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May 8, 2013

The Honorable Kathleen Sebelius
Secretary
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) – Analysis of the Complete Protocol and Complete Consent Form

Dear Secretary Sebelius:

We are writing in follow-up to Public Citizen's April 10 letter regarding the highly troubling SUPPORT study funded by the National Institutes of Health (NIH) and conducted by approximately 23 academic medical institutions of the Neonatal Research Network (NRN).¹ That letter highlighted important and material factual omissions regarding the purpose, nature, and risks of the research in both the SUPPORT study consent form template and the consent form approved by the University of Alabama at Birmingham (UAB) institutional review board (IRB). These omissions were uncovered by the Office for Human Research Protections (OHRP). As of April 10, Public Citizen only had access to very limited excerpts from the SUPPORT study protocol and from the UAB IRB-approved consent form that were presented in OHRP's March 7, 2013, letter to UAB,² as well as published reports in the medical literature communicating the results of the study^{3,4,5} and the abbreviated study description posted on the ClinicalTrials.gov website.⁶

Since April 10, we have obtained additional relevant information about the SUPPORT study following the recent public release of the complete protocol⁷ and the complete UAB IRB-

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>. Accessed April 24, 2013.

² Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf. Accessed April 24, 2013.

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 Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med*. 2012;367(26):2495-2504.

⁶ ClinicalTrials.gov. Surfactant positive airway pressure and pulse oximetry trial (SUPPORT); ClinicalTrials.gov identifier: NCT00233324. <http://clinicaltrials.gov/ct2/show/NCT00233324>. Accessed March 28, 2013.

⁷ 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 April 24, 2013.

approved consent form.⁸ We also have just obtained from NIH, under a Freedom of Information Act request, SUPPORT study consent forms that were approved by 21 other IRBs.⁹ Enclosed is a detailed report providing Public Citizen's analysis of these documents (see section II on pages 6-15 of the enclosed report), as well as responses to numerous statements issued by the SUPPORT study investigators and others attempting to defend the conduct of this study and the adequacy of the informed consent process (see sections III and IV on pages 15-23 of the enclosed report).

The new information highlighted in Public Citizen's report affirms the appropriateness of OHRP's determination in its March 7, 2013, letter to UAB that the UAB IRB-approved consent form failed to mention the serious, reasonably foreseeable risks related to the part of the study comparing two experimental strategies for managing oxygen in extremely premature infants. Those risks, correctly identified by OHRP, included increased risks of brain injury; an eye disease called retinopathy of prematurity, which can lead to blindness in severe cases; and death, depending on the randomized group assignment of each baby. Indeed, as Public Citizen's April 10 letter stated, the UAB IRB-approved consent form misled parents of prospective subjects by essentially indicating that the oxygen experiment component of the SUPPORT study presented no risk. Our review of all IRB-approved consent forms for the study reveals that none explained that death was a risk of the oxygen experiment and only two disclosed that eye disease or blindness was a risk of exposure to high oxygen levels.

Moreover, the new information demonstrates that the deficiencies of the UAB IRB-approved consent form were far more significant than those discussed in OHRP's March 7 letter. In particular, the IRB-approved consent forms in many, if not all, cases either did not disclose at all or did not accurately describe the following:

- (1) The experimental procedure of using pulse oximeters — devices used to continuously monitor blood oxygen levels — that were intentionally miscalibrated to provide the medical teams caring for the premature babies in the study with oxygen saturation readings that were either inaccurately low or inaccurately high (see section II.A, pages 6-8 of the enclosed report). (Only 11 consent forms disclosed in some way the plan to use this procedure, but none explained how this experimental procedure could have impacted important clinical decisions related to the babies' care.)
- (2) The substantial, reasonably foreseeable risks of harms from intentionally providing the medical teams caring for the babies in the study with inaccurate information regarding the babies' oxygen saturation levels (see section II.B, pages 9-12 of the enclosed report). This experimental procedure may have adversely impacted important clinical decisions regarding whether to intubate (an invasive procedure involving insertion of a tube into the trachea, the main airway leading to the lungs) a baby and start mechanical ventilation (treatment with an artificial breathing machine) or whether to extubate (remove the breathing tube from the trachea) an intubated baby and discontinue mechanical ventilation. For example, because of this experimental procedure:

⁸ IRB-approved consent form for the SUPPORT trial. <http://www.citizen.org/documents/support-study-consent-form.pdf>. Accessed May 7, 2013.

⁹ *Ibid.*

- (a) Some babies in the high-oxygen group may have undergone protocol-driven intubations and been placed on mechanical ventilation when such procedures were not clinically indicated. This could have unnecessarily exposed some babies to increased risk of: (i) trauma to the mouth and gums during intubation; (ii) trauma to the trachea, resulting in bleeding and puncture of the airway during intubation; (iii) pneumothorax (collapsed lungs, possibly resulting in the need for insertion of chest tubes); (iv) pneumonia during mechanical ventilation; and (v) death (see example on page 11 of the enclosed report).
- (b) Some babies in the low-oxygen group may have had actual clinical indications for intubation and mechanical ventilation, but because of inaccurate oxygen saturation levels, these treatments may have been inappropriately delayed. This could have unnecessarily exposed some babies in the low-oxygen group to increased risk of prolonged hypoxemia (oxygen deficiency) with inadequate oxygen delivery to the brain, resulting in neurological damage and possibly death (see example on pages 11-12 of the enclosed report).
- (3) The investigators' characterization in the protocol, but not in the consent form, of the high-oxygen target levels as being "more conventional" and, by implication, the low-oxygen target levels being less conventional (see section II.C on pages 12-13 of the enclosed report). (Only two consent forms suggested an oxygen saturation range that was most commonly used in routine practice.)
- (4) An explanation of how the experimental procedures for managing the oxygen therapy of the babies deviated from the usual standard of care the babies would have received had they not been enrolled in the study.

A particularly disturbing finding in our analysis of the complete protocol and the IRB-approved consent forms is that most of the consent forms included extraordinarily misleading statements like the following:¹⁰

"There is no known risk to your baby from monitoring with the pulse oximeters used for this study."

or

"Because all of the treatments proposed in this study are standard of care, there is no expected increase in risk for your infant."

The absence of these critical elements of information about the purpose, nature, and risks of the the SUPPORT study's complex oxygen experiment, combined with the inclusion of statements indicating that the experimental procedures had no risk, denied the parents of babies enrolled in the trial the opportunity to make an informed decision when they gave consent for the research. As stated in Public Citizen's April 10, 2013, letter to you, the failure to disclose this critically important information to the parents represented a serious violation of research ethics.

¹⁰ *Ibid.*

Thus, the newly available information demonstrates that OHRP did not go far enough in its March 7 letter to UAB. The agency should have cited UAB and the other SUPPORT study institutions for additional serious deficiencies in the IRB-approved consent form regarding the lack of disclosure of critically important information about the purpose, nature, and risks of the oxygen experiment.

Furthermore, a review of the complete protocol appears to indicate that the IRBs that approved the study lacked crucial information that would have been necessary for them to determine whether risks to the babies enrolled in the research were minimized by using procedures consistent with sound research design and that did not unnecessarily expose subjects to risk (see section II.D on pages 13-15 of the enclosed report). Important details regarding each of the following were omitted from the protocol:

- (1) a description of the usual standard of care for critically ill premature babies regarding such critical issues as the individualized adjustment of FiO_2 and decisions about intubation, extubation, and mechanical ventilation at the NRN medical centers.;
- (2) the risks associated with the experimental oxygen interventions, including those related to use of intentionally miscalibrated pulse oximeters;
- (3) the plan for unblinding the NICU medical teams when the masking procedure using intentionally miscalibrated pulse oximeters posed a threat to the health of the babies; and
- (4) the safety monitoring plan.

