor" as a study variable of interest. This multicenter, prospective observational study is currently underway. The first study site received IRB approval on 3/9/01 and enrolled the first study subject on 4/2/01. It is anticipated that the remaining four sites will be initiated by 8/15/01. Additional information about this study is contained in **Attachment C**.
- A subset of data from a study being initiated by the NIH Maternal and Fetal Network ("NIH Study") are intended to be used to specifically address the question of how long the fetal oxygen saturation can remain below 30% before fetal injury occurs.

The NIH Study is a three-arm randomized trial of fetal oximetry in nulliparous women in active labor whose fetus may, or may not (off-label use) exhibit a non-reassuring FHR pattern. Fetal oximetry sensors will be placed in two arms, and FSpO2 information will be used as an adjunct to electronic fetal heart rate monitoring in one of those arms. Women randomized to the third arm will receive conventional continuous electronic fetal monitoring without fetal oximetry. Comparative data from the first two arms (blinded/open oximetry groups) will permit assessment of the effects of fetal oximetry on overall cesarean rates and infant safety; data from the third arm will additionally permit the assessment of the effects of sensor insertion on the rate of maternal-fetal infections.

In addition, data from depressed or acidotic neonates from the arm of this three-arm study where the OxiFirst sensor is placed but the FSpO<sub>2</sub> information is not available to the physician (blinded oximetry), will be analyzed to determine the duration of time that the FSpO<sub>2</sub> was below 30 in cases where the outcome was poor.

**ATTACHMENT A**

**OxiFirst™ Postapproval Study Requirements**

**Implementation Plan**

Study Parameter	Primary Data Source (√) Secondary Data Source (x)			Comments
	General Use Study	Dystocia Study	NIH Study	
Indications for OxiFirst™ sensor placement	√	x	Off-Label	
Cesarean-section rates	√	x	x	
Maternal infection rates	√	x	x	The NIH study will also provide insight into the incidence of infection associated with sensor placement (from analysis of rates in the control vs. blinded FSpO2 arms).
Duration that fetal oxygen saturation can remain below 30% before risk of fetal injury			√	Previous analyses of both the duration of FSpO2 <30% vs. outcome and the time integral of depth below 30% vs. outcome have failed to show a clear association between either variable and multiple outcome measures in the RCT population. Therefore, this question can only be answered from a "natural history" type study where clinician behavior is not impacted by device use or protocol. The NIH study group has agreed to perform and publish the results from such an analysis on the data recorded from the blinded FSpO2 arm of their study.
Adequacy of labor		√		The "Dystocia" study prescribes a specific management protocol for women meeting a prospective definition of dystocia in order to assure adequacy of labor. Therefore, results from this study will answer the question of whether an increase in cesarean section rate for dystocia is seen in women with "adequate labor."
Neonatal outcomes (e.g., cord blood gases, Apgar scores, etc.)	√	x	x	
Use of epidural analgesia	√	x	x	All CRFs will capture epidural use, permitting the analysis of subgroups with and without epidural use.

## ATTACHMENT B

### PROTOCOL SYNOPSIS

**Protocol Name:** A MULTI-CENTER, OBSERVATIONAL STUDY OF FETAL OXYGEN SATURATION MONITORING ("OxiFirst™ General Use Study")

**Introduction:** In this non-randomized, prospective, observational study, the impact on clinical practice of the OxiFirst™ System will be observed in an obstetrical patient population following introduction of the system into general use.

**Study Purpose:** The purpose of this General Use Study is to document the impact of the Nellcor® OxiFirst™ Fetal Oxygen Saturation Monitoring System on obstetrical clinical practice following its introduction into general use in labor and delivery units at participating study sites.

#### **Study Objectives:**

##### Primary Objective

To document the impact of device use on operative delivery rates by comparing the overall rate of cesarean deliveries after the OxiFirst™ System is introduced into general use, with historical data on cesarean delivery rates (i.e., data collected by each site prior to the use of OxiFirst™).

##### Secondary Objectives

- To document the indications for use of the OxiFirst™ System in general clinical practice.
- To compare outcomes of labor in women who had the fetal oximetry sensor placed with and without epidural anesthesia.
- To document the outcome of labor and delivery and the immediate condition of the neonate when the OxiFirst™ System is used.
- To document the distribution of indications for cesarean delivery when the OxiFirst™ System is in general use.

**Study Variables:** Study variables of interest include operative delivery rates, indications for use of the OxiFirst™ System, use of epidural anesthesia and maternal/neonatal outcomes. Historical data on operative delivery rates (overall and by specific indication, if available) will be collected from each participating site for purposes of comparison to similar data collected following introduction of the OxiFirst™ System into general use.

Institutions must meet site eligibility criteria to be included in the study. Prior to enrolling subjects, a standardized training program will be implemented at those institutions not having prior experience with the use of the OxiFirst™ System to assure proficiency with the use of the device.

### **Inclusion and Exclusion Criteria:**

#### Site Inclusion Criteria

1. Participating sites must willing and able to provide historical cesarean delivery rate data.
2. Historical cesarean delivery rates must be  $\geq 20\%$  at the participating sites.
3. Participating sites must be able to sustain a delivery rate of  $\geq 1000$  annually.

