[This letter reflects the removal of an addressee that was not engaged in this human subjects research and replaces the previously issued determination letter (dated February 8, 2013).]

DEPARTMENT OF HEALTH & HUMAN SERVICES

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March 7, 2013

Richard B. Marchase, Ph.D.
V.P. for Research & Economic Development
University of Alabama at Birmingham
AB 720E
701 20th Street South
Birmingham, AL 35294-0107

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

Research Project:	The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)
Principal Investigator:	Dr. Waldemar A. Carlo
HHS Protocol Number:	2U10HD034216

Dear Dr. Marchase:

Thank you for your response to our July 18, 2011 letter and subsequent emails regarding our request that your institutions evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) and our subsequent questions and concerns regarding the above-referenced research.

The SUPPORT study was a randomized multi-site study conducted at approximately twenty-two sites and reviewed by at least twenty-three institutional review boards (IRBs). Approximately 1,300 infants were enrolled in this study from 2004 to 2009. The study was designed to 1) learn more about treatment with continuous positive airway pressure (CPAP) which is positive pressure applied with a face mask to help keep the lungs inflated, and 2) to learn the appropriate levels of oxygen saturation in extremely low birth weight infants by comparing a lower versus a higher range of levels of oxygen saturation in such infants. The University of Alabama, Birmingham (UAB) was the lead site for the portion of the study

relating to the second purpose. The CPAP portion of this study raised no concerns for OHRP and therefore will not be discussed in this letter.

In the oxygen saturation part of this study, infants were randomized to the lower or higher ranges of oxygen levels to test the effects on infants' survival, neurological development, and likelihood of developing retinopathy of prematurity (ROP), a serious - often blinding - visual disorder. Based on the consent form template and UAB consent forms, we determine that the conduct of this study was in violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably forseeable risks of blindness, neurological damage and death. (As discussed at the end of this letter, participating in the study did have an effect on which infants died, and on which developed blindness.) In the following, we provide some background regarding the history of the use of oxygen in prematurely born infants and its association with ROP, followed by an analysis of the SUPPORT trial protocol and informed consent materials.

Historical Background

Beginning in the 1940s, doctors treating premature infants saw a dramatic increase in a previously rare but frequently blinding eye disorder. Originally called retrolental fibroplasia, it was later renamed as retinopathy of prematurity.[1] Within a handful of years, it had become a major cause of blindness in children in the U.S. and some other countries, affecting more than 12,000 infants. Numerous possible causes for this condition were suggested, including exposure to increased levels of oxygen. Clinical trials to test this hypothesis began in the early 1950s. These trials – involving randomizing infants to either the "high oxygen" that was the standard of care, or to "low oxygen"-- had their controversial aspects. One reviewer of a grant application for the earliest such trial commented that "these guys are going to kill a lot of babies by anoxia [inadequate oxygen] to test a wild idea."[2] Similar concerns resurfaced during the conduct of the trial itself. As the lead researcher himself noted, "[t]he nurses were convinced that we were going to kill the babies in the low oxygen group, and indeed, at night some of the older nurses would turn the oxygen on for a baby who was not receiving oxygen, then turn it off when they would go off duty in the morning."

The results of this trial and others showed that infants receiving low oxygen had a much lower incidence of ROP than those receiving the then-standard higher oxygen levels. Within a couple of years, medical practice had dramatically changed, with a large drop in the acceptable level of oxygen used to treat premature newborns. This change resulted in "an immediate 60 percent reduction in the number of blind children in the United States."[3] Among the concerns addressed by these early trials was the possibility that even if lower oxygen led to less ROP, it might also produce other bad consequences for the health of a very

[1] Much of the early history of retinopathy of prematurity recounted here is taken from W.A. Silverman, Retrolental Fibroplasia: A Modern Parable. Grune & Stratton, Inc., New York, N.Y. (1980), available at http://www.neonatology.org/classics/parable.
[2] E. Brown. Obituary for Arnall Patz. Washington Post, March 13, 2010.
[3] L.K. Altman. Arnall Patz, a Doctor Who Prevented Blindness, is Dead at 89. New York Times, March 15, 2010.

premature infant, including possibly death. One of the largest such trials specifically looked at this question, concluding that this was not a problem.[4]