The omitted information was essential for understanding the nature of the research and its risks. Lacking this information, it is unclear how the IRBs that reviewed the study were able to make the determinations required for IRB approval under the Department of Health and Human Services (HHS) human subjects protection regulations, particularly the determination that the risks to subjects were minimized.

Some critics of OHRP's determinations regarding the SUPPORT study argue that the agency's action in this case poses a threat to biomedical research and the advancement of medical knowledge and innovation. However, the real threat to such scientific endeavors is unethical research, which understandably undermines the public's trust in the motives and conduct of researchers. Conformance with the fundamental ethical principles for conducting human subjects research must never be sacrificed in the quest to advance medical knowledge. Such conformance is necessary to preserve the public's trust in the motives and conduct of researchers.

Finally, the new information discussed in the enclosed report greatly heightens our concern regarding the seven clinical trials currently being conducted or about to be initiated by the NRN, as discussed in Public Citizen's April 15, 2013, letter to you. Six of these trials are already under way. These studies have a combined projected enrollment of more than 4,500 newborn babies, and death is a primary endpoint in six of the seven studies. More than three weeks have passed since we requested that the complete protocols, consent form templates, and all IRB-approved versions of the consent form for these seven studies immediately be made publicly available for independent review. Release of these documents could be accomplished with little time and

effort since they certainly exist in digital format. To our knowledge, none of these important documents have been made public yet. Therefore, we renew our request for the release of these documents. Any further delay in releasing these documents will be construed by the public as a cover-up by HHS of important details of ongoing studies on newborn babies by many of the same investigators who erred so grievously in the SUPPORT trial. It is also more imperative than ever that enrollment in these new trials be suspended immediately, pending independent review of the protocols and consent forms for these experiments.

We respectfully request an opportunity to meet with you to discuss these important human subjects research issues after you have had an opportunity to review our report.

Please contact us if you have any questions or need additional information.

Sincerely,

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Enclosure

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**Report Prepared for
Secretary of Health and Human Services Kathleen Sebelius**

**Analysis of the Complete Protocol and
Consent Form for the SUPPORT Study:
Lack of Informed Consent and a Failure to
Ensure That Risks Were Minimized**

May 8, 2013

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About Public Citizen

Public Citizen is a national nonprofit organization with more than 300,000 members and supporters. We represent consumer interests through lobbying, litigation, administrative advocacy, research, and public education on a broad range of issues, including consumer rights in the marketplace, product safety, financial regulation, safe and affordable health care, campaign finance reform and government ethics, fair trade, climate change, and corporate and government accountability.

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I. Background

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), funded by the National Institutes of Health (NIH), involved 1,316 extremely premature infants enrolled between 2005 and 2009 at more than 20 prominent medical research centers throughout the U.S.¹ The infants in the study were born at approximately 24 to 28 weeks gestation and weighed an average of less than two pounds.² The research centers that participated in the SUPPORT study are part of a multi-institution group known as the Neonatal Research Network (NRN), which was established in 1986 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development to conduct research studies on preterm and term newborns.

The SUPPORT study involved 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.³ Babies in one group were treated with a face mask, called a continuous positive airway pressure (CPAP) mask, to deliver pressurized air supplemented with oxygen; in this group (**CPAP group**), the babies breathed on their own. Babies in the other group were intubated (underwent an invasive procedure involving insertion of a tube inserted into the trachea, the main airway leading to the lungs); given the drug surfactant, which helps the lungs stay open; and placed on mechanical ventilation (an artificial breathing machine; **mechanical-ventilation group**).

For the other, simultaneous experiment, which is the primary focus of this report, babies assigned to both the CPAP and mechanical-ventilation groups were further randomly divided between a low-oxygen group and a high-oxygen group.⁴ 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), rather than adjust each baby's oxygen levels within the broader range of 85 to 95 percent to meet his or her individual needs, as would have been the case if the baby had not been in the study. 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.

In 2011, the Office for Human Research Protections (OHRP) — a regulatory office within the Department of Health and Human Services (HHS) Office of the Secretary that is charged with enforcing the HHS human subjects protection regulations at 45 C.F.R. Part 46 — opened a compliance oversight investigation of the SUPPORT study, apparently after receiving allegations that the study violated provisions of these regulations.⁵ On March 7, 2013, OHRP sent a

¹ 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.

² *Ibid.*

³ 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.

⁴ 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.

⁵ Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf. Accessed April 24, 2013.

compliance oversight determination letter to the University of Alabama at Birmingham (UAB) — the lead institution for the oxygen experiment component of the SUPPORT study — stating that the “the [consent forms] for this trial failed to adequately inform parents of the reasonably foreseeable risks and discomforts of research participation.” In particular, OHRP noted that the UAB IRB-approved consent forms signed by parents of babies who enrolled in the study failed to explain that:⁶

- (1) The study involved substantial risks, and there was significant evidence from past research indicating that the level of oxygen provided to a premature baby can have an important effect on many outcomes, including whether the baby could become blind, develop serious brain injury, and even possibly die;
- (2) By participating in this study, the level of oxygen a baby received would in many instances be changed from what they would otherwise receive;
- (3) Some babies would receive more oxygen than they otherwise would have, in which case, if the researchers were correct in how they supposed oxygen affects the eyes, those infants would have a greater risk of going blind; and
- (4) The level of oxygen being provided to some babies, compared to the level they would have received had they not participated, could increase the risk of brain injury or death.

In its March 7 letter, OHRP noted that the agency had reviewed the consent forms approved by the IRBs for all SUPPORT study institutions and had found problems with all of them similar to those described above.⁷ However, OHRP only required that UAB submit a plan to ensure that IRB-approved consent forms include and adequately address all elements of informed consent required under the HHS human subjects protection regulations.

On April 10, 2013, Public Citizen wrote to Secretary of Health and Human Services Kathleen Sebelius, expressing concern that OHRP did not go far enough in its determinations of noncompliance and in the scope of its required action.⁸ While agreeing with OHRP that the SUPPORT study consent forms failed to disclose the substantial risks of the research, Public Citizen asserted that based on the information presented in OHRP’s letter, the agency should have found that the UAB IRB-approved consent form failed to disclose one key purpose of the research — to see whether babies were more likely to die in the low- or high-oxygen group — and failed to identify as experimental the procedures for targeting the low and high oxygen saturation targets and explain how these procedures compared to the usual standard of care for managing oxygen therapy in premature babies not involved in the study. Public Citizen also stated that OHRP should have required that all NRN institutions that conducted the SUPPORT study take corrective actions to address the serious deficiencies in the consent forms.

⁶ *Ibid.*

⁷ *Ibid.*

⁸ 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>. Accessed April 24, 2013.

Finally, Public Citizen urged in its April 10 letter that the Secretary, along with NIH Director Francis Collins, personally apologize to the parents of the 1,316 babies enrolled in the SUPPORT study and divulge to them the information previously not disclosed regarding the purpose, nature, and risks of the experiment.

Following widespread media attention about OHRP's March 7 letter to UAB and Public Citizen's April 10 letter to the Secretary, the SUPPORT study investigators and others have issued numerous public statements defending the conduct of the study and the adequacy of the informed consent process.

As of the April 10 letter, Public Citizen only had access to very limited excerpts from the SUPPORT study protocol and from the UAB IRB-approved consent form that were presented in OHRP's March 7, 2013, letter to UAB, as well as published reports in the medical literature communicating the results of the study^{9,10,11} and the abbreviated study description posted on the ClinicalTrials.gov website.¹² Since April 10, we have obtained additional relevant information about the SUPPORT study following the recent public release of the complete protocol and the complete UAB IRB-approved consent form. Public Citizen also has just obtained from NIH, under a Freedom of Information Act request, SUPPORT study consent forms that were approved by 21 other IRBs (see the Appendix for the complete list of institutions).¹³ This report provides Public Citizen's analysis of these complete documents, as well as responses to numerous statements issued by the SUPPORT study investigators and others attempting to defend the conduct of this study and the adequacy of the informed consent process.

