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

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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 FSpO2 information is not available to the physician (blinded oximetry), will be analyzed to determine the duration of time that the FSpO2 was below 30 in cases where the outcome was poor.
## Study Parameter

<table>
<thead>
<tr>
<th>Study Parameter</th>
<th>General Use Study</th>
<th>Dystocia Study</th>
<th>NIH Study</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicates for OxiFirst™ sensor placement</td>
<td>✓</td>
<td>x</td>
<td></td>
<td>Off-Label</td>
</tr>
<tr>
<td>Cesarean-section rates</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>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).</td>
</tr>
<tr>
<td>Maternal infection rates</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>Previous analyses of both the duration of FSpO2 &lt;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 &quot;natural history&quot; 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.</td>
</tr>
<tr>
<td>Duration that fetal oxygen saturation can remain below 30% before risk of fetal injury</td>
<td></td>
<td></td>
<td>✓</td>
<td>Previous analyses of both the duration of FSpO2 &lt;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 &quot;natural history&quot; 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.</td>
</tr>
<tr>
<td>Adequacy of labor</td>
<td></td>
<td>✓</td>
<td></td>
<td>The &quot;Dystocia&quot; 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 &quot;adequate labor.&quot;</td>
</tr>
<tr>
<td>Neonatal outcomes (e.g., cord blood gases, Apgar scores, etc.)</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>All CRFs will capture epidural use, permitting the analysis of subgroups with and without epidural use.</td>
</tr>
<tr>
<td>Use of epidural analgesia</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>All CRFs will capture epidural use, permitting the analysis of subgroups with and without epidural use.</td>
</tr>
</tbody>
</table>

ATTACHMENT A

OxiFirst™ Postapproval Study Requirements

Implementation Plan

Mallinckrodt Inc.
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 ≥20% at the participating sites.
3. Participating sites must be able to sustain a delivery rate of ≥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
### DEMOGRAPHIC AND STUDY ENTRY CHARACTERISTICS

<table>
<thead>
<tr>
<th>Date of Enrollment:</th>
<th>mm/dd/yy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravida:</td>
<td></td>
</tr>
<tr>
<td>Para:</td>
<td></td>
</tr>
<tr>
<td>Gestation:</td>
<td>weeks</td>
</tr>
</tbody>
</table>

**Previous CS:**
- **YES**
- **NO**

If yes, fill in the blanks below

- # of previous C/S: 
- Indications: 

**Epidural anesthesia:**
- **YES**
- **NO**

### FETAL HEART RATE PATTERNS PRESENT DURING LABOR AT ANY TIME

- **No FHR abnormality present during labor**
- **Baseline FHR between 100-110 bpm with no accelerations > 15 bpm for > 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 with long term variability < 5 bpm**
- **Sinusoidal pattern**
- **Variable decelerations of any type**
- **Variable decelerations with a relative drop in heart rate > 70 bpm or an absolute drop to < 70 bpm for > 60 sec**
- **Variable decelerations with persistent slow return to baseline**
- **Variable decelerations with long term variability < 5 bpm**
- **Variable decelerations with tachycardia > 160 bpm**
- **Recurrent prolonged decelerations (2 or more below 70 bpm for > 90 seconds in 15 minutes)**

*(CHECK ALL THAT APPLY)*

### NEONATAL ADMIT/DISCHARGE

**Date/Time of Birth:**
- mm/dd/yy
- 24 hr clock

**Date/Time of Discharge:**
- mm/dd/yy
- 24 hr clock

**Discharge Status:**
- **Home**
- **Other:**

### MATERNAL ADMIT/DISCHARGE

**Date/Time of Admission:**
- mm/dd/yy
- 24 hr clock

**Date/Time of Discharge:**
- mm/dd/yy
- 24 hr clock

**Discharge Status:**
- **Home**
- **Other:**

### DELIVERY MODE USED

- **Spontaneous Vaginal Delivery**
- **Assisted Vaginal Delivery:**
  - **Forceps**
  - **Vacuum**
- **Cesarean Delivery**

### INDICATION FOR DELIVERY MODE USED

- **Non reassuring fetal status (NRFS)**
- **Fetal Intolerance to labor & dystocia (FILDYS)**
- **Dystocia (DYS)**
- **Ominous FHR (OFHR)**
- **Other:**

### NEONATAL OUTCOMES

- **Neonate Sex:**
  - **male**
  - **female**
- **Neonatal Weight:**
  - kg
  - Length cm
- **1-min Apgar:**
- **5-min Apgar:**
- **Cord arterial pH:**
- **Base excess:**
- **Cord arterial pCO2:**
- **PO2**

- **Received Mask Ventilation?**
  - **YES**
  - **NO**
- **Intubated & Ventilated?**
  - **YES**
  - **NO**
- **Transferred to NICU?**
  - **YES**
  - **NO**

### NEONATAL AND MATERNAL DRAEs and SAEs

#### NEONATAL:
- **Device Related Adverse Event?**
  - **YES**
  - **NO**
- **Serious Adverse Event?**
  - **YES**
  - **NO**

#### MATERNAL:
- **Device Related Adverse Event?**
  - **YES**
  - **NO**
- **Serious Adverse Event?**
  - **YES**
  - **NO**

*(If YES fill out the Neonatal/Maternal DRAE or SAE Form)*
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 FSpO₂.

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 ≥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 ≥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 then 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