As time passed, and experience with treating premature infants grew, some experts began to question the conclusion that there were no adverse health consequences from the decreased levels of oxygen. Flaws were found in the early study, which had ignored deaths that occurred during the first day of life. In 1973, an influential epidemiologic analysis concluded that "it would seem that each sighted baby gained [by limiting the use of oxygen] may have cost some 16 deaths."[5] As a result of this new information, the rather strict limitations on the use of oxygen that were implemented in the 1950s were relaxed. It became far more acceptable to treat premature infants, where there appeared to be a need, with substantial amounts of oxygen.[6] There was a greater recognition of the need for appropriate amounts of oxygen that might "maximize survival without brain damage, while minimizing the risks of [ROP]."

Even this change, however, did not resolve the clinical issues. As the ability to keep alive premature infants with ever-lower weights improved with the use of new technology, it appeared that there was an accompanying growth of cases of ROP. It remains a very serious problem, as shown by the statistics put out by the National Eye Institute. Each year, approximately 28,000 infants weighing less than 2 ¾ pounds are born prematurely in the U.S. More than half of those infants will have at least a mild form of ROP. More than 1,000 of them will have a form that is serious enough to require treatment. And about 400 to 600 of them each year will become legally blind as a result of this condition.[7] These numbers are not much lower than the 700 cases per year that constituted the original so-called "epidemic" level in the period from 1943 to 1953.

The significance of this ongoing problem is underscored by the number of relatively recent calls in the scholarly literature for doing the clinical trials needed to determine the appropriate amount of oxygen to use in treating premature infants. As one commentary noted, "[l]owering oxygen saturation targets in preterm infants in the first few weeks of life has been shown to reduce the incidence of certain complications; however, prolonged periods of hypoxemia may result in poor growth, cardiopulmonary complications of chronic lung disease, neurodevelopmental disabilities, or increased mortalities. . . . Although maintaining ranges of hemoglobin oxygen saturation in the vulnerable preterm population in the proximity of 85% to 90% is gaining increasing acceptance, marked variability in opinion exists."[8] In short, the research and data analyses that had occurred prior to the SUPPORT

[4] V.E. Kinsey. Retrolental Fibroplasia: Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen. Archives of Ophthalmology 1956;56:481.
[5] K.W. Cross. Cost of Preventing Retrolental Fibroplasia. Lancet 1973;302:954.
[6] J.F. Lucey and B. Dangman. A Reexamination of the Role of Oxygen in Retrolental Fibrolplasia. Pediatrics 1984;73:82.
[7] National Eye Institute. Facts About Retinopathy of Prematurity (ROP). Available at http://www.nei.nih.gov/rop.
[8] J.S. Greenspan, J.P. Goldsmith. Oxygen Therapy in Preterm Infants: Hitting the Target. Pediatrics 2006;118;1740. See also, e.g., an analysis of the literature performed for the Cochrane Collaboration. L.M. Askie, D.J. Henderson-

study demonstrated that the use of higher versus lower levels of oxygen could significantly affect the likelihood of a premature infant developing ROP and other aspects of morbidity and mortality.

The Protocol

The quotes provided above are consistent with what the protocol of the SUPPORT study itself said about the use of oxygen and ROP in premature infants:

> "Retinopathy of prematurity (ROP) remains a significant cause of morbidity among [extremely low birth weight] infants and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder. . . . While retrospective cohort studies have suggested that the use of lower SpO_2 ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO_2 ranges for managing [such infants]." (p.2, "Statement of Problem," 2004 protocol)

The protocol cites much of the literature described above. In its statement of the problem being studied, the protocol also specifically acknowledged the complex relationship between lowering oxygen to reduce the risk of ROP, and possibly causing other serious medical problems for an infant:

> "[O]xygen toxicity can result in increased risk for [chronic lung disease, ROP], and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. . . . While prevention of hyperoxia [excess oxygen] may decrease the risk for ROP and [chronic lung disease], efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia [low oxygen] because of the marked variability in oxygen in [extremely low birth weight] infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and [chronic lung disease] are deleterious for brain development and result in impaired neurologic outcome." (p.2 "Background," 2004 protocol)