II. Analysis of new information gleaned from the complete SUPPORT study protocol and the IRB-approved consent forms

A. Neonatal intensive care unit (NICU) medical teams caring for critically ill premature babies were intentionally provided with inaccurate oxygen saturation levels

The most disturbing finding from our review of the newly available information was the failure of half of the IRB-approved consent forms to disclose to the parents of the subjects the 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 pulse oximeters miscalibrated across the wide range of oxygen saturations between 85% and 95%. Of note, oxygen saturation measured by a pulse oximeter is a clinical parameter of such importance in monitoring critically ill patients that it is sometimes

⁹ 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.

¹⁰ 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.

¹¹ Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med.* 2012;367(26):2495-2504.

¹² ClinicalTrials.gov. Surfactant positive airway pressure and pulse oximetry trial (SUPPORT); ClinicalTrials.gov identifier: NCT00233324. <http://clinicaltrials.gov/ct2/show/NCT00233324>. Accessed March 28, 2013.

¹³ IRB-approved consent form for the SUPPORT trial. <http://www.citizen.org/documents/support-study-consent-form.pdf>. Accessed May 7, 2013.

referred to as the “fifth vital sign” (the first four vital signs being pulse, blood pressure, breathing rate, and temperature).¹⁴

Equally disturbing is our finding that *none* of the IRB-approved consent forms disclosed the dangers posed to the babies by giving the entire medical team such intentionally inaccurate information about their oxygen saturation levels.

This experimental procedure is explained in the following excerpts from the protocol:¹⁵

(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]

(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%.

The following table¹⁶ reveals the displayed (i.e., intentionally inaccurate) oxygen saturation levels relative to each actual oxygen saturation level between 85% and 95% for infants in both the high-oxygen and low-oxygen groups:

¹⁴ Neff TA. Routine oximetry: A fifth vital sign. *Chest*. 1988;94(2):227.

¹⁵ 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 April 24, 2013.

¹⁶ The table was constructed by extracting data from Table 1 on page 17 of the complete protocol and from the unnumbered figure on page 18 of the protocol.

Table: Actual and inaccurately displayed oxygen levels in high- and low-oxygen-group babies

Displayed for high oxygen group (intentionally low)	84%	85%	85%	85%	85%	86%	87%	88%	89%	90%	92%	92-94%	96%
Actual	84% <i>(Alarm)</i>	85%	86%	87%	88%	89%	90%	91%	92%	93%	94%	95%	96% <i>(Alarm)</i>
Displayed for low oxygen group (intentionally high)	84%	86-88%	88%	90%	91%	92%	93%	94%	95%	95%	95%	95%	96%

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 5% to 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.

In addition, for the high-oxygen group, a *displayed* oxygen saturation level of 85% meant the *actual* level was anywhere between 85% and 88%, whereas for the low-oxygen group, a *displayed* oxygen saturation level of 95% meant the *actual* level was anywhere between 92% and 95% (in both cases, the actual value was unknown to the medical teams caring for these babies). These differences in the actual saturation levels between groups for any given inaccurately displayed level, particularly the 5% to 6% between-group differences for the displayed range of 88% to 92%, represented clinically important differences in the babies' actual blood oxygen content. Such differences certainly could have adversely impacted the management decisions that were being made by the medical teams caring for the babies in the SUPPORT study.

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. What we do not know because the study lacked a usual standard of care control group, but suspect, is that if the medical teams had been given the correct information about oxygen saturation levels and these babies had been treated based on their individual needs as per current routine standard of practice, some deaths might have been prevented in the low-oxygen group, and some cases of severe retinopathy might have been prevented in the high-oxygen group.

B. Half of the IRB-approved consent forms did not disclose the experimental procedure for intentionally providing the NICU medical teams with inaccurate oxygen saturation levels, and none disclosed the risks of this procedure

To our dismay, half (11) of the 22 IRB-approved consent forms for the SUPPORT study did not disclose to the parents that if they enrolled their babies in this experiment, their babies' entire medical team would be intentionally given inaccurate information about the babies' oxygen saturation levels.¹⁷ Also, none of the consent forms described how this experimental procedure could have impacted important clinical decisions related to the babies' care.¹⁸ This protocol-specified procedure was a clear departure from the standard of care that these critically ill babies would have received had they not been enrolled in the study. Moreover, the protocol offered no evidence that this experimental approach was safe. Indeed, routinely providing the entire medical team with inaccurate information about blood oxygen saturation levels, a critically important clinical parameter monitored in these premature babies, may well have exposed these babies to potentially serious, life-threatening risks. This experimental procedure presented important additional risks beyond those associated with attempting to confine the premature babies' oxygen saturation levels to either a high- or low-oxygen range. No such risks were described in any of the IRB-approved consent forms. In fact, at least three of the consent forms, including the form approved by the UAB IRB, made the following extraordinarily misleading statement:¹⁹

“There is no known risk to your baby from monitoring with the pulse oximeters used for this study.”

Many other IRB-approved consent forms made statements like the following:²⁰

“Because all of the treatments proposed in this study are standard of care, there is no expected increase in risk for your infant.”

Understanding the clinical importance of oxygen saturation levels in the routine management of premature babies is essential for recognizing the serious risks of providing protocol-specified misinformation to the NICU medical teams that cared for the infants in the SUPPORT study. These risks become apparent when one considers the protocol-specified criteria that were used to make decisions about whether these babies should be intubated and placed on mechanical ventilation or extubated if they were already on a ventilator. To understand these criteria, it is important to first remember that the SUPPORT study included a second simultaneous experiment, in addition to the experiment testing differences in oxygen saturation target ranges, in the same 1,316 babies enrolled in the study. For this second experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing following delivery. Babies in one group were treated with a face mask, called a CPAP mask, to deliver pressurized air supplemented with oxygen; in this group, the babies breathed on their own. Babies in the other group were intubated; given the drug surfactant, which helps the

¹⁷ IRB-approved consent form for the SUPPORT trial. <http://www.citizen.org/documents/support-study-consent-form.pdf>. Accessed May 7, 2013.

¹⁸ *Ibid.*

¹⁹ *Ibid.*

²⁰ *Ibid.*

lungs stay open; and placed on mechanical ventilation. Babies assigned to each of these two groups were further randomly assigned to the low-oxygen group or the high-oxygen group.

Because the investigators recognized that some babies assigned to the CPAP group might not have been able to sustain adequate breathing on their own, the protocol specified rescue criteria that allowed the medical team to intubate the baby and place him or her on a ventilator. The oxygen saturation level measured by an intentionally inaccurate pulse oximeter was one such criterion. This is described in the following excerpt from the protocol:²¹

(Page 14, under heading “NICU Management”) [The babies assigned to the CPAP group] *MAY* be intubated if they meet *ANY* of the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant

Intubation:

- An $\text{FiO}_2 > .50$ ^[22] required to maintain an indicated [oxygen saturation level] $\geq 88\%$ (using the altered Pulse Oximeters) for one hour... [Emphasis in original]

Like the medical decision regarding intubation of study babies, the protocol also stipulated that for a CPAP-group baby who *had been intubated*, the medical team must attempt to extubate the baby based on criteria that included a protocol-specified threshold oxygen saturation level of 88%:²³

(Page 14, under the heading “Extubation”) An intubated CPAP-Treatment infant *MUST* have extubation attempted within 24 hours if *ALL* of the following criteria are met and documented on a single blood gas

- $\text{PaCO}_2 < 65$ torr with a $\text{pH} > 7.20$ (arterial or capillary samples)
- An indicated $\text{SpO}_2 \geq 88\%$ with an $\text{FiO}_2 \leq 50\%$
- A mean airway pressure (MAP) < 10 cm H₂O, ventilator rate ≤ 20 bpm, an amplitude $< 2X$ MAP if on high frequency ventilation (HFV)
- Hemodynamically stable...
- Absence of clinically significant PDA

[Emphasis in original]

The protocol further specified that use of these criteria for intubation and extubation decisions were to continue for the first 14 days of life.

