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August 2, 2013

Jeffrey E. Shuren, M.D., J.D.
Director, Center for Devices and Radiological Health
Food and Drug Administration
Department of Health and Human Services
WO 66, Room 5442
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Dr. Shuren:

As you may be aware, Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, sent letters to Secretary of Health and Human Services Kathleen Sebelius on April 10 and May 8, 2013, raising serious concerns about the SUPPORT study funded by the National Institutes of Health (NIH) and conducted by approximately two dozen academic medical institutions of the Neonatal Research Network.[1,2] Our letters to the Secretary highlighted important and material factual omissions — as well as many misleading statements — regarding the purpose, nature, and risks of the research in all consent forms approved by the institutional review boards (IRBs) that reviewed and approved this study.

We are writing to you now to request that the Food and Drug Administration (FDA) investigate issues related to the experimental pulse oximeter devices used in the SUPPORT study and the inclusion of one particularly misleading statement in many of the IRB-approved SUPPORT study consent forms regarding these devices. At the direction of the SUPPORT study investigators for the purposes of the research, the manufacturer of these pulse oximeters, the Masimo, intentionally miscalibrated the oximeters so that they would display either falsely low or falsely high oxygen saturation levels when the actual oxygen saturation level was between 85 and 95 percent (see enclosed letter). However, nine of the 22 IRB-approved consent forms obtained from NIH by Public Citizen misleadingly stated that the experimental pulse oximeters used in the research were "FDA-approved." In conducting its investigation, we urge the FDA to address the following questions:

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[1] Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. April 10, 2013. http://www.citizen.org/documents/2111.pdf. August 1, 2013.
[2] Carome MA, Wolfe SM, Macklin R. Letter and report to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. May 8, 2013. http://www.citizen.org/documents/2124.pdf. Accessed August 1, 2013.

(1) Did Masimo or the SUPPORT study investigators contact the FDA and seek approval to use these intentionally miscalibrated experimental pulse oximeters in clinical trials? If not, should they have?

(2) Did use of the experimentally altered pulse oximeters in the study require FDA approval of an investigational device exemption (IDE)?

(3) Did the inclusion of the misleading statement in the IRB-approved consent forms indicating that the pulse oximeters were FDA-approved violate the FDA's human subjects protection regulations?

Background

The SUPPORT study involved 1,316 extremely premature infants enrolled between 2005 and 2009 at more than 20 prominent medical research centers throughout the U.S.[3] The study comprised two simultaneous experiments. In one experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing (ventilation of the lungs) following delivery.[4] In the other, simultaneous experiment, which is the primary focus of this letter, babies were further randomly divided between a low-oxygen group and a high-oxygen group.[5] For the low-oxygen group, the SUPPORT study investigators tried to maintain the babies' blood oxygen levels in a low target range (oxygen saturation level of 85 to 89 percent) and for the high-oxygen group in a high target range (oxygen saturation level of 91 to 95 percent). The researchers then measured the impact of the two target ranges of oxygen levels for premature babies – specifically, whether infants in one group were more likely to die, suffer brain damage, or develop an eye disease called retinopathy of prematurity and blindness in comparison to the other group.

Use of Experimental Pulse Oximeter Devices

The study design used an experimental procedure under which the entire medical team caring for each premature baby in the study was intentionally given inaccurate information about the baby's blood oxygen saturation levels by using experimental pulse oximeter devices that were miscalibrated across the wide range of oxygen saturations between 85% and 95%. These experimental devices were used for the entire time the babies were on supplemental oxygen.

The use of these experimental pulse oximeters is explained in the following excerpts from the SUPPORT study protocol:[6]

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[3] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.
[4] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely premature infants. *N Engl J Med.* 2010;362(21):1970-1979.
[5] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.
[6] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed August 1, 2013.