The SUPPORT study was thus an important clinical trial designed to generate knowledge that could help physicians determine exactly how much oxygen to provide to extremely low birth weight infants in order to minimize ROP without contributing to undue increases in other problems (such as impaired brain development or even death). Infants enrolled in the study would be randomized to one of two levels of oxygen. The amount of oxygen provided

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Smart, H. Ko. Restricted Versus Liberal Oxygen Exposure for Preventing Morbidity and Mortality in Preterm or Low Birth Weight Infants. Cochrane Database of Systematic Reviews 2009(1), available at http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001077.pub2/pdf (looking at whether the level of oxygen affects "mortality, [ROP], lung function, [and] growth or development.").

to the infant would be measured not by looking at the absolute quantity of oxygen provided to the infant, but instead by providing sufficient oxygen to maintain a specified level of oxygen in the infant's blood.

In particular, a non-invasive device known as a pulse oximeter, commonly used in clinical care, would be applied to the infant's foot or hand. That device measures the blood oxygen saturation (SpO_2), which is the percentage of hemoglobin in the infant's bloodstream that has oxygen bound to it. The amount of oxygen provided to the infant would then be adjusted to try to keep the SpO_2 within one of two discrete ranges of oxygen levels, *i.e.*, a "low" range of 85% to 89%, or a "high" range of 91% to 95%. Infants were randomly assigned to the low or the high range.

The investigators noted that the institutions participating in the study were using a range of 85% to 95% for clinical care purposes. In contrast, the oxygen level of an infant enrolled in the study would be confined to either the lower or the upper portion of the range received by infants not participating in the study. Altering the range of oxygen level an infant was supposed to receive was a crucial part of the study design. By creating two groups receiving two discrete ranges of oxygen levels, the study increased the likelihood that there would be significant differences in outcomes observed between the two groups, as compared to a study comprised of a group of the lower or the higher range and a group receiving a level of oxygen anywhere along the range of 85% to 95%.

With regard to those possible differences in outcome, the researchers were specifically looking at both whether the infant survived, and whether the infant developed a fairly significant level of ROP (what is called "threshold" disease). As the protocol put it, the primary hypothesis they were testing was "that relative to infants managed with a higher SpO_2 range that the use of a lower SpO_2 range will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention."

The protocol included the usual section entitled "Risks and Benefits." That section did not identify any risks relating to randomizing subjects to the low or high range of oxygen.

The Consent Form Template

With regard to the purposes of the trial, the 2-1/2 page consent form template used to develop the actual consent form states that the study will compare a low range of oxygen levels (85-89%) with a high range (91-95%) "to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen)." The template also states that the oxygen level currently being used at the sites was "between 85% and 95%," and thus both treatment groups "fall within that range."

The risks of the study (not just for the oxygen intervention, but also for the CPAP intervention) are discussed in this paragraph:

> "Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician deems this necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document."

Several observations are appropriate with regard to this paragraph:

1. The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and ROP, and what that work indicates about how changing the oxygen range might affect whether an infant develops ROP.

2. The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and mortality and other forms of morbidity (apart from developing ROP).

3. The paragraph does not identify any specific risk relating to randomizing infants to a high or low range of oxygen.

Although the consent form did not identify a single specific risk relating to the randomization to high or low oxygen ranges, it did include a section that was quite specific in noting possible benefits to participating infants from the change in oxygen ranges. That paragraph observed that "[t]here may be benefits to your child directly, including . . . a decrease in the need for eye surgery as a result of exposure to oxygen." It did go on to point out that since it was not known in advance which treatment a particular child would be randomized to, it was "possible that your baby will receive no direct benefit."

Summary

Given the complexity of these issues, it is worth summarizing some of the key points:

a. The relationship between oxygen and development of severe retinopathy of prematurity had been examined for over 50 years. While the details of that relationship were not fully known, it was well recognized that changing a premature infant's amount of exposure to oxygen could have an impact on a number of important health outcomes, including the development of severe eye disease (and possibly blindness); reduced

neurologic development, including brain damage; chronic lung disease; and could even lead to death.

b. The SUPPORT study was designed as an interventional study. It specifically enrolled very premature infants and randomized them to one of two levels of oxygen. For many of those infants, the level of oxygen they received was different from what they would have received had they not participated in the study. A major purpose for doing this was to increase the likelihood that there would be a measurable difference in the outcomes of the two groups. The primary outcome of interest for the researchers was whether the infants would develop severe eye disease or would die before being discharged from the hospital.

c. The template for the consent form used in this study did not mention any risks relating to the randomization between the higher and lower levels of oxygen, instead suggesting that this was a low risk study, noting that all of the treatments in the study were "standard of care," and that there was "no predictable increase in risk for your baby."

d. While it would have been unwarranted to predict, ahead of time, specific outcomes (*i.e.*, which infants developed which outcomes), the researchers had sufficient available information to know, before conducting the study, that participation might lead to differences in whether an infant survived, or developed blindness, in comparison to what might have happened to a child had that child not been enrolled in the study.