²¹ 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 April 24, 2013.

²² FiO_2 means the fraction of inspired oxygen, which is the oxygen composition of the inspired air. Room air has an FiO_2 of .21 (21% oxygen). The FiO_2 can be increased to a maximum of 1.00, which would be 100% oxygen.

²³ 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 April 24, 2013.

The fact that the protocol-specified criteria for making the crucial medical decisions regarding whether to intubate or extubate critically ill premature babies were based on oxygen saturation levels, as measured by a pulse oximeter, is important for two reasons. First, it underscores the vital importance of the actual, real oxygen saturation levels in the hour-to-hour management of FiO₂s settings (the level of supplemental oxygen), mechanical ventilation treatments, and many other clinical decisions in critically ill premature babies.

Second, and more relevant to the babies who were enrolled in the SUPPORT study, the intentional provision of inaccurate oximetry information to the medical teams caring for these babies posed significant risks for these babies. For example, the inaccurate oxygen level readings could have led the medical teams to intubate and artificially ventilate some babies who did not need to undergo these medical procedures, thus unnecessarily exposing the babies to the risks of intubation and mechanical ventilation. On the other hand, the inaccurate oxygen level readings could have led the medical teams to *not* intubate and mechanically ventilate other babies who did need these medical procedures, thus exposing them to risks of inadequate oxygen delivery.

The risks of intentionally providing the medical teams with *inaccurate* oxygen saturation levels are best understood by considering how this inaccurate data, combined with the protocol-specified criteria for intubating or extubating CPAP-group babies — criteria presumably based on *accurate* oxygen saturation levels in the setting of routine standard of care — could have altered the care of a baby assigned to the high-oxygen group versus a baby assigned to the low-oxygen group.

First consider a baby in the CPAP group who was randomly assigned to the high-oxygen target range and therefore had not been intubated. Let us suppose the baby, during the first day of life, needed an FiO₂ of 0.55 to breathe in order to maintain an oxygen saturation level of 88% as *inaccurately displayed* on the miscalibrated pulse oximeter. The baby really would have had an *actual* oxygen saturation level of 91%. If the medical team had had an *accurate* pulse oximeter reading of 91%, the team likely would have lowered the FiO₂ to 0.50. If the baby's actual oxygen saturation level subsequently remained at or above 88%, the baby would not have needed to be intubated. However, because the medical team received only the inaccurate pulse oximetry reading of 88%, the team could well have decided, under the protocol-specified rescue criteria for babies in the CPAP group, to intubate the baby and start mechanical ventilation when it likely was not clinically necessary. This could have unnecessarily exposed some high-oxygen group babies to increased risk of: (a) trauma to the mouth and gums during intubation; (b) trauma to the trachea, resulting in bleeding and puncture of the airway during intubation; (c) pneumothorax (collapsed lungs, possibly resulting in the need for insertion of chest tubes); (d) pneumonia during mechanical ventilation; and (e) death. If the now inappropriately intubated baby survives to be subsequently extubated, the same circumstances that led to the first inappropriate intubation could recur, leading to a second inappropriate intubation and unnecessary exposure again to the same risks.

Now consider a second baby in the CPAP group who was randomly assigned to the low-oxygen target group. Let us suppose the baby, during the first day of life, maintained an *inaccurate* oxygen saturation level displayed as 88% on the miscalibrated pulse oximeter while breathing an FiO₂ of 0.50. In reality, the baby *actually* would have had an oxygen saturation level of 85% to

86%, already below the threshold that should have triggered rescue intubation and mechanical ventilation. If the medical team had had an *accurate* pulse oximeter reading, the team likely would have raised the FiO₂ above 0.50 to try to increase the oxygen saturation level. If after one hour, the *actual* oxygen saturation remained at or below 88% on the higher FiO₂, the baby likely could have been intubated. However, because the medical team received only the inaccurate pulse oximetry reading of 88%, clinically indicated intubation of the baby may have been delayed. Inappropriate delays in making necessary changes in care, including making adjustments in the FiO₂ and performing clinically indicated intubation, could have unnecessarily exposed some babies in the low-oxygen group to increased risk of prolonged hypoxemia with inadequate oxygen delivery to the brain, resulting in neurological damage and possibly death.

Finally, continuing one step further with the example of the baby in the low-oxygen group, let us suppose this baby was finally intubated when the *inaccurately* displayed oxygen saturation level fell to 85% for more than one hour while breathing on an FiO₂ of 0.55. Inappropriate extubation subsequently could have occurred *too soon* when the *inaccurately* displayed oxygen saturation level increased to greater than 88% on the miscalibrated pulse oximeter while the baby was on an FiO₂ less than 0.50 (with all other criteria for extubation met), when in fact the *actual* oxygen saturation level was 85% to 86%. Like the first example, this sequence could have repeated itself leading to a second inappropriately delayed intubation followed by another too-soon extubation.

Remarkably, the following statement from the protocol indicates that the investigators were well aware that the criteria of intubating and extubating the babies in the CPAP group, in the context of inaccurate oxygen saturation reading, could lead to inappropriate intubations and extubations and must have understood the risks:²⁴

(Page 15, under the heading “D/C CPAP) *CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.* [Emphasis in original]

It is truly disturbing that the investigators failed to clearly describe in the protocol and the consent forms the potential for both (a) protocol-driven intubations and extubations that *would not be* clinically indicated; and (b) protocol-driven delays in intubations or extubations that *would be* clinically indicated, as well as the risks of such protocol-driven events related to the oxygen experiment in the SUPPORT study. Equally disturbing is the apparent failure of the reviewing IRBs to recognize these risks.

C. None of the 22 IRB-approved consent forms disclosed that the high-oxygen saturation target was considered “more conventional” by the investigators, despite this being stated in the protocol

Another disturbing revelation gleaned from the just-released SUPPORT study protocol is the following summary statement of the oxygen experiment design:²⁵

²⁴ *Ibid.*

²⁵ *Ibid.*

(Page 9, section 2.1, Study Design) 2) A prospective comparison of a lower SpO₂ range (85% to 89%) with a **higher more conventional SpO₂ range (91% to 95%)** until the infant is no longer requiring ventilatory support or oxygen. [Emphasis added]

Thus, the IRBs were informed by the investigators that the high-oxygen saturation target range was considered to be “more conventional” treatment for premature babies receiving routine standard of care, which implicitly means that the low-oxygen saturation target range was more unconventional. This characterization of the relative difference between the low and high oxygen targets used in the two experimental oxygen groups is in clear conflict with the following misleading statement presented to parents of the premature babies in the UAB IRB-approved consent form, which implied that both the low and the high range were equally conventional:²⁶

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.** [emphasis added]

Similar statements were made in the consent forms approved by IRBs at nearly all of the other participating institutions.

Two consent forms appeared to suggest that oxygen saturation ranges other than the two target ranges used in the SUPPORT study were most commonly used. For example, the IRB-approved consent form for Duke University Health System (DUHS) noted that the “aim in many units is to keep oxygen saturations between 88 and 92%,” although it did not explain whether this was the case at DUHS.²⁷ Likewise, the IRB-approved consent form for Tufts Medical Center stated that at “Tufts Medical Center oxygen saturation is kept between 88-94%.”²⁸ Disclosures of the oxygen saturation ranges most commonly targeted when caring for premature babies, such as the statement made in the Tufts Medical Center IRB-approved consent form, should have been made in the consent forms for all SUPPORT study institutions.