#### Patient Inclusion Criterion

The patient is admitted to the labor and delivery unit with an expectation of delivery within 24 hours.

#### Patient Exclusion Criteria

1. The patient is admitted to the L&D unit for a planned, elective cesarean delivery.
2. The patient is unwilling or unable to provide written informed consent.

**Projected Number of Subjects:** 1,750

**Projected Number of Sites:** 4

**Projected Study Duration:** 12 months

**Primary Case Report Form:** Attachment B1

Site No. <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> </div>	Patient Initials <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> </div>	Patient No. <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> </div>
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<p><b>DEMOGRAPHIC AND STUDY ENTRY CHARACTERISTICS</b></p> <p>Date of Enrollment: _____/_____/_____ (mm/dd/yy)</p> <p>Gravida: ____ Para: ____ Gestation: ____ weeks ____ /7 days</p> <p>Previous CS : <input type="checkbox"/> YES <input type="checkbox"/> NO <i>If yes, fill in the blanks below</i></p> <p># of previous C/S: _____ Indications: _____</p> <p>_____</p> <p>_____</p> <p>Epidural anesthesia: <input type="checkbox"/> YES <input type="checkbox"/> NO</p>	<p><b>HOSPITAL ADMIT/DISCHARGE</b></p> <p><b>NEONATAL:</b>                  Date/Time of Birth: _____/_____/_____ : _____  <span style="margin-left: 100px;">mm/dd/yy</span> <span style="margin-left: 100px;">24 hr clock</span></p> <p>Date/Time of Discharge: _____/_____/_____ : _____  <span style="margin-left: 100px;">mm/dd/yy</span> <span style="margin-left: 100px;">24 hr clock</span></p> <p>Discharge Status: <input type="checkbox"/> Home <input type="checkbox"/> Other: _____</p> <p><b>MATERNAL:</b>                  Date/Time of Admission: _____/_____/_____ : _____  <span style="margin-left: 100px;">mm/dd/yy</span> <span style="margin-left: 100px;">24 hr clock</span></p> <p>Date/Time of Discharge: _____/_____/_____ : _____  <span style="margin-left: 100px;">mm/dd/yy</span> <span style="margin-left: 100px;">24 hr clock</span></p> <p>Discharge Status: <input type="checkbox"/> Home <input type="checkbox"/> Other: _____</p>
<p><b>FETAL HEART RATE PATTERNS PRESENT DURING LABOR AT ANY TIME</b></p> <p><input type="checkbox"/> No FHR abnormality present during labor  <i>(If the box above is checked do not check any boxes below)</i></p> <p><input type="checkbox"/> Baseline FHR between 100-110 bpm with no accelerations &gt; 15 bpm for &gt; 15 seconds</p> <p><input type="checkbox"/> Baseline FHR &lt; 100 bpm with accelerations</p> <p><input type="checkbox"/> Increased variability &gt; 25 bpm for &gt; 30 minutes</p> <p><input type="checkbox"/> Mild or moderate variable decelerations for &gt; 30 minutes                  (variables with (a relative drop of <math>\leq 70</math> bpm or an absolute drop to <math>\geq 70</math> bpm) for &lt; 60 sec)</p> <p><input type="checkbox"/> Late decelerations (at least 1 per 30 minutes)</p> <p><input type="checkbox"/> Decreased variability &lt; 5 bpm for &gt; 30 minutes</p> <p><input type="checkbox"/> Persistent late decelerations (&gt;50% of contractions) for &gt; 15 minutes</p> <p><input type="checkbox"/> Tachycardia &gt; 160 with long term variability &lt; 5 bpm</p> <p><input type="checkbox"/> Sinusoidal pattern</p> <p><input type="checkbox"/> Variable decelerations of any type</p> <p><input type="checkbox"/> Variable decelerations with a relative drop in heart rate <math>\geq 70</math> bpm or an absolute drop to <math>\leq 70</math> bpm for &gt; 60 sec</p> <p><input type="checkbox"/> Variable decelerations with persistent slow return to baseline</p> <p><input type="checkbox"/> Variable decelerations with long term variability &lt; 5 bpm</p> <p><input type="checkbox"/> Variable decelerations with tachycardia &gt; 160 bpm</p> <p><input type="checkbox"/> Recurrent prolonged decelerations (2 or more below 70 bpm for &gt; 90 seconds in 15 minutes)</p> <p style="text-align: center;"><b>(CHECK ALL THAT APPLY)</b></p>	<p><b>DELIVERY MODE USED</b></p> <p><input type="checkbox"/> Spontaneous Vaginal Delivery</p> <p><input type="checkbox"/> Assisted Vaginal Delivery:  <span style="margin-left: 40px;"><input type="checkbox"/> Forceps <input type="checkbox"/> Vacuum</span></p> <p><input type="checkbox"/> Cesarean Delivery</p> <p><b>INDICATION FOR DELIVERY MODE USED</b></p> <p><input type="checkbox"/> Non reassuring fetal status (NRFS)</p> <p><input type="checkbox"/> Fetal Intolerance to labor &amp; dystocia (FILDYS)</p> <p><input type="checkbox"/> Dystocia (DYS)</p> <p><input type="checkbox"/> Ominous FHR (OFHR)</p> <p><input type="checkbox"/> Other: _____</p> <p><b>NEONATAL OUTCOMES</b></p> <p>Neonate Sex: <input type="checkbox"/> male <input type="checkbox"/> female</p> <p>Neonatal Weight: # _____ kg Length _____ cm</p> <p>1-min Apgar: _____ 5-min Apgar: _____</p> <p>Cord arterial pH: _____ Base excess: _____</p> <p>Cord arterial pCO<sub>2</sub>: _____ PO<sub>2</sub> _____</p> <p>Received Mask Ventilation? <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Intubated &amp; Ventilated? <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Transferred to NICU? <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><b>NEONATAL AND MATERNAL DRAEs and SAEs</b></p> <p><b>NEONATAL:</b>                  Device Related Adverse Event? <input type="checkbox"/> YES <input type="checkbox"/> NO                  Serious Adverse Event? <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><b>MATERNAL:</b>                  Device Related Adverse Event? <input type="checkbox"/> YES <input type="checkbox"/> NO                  Serious Adverse Event? <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p style="text-align: center;"><i>(If YES fill out the Neonatal/Maternal DRAE or SAE Form)</i></p>