The UAB Consent Form

We reviewed the UAB IRB records, including the study protocol, informed consent documents and data safety monitoring committee (DSMC) reports. We also reviewed consent documents approved by 23 IRBs, and found problems with all of them similar to those described above with regard to the template consent form.

The version of the UAB consent form provided to us (approved on June 4, 2008) provides the following information that is specific to the study of the levels of oxygen in premature infants:

At the front of the form:

"We will also be looking at the ranges of oxygen saturation that are currently being used with these same babies".

In the section labeled "Introduction":

"Another part of the study will be looking at the ranges of oxygen saturation that are currently being used with premature infants. Doctors, nurses, and others taking care of your baby use a machine called a pulse oximeter in routine daily care to help them adjust

> the oxygen to meet the baby's needs. Sometimes higher ranges are used and sometimes lower ranges are used. All of them are acceptable ranges. In this part of the study, we would like to pinpoint the exact range that should be used to help prevent some of the problems that occur with premature babies such as Retinopathy of Prematurity (ROP). This is when there is abnormal blood vessel growth in the eye. It causes scar tissue to build up around the retina and if it pulls on the retina hard enough, it can cause blindness. It is known that ROP is increased by prolonged use of supplemental oxygen from observations published in the 1950s, but the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known. In going back and looking at how babies in the past were managed, it is being suggested that the use of lower saturation ranges may result in a lower incidence of severe ROP."

In the section labeled "Procedures":

> "The babies in this study will also be placed randomly (again, like the flip of a coin) into a group monitored with lower oxygen saturation ranges or higher oxygen saturation ranges. Oxygen saturation is measured on a baby with a machine called a pulse oximeter. It uses a tiny sensor on the hand or foot of the baby and can give the doctors a measurement of how saturated the baby's blood is with oxygen. Oximeters are not painful and can provide oxygen saturation measurements 24 hours a day. The babies in the lower range group will have a target saturation of 85-89%, while the babies in the higher range group will have a target saturation of 91-95%. All of these saturations are considered normal ranges for premature infants. If the saturation falls below 85% or goes higher than 95% then the pulse oximeter will alarm so that the doctors and nurses know when to turn your baby's oxygen up or down."

In the section labeled "Possible Benefits":

> "It is possible that using lower pulse oximeter ranges will result in fewer babies with severe Retinopathy of Prematurity (ROP)."

In the section labeled "Possible Risks":

> "There is no known risk to your baby from monitoring with the pulse oximeters used for this study. The possible risk of skin breakdown at the site will be minimized by your baby's nurse moving the oximeter to another arm or leg a couple of times a day."

With regard to this information, OHRP notes the following:

1. The form does not say that there may be a greater or lesser risk of death depending on whether the infant is in the lower or upper range group.

2. While the form says that being in the *lower* range group may result in the *benefit* of decreasing the chances of developing severe ROP, in the "Possible Risks" section it

does not say that being in the *upper* range group may result in the greater *risk* of developing ROP.

3. The only risk related to the part of the study involving the two ranges of oxygen levels described in the "Possible Risks" section is the risk of the pulse oximeter to the infant's skin.

A. Determinations Regarding the Consent Documents

1) It was alleged, and we determine, that the IRB approved informed consent documents for this study failed to include or adequately address the following basic element required by HHS regulations at 45 CFR 46.116(a):

Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts.

OHRP is concerned that the failure to disclose adequately the risks of the research derives in part from the belief that participation in the research study did not involve an appreciable amount of risk, because the lower and upper ranges of oxygen saturation utilized in the research fall within the range of values that doctors were using as standard care at the participating institutions. OHRP asked UAB for information regarding the oxygen levels that were being used as standard care prior to commencing this study, and UAB confirmed that standard care was to keep infants somewhere in the range between 85% and 95%, without any greater specificity, and the consent form also described this as the normal range.