To summarize the deficiencies in the SUPPORT study consent process, the information now available from the complete SUPPORT study protocol and the IRB-approved consent forms demonstrates that parents gave consent for their babies to be enrolled in the SUPPORT study based on misleading information and without being provided with critically important information about the purpose, nature, and risks of this complex oxygen experiment.

D. The SUPPORT study protocol omitted critically important information necessary for understanding the full range of risks of the study and for assessing whether the risks to the subjects would be minimized

Finally, it is important to recognize the essential information that was *not* included in the full SUPPORT study protocol.

²⁶ IRB-approved consent form for the SUPPORT trial. <http://www.citizen.org/documents/support-study-consent-form.pdf>. Accessed May 7, 2013..

²⁷ *Ibid.*

²⁸ *Ibid.*

First, the protocol lacked a robust, detailed explanation of the usual standard of care regarding such critical issues as the individualized adjustment of FiO_2 and decisions about intubation, extubation, and mechanical ventilation in critically ill premature infants at the NRN medical centers. For example, the protocol should have described in detail the clinical factors taken into account by expert neonatologists at these centers when making individualized decisions to adjust FiO_2 in extremely premature newborns. The protocol also should have described the criteria under the usual standard of care for making decisions about intubation, extubation, and mechanical ventilation, including the role of actual oxygen saturation levels. Without such information, it was not possible for the IRBs that approved this experiment to determine whether risks to the babies were minimized given: (a) the complexity of usual medical care in the NICU setting, (b) the added complexity of the experimental interventions in the study, and (c) the interactions between (a) and (b).

Second, the protocol failed to indicate whether it was ever standard of care at *any* participating NICU to routinely attempt to maintain the oxygen saturation levels for all extremely premature babies, regardless of their clinical status, within the range of 85% to 89%, and if so, how frequently this was the case. This information was particularly relevant to understanding the risks of the research and whether they were minimized because the investigators had indicated that the oxygen saturation target range of 91% to 95% was the “more conventional” of the two target oxygen saturation ranges being tested. This important acknowledgement by the investigators warranted further explanation. Of concern, the protocol offered no evidence that before developing the protocol, the SUPPORT study investigators had conducted a systematic survey of previous medical records of NICU babies in order to document current routine standard of practice for managing oxygen treatment in premature babies within their own NICUs.

Third, given the complexities of routine medical management of extremely premature infants and the interaction between the different complex experimental interventions of the SUPPORT study, the minimization of the risks to babies enrolled in the study would have required a detailed plan for unblinding the NICU medical teams when the masking procedure using intentionally miscalibrated pulse oximeters posed a threat to the health of the babies. The complete SUPPORT study protocol lacked such a detailed plan.

Fourth, because (a) the oxygen experiment involved only two experimental groups and no control group, and (b) the primary efficacy endpoint was a composite of the two competing harms of death and retinopathy, adequate safety monitoring would have required periodic checking for differences between the low-oxygen and high-oxygen groups for both death and retinopathy *separately*. This is reflected in the way the results were presented in the published paper.²⁹ According to the protocol, death was monitored as an adverse event, but retinopathy was not. The IRBs that reviewed and approved the study did not appear to understand the complexities of the oxygen experiment component of the SUPPORT study and the off-setting risks involved, and as a result, they were unable to determine whether the monitoring plan was sufficient to ensure the safety of the babies and minimize risks to them.

²⁹ 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.

For example, retinopathy should have been monitored as an adverse event and monitored closely. For the low-oxygen group babies, death was a risk and was monitored. For the high-oxygen group babies, retinopathy was the risk and should have been monitored as an adverse event, but the protocol safety monitoring plan did not indicate that it was. Because retinopathy, part of the primary composite efficacy endpoint, often requires surgery and can lead to blindness, it represented a clear potential harm to the babies of significant enough degree to require monitoring. The study demonstrated that the high-oxygen group babies had a highly significant increase in retinopathy in comparison to the low-oxygen group babies ($p < 0.001$).³⁰ If the incidence of retinopathy had been monitored separately as an important adverse event in the high-oxygen group at increased risk for this adverse outcome and compared to the incidence in the low-oxygen group, a recommendation to stop the trial early probably could have been made by the data and safety monitoring board, potentially saving lives in the low-oxygen group due to hypoxemia and decreasing the need for retinal surgery in the high-oxygen group.

It is very troubling that the protocol omitted so many crucial details regarding the usual standard of care for the individualized adjustment of FiO₂ and decisions about intubation, extubation, and mechanical ventilation in critically ill premature infants at the NRN medical centers; the risks associated with the experimental oxygen interventions; and the safety monitoring plan, all of which were essential for understanding the nature of the research and its risks. Lacking this information, it is unclear how the IRBs that reviewed the study were able to make the determinations required for IRB approval under the HHS human subjects protection regulations, particularly the determination that the risks to subjects were minimized.

III. General response to criticisms by the SUPPORT study investigators and others who have objected to OHRP's determinations of consent-form deficiencies

In response to OHRP's March 7 letter to UAB, the SUPPORT study investigators and others have issued numerous public statements in an attempt to defend the conduct of this study and the adequacy of the informed consent process. We therefore want to take this opportunity to explain some of the important, serious flaws in the arguments being made publicly by the investigators^{31,32} and their supporters.^{33,34}

The primary argument offered by those objecting to OHRP's finding of inadequate disclosure of study risks essentially goes as follows: The usual care for all critically ill, extremely premature infants in major academic NICUs across the U.S. at the time the study was conducted involved targeting their oxygen saturation *anywhere* between 85% and 95% without regard to *any* individual-specific clinical factors. For *all* such premature babies at *any time* during their NICU

³⁰ *Ibid.*

³¹ Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med*. Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.

³² Finer NN, Bell EF, Van Meurs K. Consent forms in a clinical trial for premature babies (letter to the editor). *The New York Times*. April 19, 2013. <http://www.nytimes.com/2013/04/19/opinion/consent-forms-in-a-clinical-trial-of-premature-babies.html?ref=todayspaper>. Accessed April 24, 2013.

³³ Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT (editorial). *N Engl J Med*. Published online April 17, 2013. DOI: 10.1056/NEJMe1304996.

³⁴ Magnus D, Caplan AL. Risk, Consent, and SUPPORT. *N Engl J Med*. Published online April 18, 2013. DOI: 10.1056/NEJMp1305086.

stay, adjusting oxygen therapy to achieve *any* more narrowly defined target oxygen saturation band within the broader 85-95% range represented usual standard of care. Therefore, the experiment presented no risk to the babies.

This argument does not survive serious scrutiny. First, as noted above, the investigators themselves stated in the protocol that the higher oxygen saturation target range was the “more conventional” of the two oxygen saturation target ranges that were to be tested.

Second, taken to its logical conclusion, this argument would allow one to posit that the SUPPORT study’s oxygen experiment could have been conducted with even more narrowly defined oxygen saturation target bands at the extremes of the 85% to 95% “normal range” without exposing premature babies to increased risks in comparison to usual standard of care in 2005. Experimental interventions limiting the target oxygen saturation ranges to increasingly narrower bands at opposite ends of the 85% to 95% range, combined with intentionally providing the medical team with inaccurate information about the babies’ oxygen saturation levels, would have had an even more profound adverse impact on the morbidity and mortality risks for premature babies.