## ATTACHMENT C

### PROTOCOL SYNOPSIS

**Protocol Name:** DYSTOCIA IN NULLIPAROUS PATIENTS MONITORED WITH FETAL PULSE OXIMETRY

**Introduction:** This non-randomized, prospective, cohort observational study will evaluate the incidence and management of dystocia in a study population with non-reassuring fetal heart rate patterns managed with FHR and FSpO<sub>2</sub>

**Study Purpose:** The purpose of this prospective cohort study is to examine the relationship(s) between non-reassuring fetal heart rate tracings and the incidence of dystocia, and to examine if the application of a prospectively defined protocol for the diagnosis and management of dystocia, incorporating the use of OxiFirst™, affects maternal and/or neonatal outcomes in this population.

#### **Study Objectives:**

##### Primary Objective

To examine the relationship between non-reassuring fetal heart tracings and the incidence of operative delivery for dystocia in a population for whom the use of the fetal pulse oximeter is indicated.

##### Secondary Objectives

- To determine if non-reassuring variable decelerations predict dystocia more frequently than other non-reassuring patterns.
- To determine if non-reassuring fetal heart rate patterns specifically predict dystocia, as characterized by an arrest of labor beyond 4 cm dilatation.
- To examine the relationship between the position of the occiput at delivery, fetal heart rate patterns associated with the position of the occiput at delivery and the incidence of dystocia.

To document the outcome of labor and delivery and the immediate neonatal condition in the presence of a non-reassuring FHR pattern(s) and abnormal progress of labor.

- To document the outcome of labor and delivery and the immediate neonatal condition in the presence of a non-reassuring FHR pattern(s) and adequate progress of labor.

**Study Variables:** Study variables of interest include fetal heart rate pattern(s) recorded throughout the course of labor, status of the progress of labor at the time of dystocia diagnosis, interventions used for the management of adequate progress of labor and abnormal progress of labor, indication for delivery, mode of delivery, and maternal and neonatal outcomes.

#### **Inclusion and Exclusion Criteria:**

During this study all patients who have been admitted to the labor and delivery units of any participating institution, that develop non-reassuring fetal heart tracings will be approached to determine willingness to participate in the study and provide written informed consent. Study eligibility criteria include the following:

##### Inclusion Criteria

1. The fetus exhibits one or more non-reassuring fetal heart tracings.
2. Nulliparous with singleton gestation.
3. Gestation  $\geq 36$  weeks 0 days.
4. Vertex presentation.
5. Labor may be spontaneous or induced.
6. Ruptured membranes either spontaneously or artificially.
7. Cervical dilation of  $\geq 2$  cm.
8. Presenting part at  $-2$  station or lower.

##### Exclusion Criteria

1. The patient is unable or unwilling to provide written informed consent according to applicable state law prior to study entry.
2. The patient is participating in another conflicting clinical study.
3. The patient is scheduled for an elective CS.
4. The pregnancy is less than 36 weeks and 0 days.
5. The pregnancy is a multiple gestation.
6. The patient has documented or suspected placenta previa.
7. The fetus is in the non-vertex position.
8. There is an immediate need for delivery unrelated to FHR pattern, such as active uterine bleeding.
9. There is an ominous FHR pattern that requires immediate intervention.
10. The patient has active genital herpes or other infection, which precludes internal monitoring (Maternal fever and Group B strep are not exclusions).
11. The patient is parous (previous birth at >20 weeks).
12. The patient is seropositive for human immunodeficiency virus (HIV).

**Projected Number of Subjects: 500**

**Projected Number of Sites: 5**

**Projected Study Duration: 12 months**