In the SUPPORT study, the intervention differed from such standard care (as UAB described it). Half of the subjects were assigned to values that put them in the upper end of that range (91-95%), and the other half were assigned to values that put them in the lower end of that range (85-89%). The purpose of the study was to find out whether there was a difference between the infants assigned to receive a higher or lower range of oxygen saturation in terms of likelihood of dying, experiencing neurological problems, or developing ROP. By assuring that the infants in the two groups were receiving different levels of oxygen, the study design made it more likely that differences in the outcomes of the two groups could be detected.

According to the study design, on average, infants assigned to the upper range received more oxygen than average infants receiving standard care, and infants assigned to the lower range received less. Thus the anticipated risks and potential benefits of being in the study were not the same as the risks and potential benefits of receiving standard of care. For the infants assigned to the upper range, based upon the premises of the researchers, the risk of ROP was greater, while for the infants assigned to the lower range the risk of ROP was lower. And, as described above, there were also risks relating to neurological development and possibly death. The

SUPPORT study involved changing the treatment of enrolled infants from the treatment of infants according to standard care, with attendant changes in the risks and potential benefits.

Some researchers and observers of the SUPPORT study appear to believe that because all the infants were randomized to oxygen values that were within the range of values that doctors were using as standard care at the participating institutions (the range from 85% to 95%), it follows that the study involves no more than minimal risk. This interpretation of the facts is more fully spelled out in an article written by several of the SUPPORT investigators discussing the possible non-representativeness of the subjects in the SUPPORT study. In that article, these researchers discussed an earlier proposal for allowing waiver of informed consent under certain circumstances.[9] They noted that "one could make the argument that the SUPPORT trial could have been carried out under waiver." Under that proposal, the criteria for such a possible waiver included there must be "minimal additional risk compared with the alternative clinical treatment," and that "a reasonable person would [not] have a preference between the 2 treatments."

In a commentary accompanying that article (by a scholar not involved in the SUPPORT study), the commentary author specifically faulted the eighteen IRBs that reviewed the study for having "all required that consent be obtained, even though these interventions are routinely provided without specific consent in everyday practice."[10] As discussed above, OHRP notes that the risks of participating in the SUPPORT trial were not the same as those of receiving standard care.

It would have been appropriate for the consent form to explain (i) that the study involves substantial risks, and that there is significant evidence from past research indicating that the level of oxygen provided to an infant can have an important effect on many outcomes, including whether the infant becomes blind, develops serious brain injury, and even possibly whether the infant dies; (ii) that by participating in this study, the level of oxygen an infant receives would in many instances be changed from what they would have otherwise received, though it is not possible to predict what that change will be; (iii) that some infants would receive more oxygen than they otherwise would have, in which case, if the researchers are correct in how they suppose oxygen affects eye development, those infants have a greater risk of going blind; and (iv) that the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death.

[9] W. Rich et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. Pediatrics 2012;129:480.
[10] S.N. Whitney. The Python's Embrace: Clinical Research Regulation by Institutional Review Boards. Pediatrics 2012;129:576.

Accordingly, we determine that the informed consent document for this trial failed to adequately inform parents of the reasonably foreseeable risks and discomforts of research participation.

UAB Required Actions: Please provide a plan that the IRB will use to ensure that approved informed consent documents include and adequately address the basic elements of consent as required by HHS regulations at 45 CFR 46.116(a).

2) It was also alleged that the IRB approved informed consent documents for this study that failed to adequately explain the purposes of the research. OHRP makes no finding with regard to this allegation.

Results from the SUPPORT Study

The results of the SUPPORT study were published in the *New England Journal of Medicine* in 2010.[11] The rate of severe ROP among the infants who survived was significantly different between the low and high oxygen groups. Among the infants who were treated with low oxygen, only 41 out of 475 developed severe ROP, or 8.6%. In the high oxygen arm, more than double that percentage of infants developed severe eye disease: 91 out of 509, for a rate of 17.9%. The difference between these two groups was highly significant, with a P-value less than 0.001.