Third and most important, despite the gaps in scientific knowledge regarding oxygen management in premature infants at the time the SUPPORT study was initiated, it is inconceivable that in 2005, highly trained, expert neonatologists providing routine individualized care outside the research context did not adjust FiO₂ levels to achieve different oxygen saturation levels — in different babies and at different times for the same baby — within the broad range of 85-95% based on important clinical indicators of tissue oxygenation. These indicators would include base deficit levels (an elevated base deficit generally would be indicative of inadequate oxygen delivery to tissues of the body, and increasing the FiO₂ in order to increase the baby’s oxygen saturation level would be one major treatment change to address this problem), other individual clinical factors, and consultations with parents regarding balancing of specific risks.

Thus, condensed and incomplete descriptions of the complex usual standard of care for managing supplemental oxygen treatments in extremely premature babies — such as the informed consent statements that “All of these saturations [i.e., 85-89% and 91-95%] are considered normal ranges for premature infants”³⁵ — were misleading to parents who gave consent for their babies to be in the SUPPORT study and, when repeated today, mislead the public.

To accomplish the goals of their oxygen experiment, the investigators first allowed a computer to randomly assign extremely premature babies to one of two narrowly constrained target oxygen saturation ranges, rather than individually adjusting oxygen based solely on the expert judgment of highly trained neonatologists. The investigators then provided the entire medical team caring for these babies with pulse oximeters that were intentionally programmed to provide inaccurate information regarding the oxygen saturation levels. Thus, because of these two protocol-specified procedures, babies in the study received experimental oxygen management

³⁵ IRB-approved consent form for the SUPPORT trial. <http://www.citizen.org/documents/support-study-consent-form.pdf>. Accessed May 7, 2013..

interventions that were substantially different from the usual standard of care they would have otherwise received had their parents not consented to the research.

IV. Responses to specific statements by the SUPPORT study investigators and others who have objected to OHRP's determinations of consent-form deficiencies

Beyond this flawed primary argument, Public Citizen addresses below some of the other public statements recently made by the SUPPORT study investigators,³⁶ the editors of *The New England Journal of Medicine (NEJM)*,³⁷ and two bioethicists who authored a *NEJM* perspective article,³⁸ all of which attempt to defend the conduct of the SUPPORT study, especially the adequacy of the informed consent process.

A. SUPPORT study investigators

The following are some recent statements made by the SUPPORT study investigators, with our comments in response in italics after each:

Investigators: Death was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected.³⁹

Our comments: The investigators argue that they did not expect to see an increased rate of death in the low-oxygen group, and therefore it was not a risk that needed to be disclosed in the consent forms signed by parents of babies enrolled in the study. However, this argument is belied by multiple other statements made by the investigators in the protocol and elsewhere.

First, the purpose of the SUPPORT study was to test different experimental strategies for managing oxygen and ventilation therapy in premature infants and assess their effects on primary composite endpoints that all included death as an outcome. This is reflected in the study's primary hypotheses and in the protocol's statistical analysis plan.⁴⁰ Death obviously was the most important component for these primary endpoints. Death alone also was pre-specified as an important secondary endpoint across all four study groups. Comparisons of the primary and secondary outcomes across all four study groups was planned and performed with two-sided P-values.^{41,42} The plan to use two-tailed P-values

³⁶ Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med*. Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.

³⁷ Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT (editorial). *N Engl J Med*. Published online April 17, 2013. DOI: 10.1056/NEJMe1304996.

³⁸ Magnus D, Caplan AL. Risk, Consent, and SUPPORT. *N Engl J Med*. Published online April 18, 2013. DOI: 10.1056/NEJMp1305086.

³⁹ Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med*. Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.

⁴⁰ 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 April 24, 2013.

⁴¹ *Ibid.*

⁴² 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.

when analyzing the data for the primary and secondary endpoints is an acknowledgement that the investigators wanted to test for two plausible possibilities. Thus, for the comparison between the low- and high-oxygen groups, the investigators clearly planned to assess whether the composite efficacy endpoint of death plus retinopathy, as well as the secondary endpoint of death alone, would have been higher or lower in one group versus the other.

Second and more important, by correctly stating that “[death] competes with retinopathy,”⁴³ the investigators acknowledged that they also were aware — prior to the initiation of the study — that trying to decrease the risk of retinopathy could potentially increase the risk of death. The fact that the investigators may not have expected that there would be a difference in mortality between the two experimental groups is not a valid basis for concluding that death was not a risk of the experiment.

There should have been a concern among both the investigators and the IRBs at the time the research protocol was developed and reviewed that mortality could be increased in the low-oxygen group. An increase in retinopathy also should have been recognized as a risk for the high-oxygen group. Moreover, because the study lacked randomization of babies to a routine standard-of-care control group, we are left not knowing how the two experimental treatments compared to usual standard of care at the time.

Clearly, the parents should have been told that: (a) one primary purpose of the experiment was to determine which range of oxygen level would have a higher rate of death, and (b) death was a risk of the research depending on the randomized group assignment of each baby. The failure to disclose this information represented a serious violation of research ethics.

Investigators: The best evidence available when we planned the study was that oxygen saturations of 70 to 90% were associated with less retinopathy without an increase in mortality.⁴⁴

*Our comments: To support this statement, the investigators cite a small, non-randomized, uncontrolled, retrospective, observational study of premature babies born in northern England between 1990 and 1994 as their “best evidence” for believing that oxygen saturation targets could be as low as 70% without increasing mortality.⁴⁵ The study compared survival rates and incidence of retinopathy of prematurity in four cohorts of premature babies who had been cared for in neonatal intensive care units that used different target saturation ranges (88-98%, 85-95%, 84-94%, and 70-90%). The authors of the cited study themselves noted that “**Staff always aimed to maintain saturation in the top half of the target range (particularly when the lower limit of this range was less than 85%)**” [emphasis added]. The study also provided incomplete data on baseline clinical parameters that could have affected prognosis for babies in each cohort. Most*

⁴³ Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med*. Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.

⁴⁴ *Ibid.*

⁴⁵ Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed*. 2001;84:F106-F110.

importantly, the study provided no data on the actual oxygen saturation levels achieved for babies in each cohort. As a result, no useful or valid conclusions can be drawn from this study about oxygen management in extremely premature infants, and the data certainly were insufficient to provide any reasonable assurance that the lower oxygen saturation target in the SUPPORT study would be “without an increase in mortality [risk]”. Indeed, as discussed above, that was one of the primary questions to be answered by the SUPPORT study’s oxygen experiment.

Investigators: Families were clearly informed that retinopathy was a known risk to their babies and that the SUPPORT study was conceived to test oxygen targets at the lower end of the recommended range to reduce the risk of retinopathy.⁴⁶

Our comments: Families eventually may have been informed in the context of the babies’ clinical care post-delivery about retinopathy being a well-known complication of extreme prematurity, but a detailed discussion of this issue was unlikely to have occurred in the midst of premature labor, when informed consent was to have been sought. Twenty of the 22 IRB-approved consent forms for the oxygen experiment certainly failed to disclose that assignment to the high-oxygen group could have increased the risk of retinopathy. This is in striking contrast to the benefits section of the majority of the consent forms, which did tell parents that the low-oxygen experimental group had the possible benefit of lowering the risk of retinopathy. To present only a description of the potential benefits of lowering the risk of retinopathy if the baby was assigned to the low-oxygen group without disclosing any risks of the experiment again was misleading to the parents of the enrolled babies.

Investigators: The infants in both treatment groups had lower rates of death before discharge (16.2% in the higher-oxygen-saturation group and 19.9% in the lower-oxygen-saturation group) than did those who were not enrolled (24.1%) and historical controls (23.1%), and rates of blindness did not differ between the treatment groups.⁴⁷

Our comments: It is not clear why the investigators think these data are important or relevant since they claimed — incorrectly, as discussed above — that all babies enrolled in the study received the same care as babies not in the study (i.e., the usual standard of care). Regardless, such post hoc comparisons to a contemporaneous group of babies not enrolled in a prospective, randomized clinical trial or to a historical comparison group are subject to bias and confounding factors and are incompatible with making definitive scientific conclusions. If the investigators thought that such a standard-of-care control group was necessary, it should have been incorporated into the design of their randomized controlled study.