> (Page 12, section 3.7, Randomization) The Pulse Oximeters (PO) will have unique identifying labels and the oximeter specified in the randomization will be identified by a unique number which will match the number of the study Pulse Oximeter assigned for that infant. **All caretakers including the coordinators will be blinded to the [actual] Pulse Oximeter Range**… [Emphasis added]
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> (Page 17, 4.1 B Study Intervention: Low versus High SpO2 Range) There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) are described below, and will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. See below for further explanation. This deviation is similar to the BOOST trial which used a continuous 3% offset. As an added safety feature, the POs used in this trial will revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

Note that for any displayed oxygen saturation level between 88% and 92%, the absolute difference between the actual oxygen saturation levels for the high- versus low-oxygen groups was 6%. For example, when the *displayed* oxygen level was 90%, the *true* oxygen level was 93% for the high-oxygen group and 87% for the low-oxygen group.

Disturbingly, the SUPPORT study protocol offered no evidence that it was safe to use these miscalibrated experimental medical devices that provided the entire medical teams caring for these critically ill premature babies with inaccurate information regarding oxygen saturation levels. Because of the inaccurately high oxygenation saturation values provided to the medical team by the pulse oximeters for babies in the low-oxygen experimental group, it is plausible that the medical team may have treated some critically ill babies with too little oxygen, potentially resulting in brain injury and death secondary to hypoxemia (deficient oxygen). In contrast, because of the inaccurately low oxygenation saturation values provided to the medical team by the pulse oximeters for babies in the high-oxygen experimental group, it is also plausible that the medical team may have treated those babies with more oxygen than they needed, resulting in severe retinopathy of prematurity, requiring surgery and possibly causing blindness.

Misleading Statement in the IRB-Approved Consent Forms

The miscalibrated experimental pulse oximeters used in the SUPPORT study certainly could not be considered in any way to be "FDA-approved." And yet, our review of the IRB-approved study consent forms revealed that nine of them included a statement identical or very similar to the following:[7]

[7] IRB-approved consent forms for the SUPPORT study. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed August 1, 2013.

> The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes.

The consent forms that included such a statement were approved by the IRBs for the following institutions:[8]

- Duke University Health System
- Stanford University School of Medicine
- Tufts Medical Center
- University of California, San Diego
- University of New Mexico Health Sciences Center
- University of Texas Health Science Center, Houston
- University of Texas Southwestern Medical Center at Dallas
- Wayne State University
- Women and Infants Hospital of Rhode Island

To state that these devices were FDA-approved was misleading and only served to provide false assurances about the safety of the experiment to the parents of premature infants enrolled in the study. The consent forms instead should have informed parents of prospective subjects that the pulse oximeters being used in the study: (a) were experimental devices, (b) would never have been used in routine clinical care of critically ill premature babies, and (c) had **not** been approved by the FDA for use in a clinical care or research setting.

Conclusions and Summary of Requested Actions

In conclusion, the use of the experimental pulse oximeter devices during the conduct of the SUPPORT study raises important questions regarding compliance with FDA medical device regulations. Furthermore, the misleading statement that the experimental pulse oximeters being used in the research were "FDA-approved" was among the many serious problems with consent process for the SUPPORT study. These problems ultimately resulted in a failure of the investigators to obtain the legally effective informed consent of the parents of the subjects enrolled in the study, thus making the conduct of the study highly unethical.

We therefore request that the FDA investigate issues related to the experimental pulse oximeter devices used in the SUPPORT study and the inclusion of the misleading statement in the IRB-approved SUPPORT study consent forms indicating that these devices were FDA-approved. In conducting its investigation, we urge the FDA to address the following questions:

(1) Did Masimo or the SUPPORT study investigators contact the FDA and seek approval to use these intentionally miscalibrated experimental pulse oximeters in clinical trials? If not, should they have?

[8] *Ibid*.

(2) Did use of the experimentally altered pulse oximeters in the study require FDA approval of an IDE?

(3) Did the misleading statements in the IRB-approved consent forms indicating that the pulse oximeters were FDA-approved violate the FDA's human subjects protection regulations?

Thank you for your prompt attention to these important human subjects research issues. Please contact us if you have any questions or need additional information.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

Enclosure: June 30, 2004, letter from Masimo

cc: Dr. Margaret Hamburg, Commissioner, FDA
Dr. Francis Collins, Director, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Development
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borror, Director, Division of Compliance Oversight, OHRP