On the other hand, the low oxygen group had a higher percentage of deaths before discharge. 130 out of the 654 infants in that group died (19.9%), in comparison to the 107 out of 662 infants who died in the high oxygen group (16.2%). This difference was not as large as that seen with regard to developing eye disease, but it was nonetheless statistically significant (P=0.04).

Thus, it appeared that while low oxygen produced fewer cases of severe ROP in the infants who survived, this was being accomplished at the cost of fewer infants surviving. In their discussion of these results, the authors noted how this in many ways echoed results from earlier studies. For example, they observed that the increase in mortality seen in the 1950s, when oxygen restriction was first begun, was 4.9 percentage points, which was not all that different from the 3.7 percentage points difference seen between the two groups in this study. Moreover, with regard to the rate of development of ROP, they also saw confirmation of prior results: like "most non-randomized studies, our trial confirmed that lower target rates of oxygenation result in a large reduction in the incidence of severe retinopathy among survivors. However, our data suggest that there is one additional death for approximately every two cases of severe retinopathy that are prevented." They ended their discussion with the conclusion that "caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased

[11] SUPPORT Study Group. Target Ranges of Oxygen Saturation in Extremely Preterm Infants. New England Journal of Medicine 2010;362:1959.

mortality." (A subsequent publication analyzing the results from longer-term follow-up did show that among the infants that did survive, there was no difference in neurological development between the infants who received low oxygen and those who received higher oxygen.[12])

The SUPPORT study had been designed in collaboration with researchers from other countries, and very similar versions of that study were still on-going at the time these results were published. In a letter to the editor of the *New England Journal* published in April of 2011, representatives of the United Kingdom and Australia studies provided an update regarding a December 2010 joint safety analysis that had been undertaken by the data and safety monitoring boards.[13] That analysis pooled data from the 1,316 infants in the SUPPORT study, together with 2,315 infants in the U.K., Australia and New Zealand trials. The results for the entire group of 3,631 infants showed a survival advantage for the high-oxygen group that was statistically significant with a P-value of 0.015. As a result of these findings, both the U.K. and Australia trials were terminated early.

Requested Response

Please provide responses to the above determinations by March 22, 2013, including a corrective action plan to address the determination. If you identify any additional areas of noncompliance, please describe corrective actions that you have taken or plan to take to address the noncompliance.

We appreciate the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Lisa R. Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Sheila D. Moore, Director, Office of the IRB, UAB
Dr. Ferdinand Urthaler, Chair, UAB IRBs
Mr. E. Ward Sax, V.P., Chief Risk Officer, Research Triangle Institute (RTI)
Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI

[12] Y.E. Vaucher et al. Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial. New England Journal of Medicine 2012;367:2495.
[13] B. Stenson, P. Brocklehurst, and W. Tarnow-Mordi. Increased 36-Week Survival with High Oxygen Saturation Target in Extremely Preterm Infants. New England Journal of Medicine 2011;364:1680.

Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Dr. Yvonne Maddox, Deputy Director, NICHD
Dr. Rosemary Higgins, Program Scientist, NICHD
Dr. Robert H. Miller, Case Western Reserve University
Dr. Nancy C. Andrews, Duke University
Dr. Janice D. Wagner, Wake Forest University School of Medicine
Mr. Thomas Hughes, Women and Infants Hospital of Rhode Island
Dr. Clyde L. Briant, Brown University
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Dr. Jane Strasser, University of Cincinnati
Ms. Susan Blanchard, BBA, Tufts Medical Center
Ms. Angela Wishon, University of Texas Southwestern Medical Center
Dr. David Wynes, Emory University School of Medicine
Dr. Gary Chadwick, MPH, University of Rochester, School of Medicine and Dentistry
Dr. Jorge Jose, Indiana University School of Medicine
Ms. Nancy J. Lee, Stanford University School of Medicine
Dr. John L. Bixby, University of Miami, Miller School of Medicine
Dr. Hilary H. Ratner, Wayne State University
Dr. James C. Walker, University of Iowa
Dr. Andrew Rudczynski, Yale University School of Medicine
Dr. Gary S. Firestein, University of California, San Diego
Dr. Daniel L. Gross, Sharp Mary Birch Hospital for Women and Newborns
Dr. Paul B. Roth, University of New Mexico Health Sciences Center