Furthermore, the investigators’ comparison of the mortality rates seen in the SUPPORT study babies to the mortality rate of 24.1% for a non-enrolled patient group appears to be derived from the research paper published by the SUPPORT study investigators in

⁴⁶ Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med*. Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.

⁴⁷ *Ibid.*

the March 2012 issue of the journal Pediatrics, entitled “Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative.”⁴⁸ The paper compared key baseline demographic and clinical factors for the 1,316 premature babies enrolled in the SUPPORT study (enrolled babies) to those of 3,054 premature babies at the SUPPORT study hospitals who were eligible for the study but did not enroll (non-enrolled babies). Important data from the Pediatrics paper demonstrates that the non-enrolled babies overall were sicker and, at the start, more at risk of death than babies in the SUPPORT study. Thus, the data from this paper do not support the conclusion that enrollment in the study resulted in better survival.

Finally and most important, such post hoc comparisons are ultimately irrelevant with respect to assessing the risks of the experiment and the adequacy of the consent form and process at the time the study was submitted to the IRBs for initial review.

B. Editorial in *The New England Journal of Medicine (NEJM)*

The following are some statements made in a recent *NEJM* editorial attempting to defend the unethical conduct of this study and criticizing the actions taken by OHRP in this case, with our comments in response:

NEJM: So it is easy to imagine the stress when, in 2005, your new baby decides to come into the world after only 6 months of gestation, long before your pregnancy has reached term. You know that extremely premature babies like yours may not survive, but you are reassured that you are giving birth at an academic medical center with a sophisticated nursery for premature newborns and with physicians who have extensive experience with very preterm infants.⁴⁹

Our comments: The editorial correctly calls attention to the circumstances under which consent was sought from the parents of babies enrolled in the SUPPORT study. Mothers (and fathers, if present) were approached about enrolling in the study just prior to the months-too-early delivery of their babies that placed the parents under significant psychological and emotional stress. Moreover, many of these parents were likely very young and educationally or economically disadvantaged. Any of these factors alone or in combination made the parents highly vulnerable to coercion or undue influence. They were likely to be very trusting of the doctors caring for them. Many, if not most, were ill-prepared to understand the complexities of usual standard of care for premature babies, let alone the complexities of the experimental interventions, even if the investigators had provided a complete disclosure of the purpose, nature, and risks of the research.

A review of the SUPPORT study protocol reveals no discussion of the additional protections that were to have been put in place to ensure that these highly vulnerable parents were protected from undue influence or coercion. For example, independent

⁴⁸ Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics*. March 2012;129(3):480-484.

⁴⁹ Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT (editorial). *N Engl J Med*. Published online April 17, 2013. DOI: 10.1056/NEJMe1304996.

monitors of the consent process would have been an appropriate procedure. It would be important to know whether any IRB that reviewed and approved this study required implementation of such additional protections.

NEJM editorial: Without research studies your neonatologist would simply be guessing about what is best rather than knowing what is best for your child...

For a baby not enrolled in any of these trials, the specific range of oxygen saturation targeted within these broader guidelines was left to the discretion of the child's physician, who lacked data to guide decision making.⁵⁰

Our comments: It is misleading to suggest that neonatologists at the time the SUPPORT study was conducted were simply guessing when making individualized treatment decisions about oxygen management for their patients. Although imperfect, there were substantial data in the medical literature to guide oxygen therapy in premature babies. These data were supplemented to varying degrees by extensive clinical experience. In addition, this statement suggests a belief, also apparently held by the investigators, that there exists some yet-to-be-determined universal "sweet-spot" oxygen saturation level for all premature babies, the details of which could be found from such an experiment. It is implausible that such a universal sweet spot exists.

NEJM editorial: This response is disappointing, because it does not take into account either the extent of clinical equipoise at the time the study was initiated and conducted or that the consent form, when viewed in its entirety, addressed the prevalent knowledge fairly and reasonably.⁵¹

Our comments: First, whether clinical equipoise between the two oxygen study groups existed at the time the SUPPORT study was conducted is completely irrelevant to whether the consent form and process were adequate. Second, the existence of clinical equipoise between study groups within a randomized clinical trial does not mean that the study is without risk. Third, for many babies in the study, clinical equipoise likely did not exist between the low- and high-oxygen experimental groups. Finally, as discussed in earlier sections of this report, the descriptions of the study's experimental procedures in the consent form were incomplete and misleading.

C. *NEJM* perspective article

Finally, the following are some statements made in a recent *NEJM* perspective piece attempting to defend the unethical conduct of the SUPPORT study and criticizing the actions taken by OHRP in this case, with our comments in response:

NEJM perspective article: A great deal of effort is under way to make it easier and less expensive to conduct prospective, randomized comparative effectiveness research. Some of the options for conducting such research take advantage of the fact that there is no

⁵⁰ *Ibid.*

⁵¹ *Ibid.*

additional risk to being randomly assigned to one or another equally well-supported treatment option that falls within the standard range of care in clinical practice... The OHRP reprimand is troubling both because it has sown confusion and focused unwarranted negative attention on valuable research and because it incorrectly suggests that the risk of comparative effectiveness research involving infants, or any other group, is equivalent to the risk of research involving randomization to a novel intervention...

The SUPPORT investigators believed that since all the study infants would receive oxygen levels within the prevailing standard of care, there was no additional risk to being enrolled in the trial. Indeed, it has been argued that the research should have been eligible for a waiver of documentation of informed consent, since there was no basis for claiming an increase in risk from enrolling in the trial versus receiving standard clinical care.⁵²

Our comments: These statements demonstrate a lack of understanding of how the SUPPORT study was conducted, the difference between the complex experimental procedures used in the study to manage and monitor oxygen levels in the subjects and usual standard of care for premature infants, and the risks posed by these experimental procedures, as discussed in detail above in prior sections of this report.

Labeling the SUPPORT study as “comparative effectiveness research” is a gross mischaracterization because the two experimental oxygen interventions were clearly novel and not consistent with the usual standard of care. Furthermore, even if this characterization were accurate, the presumption that all randomized “comparative effectiveness research” studies pose no risk to subjects is nonsensical.

Attempts to discount the risks posed by the SUPPORT study’s oxygen experiment by using the benign-sounding label “comparative effectiveness research” only serve to confuse the public. Other much more appropriate terms that could be used to describe the SUPPORT study and more accurately convey its nature are “comparative safety research” or “comparative harmfulness research.” However, the use of such terms would have drawn even more attention to the absence of risk information regarding the oxygen experiment part of the study in the consent forms.

NEJM perspective article: Among neonatologists, the standard of care varied — too much oxygen was associated with retinopathy of prematurity and possible blindness, but too little oxygen risked neurologic damage and death.⁵³

Our comments: This statement accurately portrays the tradeoff in risk of retinopathy from exposure to too much oxygen and the risk of brain injury and death from too little oxygen, a tradeoff that the SUPPORT study investigators, but not the parents, also must have been aware of.

⁵² Magnus D, Caplan AL. Risk, Consent, and SUPPORT. *N Engl J Med*. Published online April 18, 2013. DOI: 10.1056/NEJMp1305086.

⁵³ *Ibid.*

NEJM perspective article: Given that there was variation in clinical practice at the time the study was mounted, it is not clear how randomization among treatment options could have created novel risk over random physician preference.⁵⁴

Our comments: Variation in clinical practice does not mean that physician preferences are random. Furthermore, given the information presented in prior sections of this report, it is misleading to suggest that neonatologists at the time the SUPPORT study was conducted were simply guessing and randomly choosing oxygen saturation targets when making decisions about oxygen management. More important, the investigators themselves stated in the SUPPORT protocol that the higher oxygen range was the “more conventional” target range for managing oxygen therapy in premature infants. Finally, as also discussed in detail in section II of this report, the research procedures involved more than just randomization to one of two experimental oxygen saturation target groups. The experiment also involved provision of intentionally inaccurate oximetry information to the medical teams caring for the premature babies enrolled in the SUPPORT study. This experimental intervention cannot reasonably be construed as standard clinical practice.

NEJM perspective article: With regard to SUPPORT, the OHRP is asking that research be described as riskier than it really is and is suggesting that the parents were duped into enrolling their frail infants in dangerous research.⁵⁵

Our comments: As previously discussed in detail in prior sections of this report, the oxygen experiment component of the SUPPORT study posed significant, life-threatening risks to the frail babies enrolled in the study. The failures to disclose critically important information regarding the purpose, nature, and risks of the research to parents of the SUPPORT study babies represented a serious violation of research ethics.

V. Conclusions

The new information discussed in this report affirms the appropriateness of OHRP’s determination in its March 7, 2013, letter to UAB that the UAB IRB-approved consent form failed to mention the serious, reasonably foreseeable risks related to the part of the study comparing two experimental strategies for managing oxygen in extremely premature infants. Those risks, correctly identified by OHRP, included increased risks of brain injury; retinopathy of prematurity, which can lead to blindness in severe cases; and death, depending on the randomized group assignment of each baby. Indeed, the UAB IRB-approved consent form misled parents of prospective subjects by essentially indicating that the oxygen experiment component of the SUPPORT study presented no risk.

Moreover, the new information demonstrates that the deficiencies of the UAB IRB-approved consent form were far more significant than those discussed in OHRP’s March 7 letter. The agency should have cited UAB and all other participating institutions for additional serious deficiencies in the IRB-approved consent form regarding the lack of disclosure of critically

⁵⁴ *Ibid.*

⁵⁵ *Ibid.*

important information about the protocol-specified purpose and nature of the oxygen experiment. In particular, the IRB-approved consent forms in many, if not all, cases either did not disclose at all or did not accurately describe the following:

- (1) The experimental procedure of using pulse oximeters that were intentionally miscalibrated to provide the medical teams caring for the premature babies in the study with oxygen saturation readings that were either inaccurately low or inaccurately high. (Only 11 consent forms disclosed this procedure in some way, but none explained how this experimental procedure could have impacted important clinical decisions related to the babies' care.)
- (2) The substantial, reasonably foreseeable risks of harm from intentionally providing the medical teams caring for the babies in the study with inaccurate information regarding the babies' oxygen saturation levels. This experimental procedure may have adversely impacted important clinical decisions regarding whether to intubate a baby and start mechanical ventilation or whether to extubate an intubated baby and discontinue mechanical ventilation. For example, because of this experimental procedure:
 - (a) Some babies in the high-oxygen group may have undergone protocol-driven intubations and been placed on mechanical ventilation when such procedures were not clinically indicated. This could have unnecessarily exposed some babies to increased risk of: (i) trauma to the mouth and gums during intubation; (ii) trauma to the trachea, resulting in bleeding and puncture of the airway during intubation; (iii) pneumothorax (collapsed lungs, possibly resulting in the need for insertion of chest tubes); (iv) pneumonia during mechanical ventilation; and (v) death.
 - (b) Some babies in the low-oxygen group may have had actual clinical indications for intubation and mechanical ventilation, but because of inaccurate oxygen saturation levels, these treatments may have been inappropriately delayed. This could have unnecessarily exposed some babies in the low-oxygen group to increased risk of prolonged hypoxemia with inadequate oxygen delivery to the brain, resulting in neurological damage and possibly death.
- (3) The investigators' characterization in the protocol, but not in the consent form, of the high-oxygen target levels as being "more conventional" and, by implication, the low-oxygen target levels being less conventional. (Only two consent forms suggested an oxygen saturation range that was most commonly used in routine practice.)
- (4) An explanation of how the experimental procedures for managing the oxygen therapy of the babies deviated from the usual standard of care the babies would have received had they not been enrolled in the study.

A particularly disturbing finding in Public Citizen's analysis of the complete protocol and the IRB-approved consent forms is that most consent forms included an extraordinarily misleading statement, such as the following:⁵⁶

⁵⁶ IRB-approved consent form for the SUPPORT trial. <http://www.citizen.org/documents/support-study-consent-form.pdf>. Accessed May 7, 2013.

“There is no known risk to your baby from monitoring with the pulse oximeters used for this study.”

or

“Because all of the treatments proposed in this study are standard of care, there is no expected increase in risk for your infant.”

The absence of critical elements of information about the purpose, nature, and risks of the complex SUPPORT study’s oxygen experiment, combined with the inclusion of statements indicating that the experimental procedures had no known risks, denied the parents of babies enrolled in the trial the opportunity to make an informed decision when they gave consent for the research. The failure to disclose this critically important information to the parents represented a serious violation of research ethics.

Finally, a review of the complete protocol appears to indicate that the IRBs that approved the study lacked crucial information that would have been necessary for them to determine whether risks to the babies enrolled in the research were minimized by using procedures consistent with sound research design and that did not unnecessarily expose subjects to risk. Important details regarding each of the following were omitted from the protocol:

- (1) a description of the usual standard of care for critically ill premature babies regarding such critical issues as the individualized adjustment of FiO_2 and decisions about intubation, extubation, and mechanical ventilation at the NRN medical centers;
- (2) the risks associated with the experimental oxygen interventions, including those related to use of intentionally miscalibrated pulse oximeters;
- (3) the plan for unblinding the NICU medical teams when the masking procedure using intentionally miscalibrated pulse oximeters posed a threat to the health of the babies; and
- (4) the safety monitoring plan.

The omitted information was essential for understanding the nature of the research and its risks. Lacking this information, it is unclear how the IRBs that reviewed the study were able to make the determinations required for IRB approval under the HHS human subjects protection regulations, particularly the determination that the risks to subjects were minimized.

Some critics of OHRP’s determinations regarding the SUPPORT study argue that the agency’s action in this case poses a threat to biomedical research and the advancement of medical knowledge and innovation. However, the real threat to such scientific endeavors is unethical research, which understandably undermines the public’s trust in the motives and conduct of researchers. Conformance with the fundamental ethical principles for conducting human subjects research must never be sacrificed in the quest to advance medical knowledge. Such conformance is necessary to preserve the public’s trust in the motives and conduct of researchers.

Appendix

Public Citizen Reviewed IRB-Approved SUPPORT Study Consent Forms for the Following Institutions:

- Cincinnati Children's Hospital
- Duke University Health System
- Emory University School of Medicine/Grady Memorial Hospital and Crawford W. Long Hospital
- Indiana University-Purdue University of Indiana and Clarian
- Intermountain Medical Center and Primary Children's Medical Center
- Sharp Mary Birch Hospital for Women
- Stanford University
- Tufts Medical Center
- University Hospitals Case Medical Center, Cleveland, OH
- University of Alabama at Birmingham
- University of California, San Diego
- University of Iowa
- University of Miami/Jackson Memorial Hospital (Approved by the Western IRB in Olympia, WA)
- University of New Mexico Health Sciences Center
- University of Rochester Medical Center
- University of Texas Health Science Center and Memorial Hermann Children's Hospital
- University of Texas Southwestern Medical Center at Dallas/Parkland Health & Hospital System and Children's Medical Center
- University of Utah
- Wake Forest University School of Medicine, Forsyth Medical Center
- Wayne State University/Hutzel Women's Hospital
- Women and Infant's Hospital of Rhode Island
- Yale University School of Medicine/Yale-New Haven Hospital