DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 4, 2013

Richard B. Marchase, Ph.D.
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University of Alabama at Birmingham
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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:

In the wake of extensive scientific and public discussions since our March 7, 2013, determination letter in the SUPPORT study, OHRP has become aware of widespread misunderstanding about the risks that are required to be disclosed in obtaining informed consent for certain types of clinical trials. Our goal in this letter is to clarify several issues related to our determination.

At the outset, we wish to emphasize that OHRP does not and has never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care. Rather, consistent with OHRP's mission to protect human subjects of research, the overarching concern of our determination was the adequacy of informed consent, a bedrock principle of research involving human subjects.

To make truly informed decisions about whether or not to participate in a research study, potential volunteers or their parents or guardians are entitled to certain information, including a description of reasonably foreseeable risks. We acknowledge that the UAB consent form included language that reflected then-current research suggesting that lower saturation targets reduced the risk of retinopathy of prematurity (ROP), as well as language about the potential risks of ROP with prolonged use of supplemental oxygen. However, the "Risks" section of that form failed to mention and appropriately describe, as it should have, that relationship. More

significantly, neither the "Risks" section nor any other portion of the form mentioned any risks associated with lower oxygen levels.

OHRP recognizes that the SUPPORT investigators did not design the study with the expectation that they would find a difference in mortality rates between the high and low oxygen groups. Whereas much earlier studies of oxygen supplementation in premature babies had shown risks of mortality and neurological damage at very low oxygen levels, more recent studies did not demonstrate such risks. Consequently, when the SUPPORT study was initiated, there was no clear recent evidence indicating that different oxygenation levels within the then-current standard of care (85%-95%) would produce differences in neurological damage or survival.

However, the medical profession looks at many factors when assessing potential risks. At the outset of the SUPPORT study, many in the research and clinical communities remained concerned about the possible relationship between low oxygen and increased mortality and neurodevelopmental problems within the oxygen ranges that were to be evaluated in that study.[1] Indeed, such concerns were a core reason why the study was conducted. Those concerns were sufficient to affect clinical decisions and discouraged some doctors from treating premature infants at lower oxygen levels.

Indeed, descriptions of the process of designing the SUPPORT study and four similar studies conducted in other countries indicate a clear awareness of such concerns and the need to resolve them. This is evidenced by multiple statements from the SUPPORT investigators and other experts,[2] who identified the important need for a large randomized study with sufficient power to detect differences in mortality rates of 5% or greater.

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[1] See note 2, below.

[2] "In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct [what would become known as] the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration." Askie et al., BMC Pediatrics 2011 11:6, at page 3. That collaboration eventually included the SUPPORT study and four similar studies conducted within Canada (COT), the United Kingdom (BOOST-II UK), Australia (BOOST-II), and New Zealand (BOOST NZ). The initial thinking behind this group of studies was "outlined in a [2003] commentary in *Pediatrics*" in which Cole et al., Resolving Our Uncertainty About Oxygen Therapy, *Pediatrics* 2003;112:1415, discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." They also noted a particular challenge in recruiting neonatal units to participate: some units "regard [oxygen levels greater than 90%] as mandatory," and might therefore be unwilling to participate in a study in which one-half of the infants would be randomized to levels below 90%. To recruit such units, they suggested using "cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy."

Subsequent official statements regarding SUPPORT and the other four trials, issued prior to the 2010 results from SUPPORT, demonstrate that resolving those "real concerns" about mortality risks at the low oxygen end remained a major issue for these studies. On the official registration system for clinical trials in the U.S., clinicaltrials.gov, the SUPPORT researchers, in 2005, provided a one-sentence description, saying that it "will determine whether or not [the] two management strategies affect chronic lung disease and survival of premature infants." http://clinicaltrials.gov/archive/NCT00233324/2005_10_04 The description provided on that same database for the

Some commentators, in discussing the risks involved in the SUPPORT study, have attached great importance to the fact that all the oxygen levels to which the infants were assigned were within the range of the standard care.[3] But they draw inappropriate conclusions from that fact. Medicine is an imperfect science. When considerable uncertainty exists about the best way to treat a particular medical problem, the range of what can be considered standard care often is quite broad, to allow physicians to exercise clinical judgment on behalf of their patients.[4] Indeed, a core principle of medical ethics requires physicians to make such judgments, even in the face of uncertainty. All of us, as patients, rely on our doctors to do precisely that.

This principle has direct bearing on the SUPPORT study. When there is a range of oxygen levels within the standard of care, clinicians (and their institutions) often do, in fact, make their own determinations regarding which oxygen levels within that range to employ in treating their patients. Some physicians, recognizing the particular concerns about risks near the low (85%) and high (95%) ends of that range, might choose to avoid one or both of those regions.

The version of the consent form used at one SUPPORT site specifically acknowledged this to be the case; at that center, for clinical purposes, oxygen saturation was "kept between 88 and 94%."[5] Assuming the researchers achieved the distribution of oxygen levels they were trying to attain, research subjects at that site had a greater than 25% chance of being treated with an oxygen saturation between 85 and 88%, whereas, for those treated outside the study, the likelihood of being treated with oxygen in that range was quite small. Thus, by participating in

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Canadian trial in 2008 states that a randomized trial "is urgently needed and long overdue to determine whether oxygen exposure can be reduced safely in extremely preterm infants without increasing the risk of hypoxic death or disability." The United Kingdom protocol noted that "restricting oxygen exposure to minimize [the possibility of severe retinopathy] risks increasing early mortality." http://clinicaltrials.gov/archive/NCT00637169/2008_03_14 See also Silverman WA: A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004 (113):394-396 ("For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP blindness, chronic lung disease, and brain damage) was, and remains to this day, unknown"); Tin et al, 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 ("Because mortality went undocumented in the first of the large trials of oxygen administration, we do not even know if there is a price to be paid for controlling administration strictly enough to minimise the risk of severe retinopathy.") . A Cochrane Collaboration review in 2009 specifically looked at the relationship between oxygen levels and mortality, concluding that the correct range to use was still not yet known. With regard to the most recent studies (from 2001 to 2004) showing no increased mortality at lower oxygen ranges, it noted: "these non-randomized studies lack adequate statistical power to exclude possible small, but important, increases in death and disability that could have major implications if a policy of lower oxygen targeting was implemented worldwide," and that the SUPPORT and other four studies were collecting data to "help resolve this remaining question." Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review). Cochrane Database of Systematic Reviews 2009(1).

[3] Drazen JM, Solomon CG, Greene MF. Informed Consent and SUPPORT. N Engl J Med 2013;368:1929; Magnus D, Caplan AL. Risk, Consent and SUPPORT. N Engl J Med 2013;368:1864; Lantos JD. OHRP and Public Citizen are Wrong about Neonatal Research on Oxygen Therapy. Hastings Center Bioethics Forum, April 18, 2013;.

[4] Shepherd L. The SUPPORT Study and the Standard of Care. Hastings Center Bioethics Forum, May 17, 2013.

[5] SUPPORT consent form, Tufts Medical Center, available at http://www.citizen.org/documents/support-study-consent-form.pdf.

the study, the treatment of such subjects was substantially altered to make it much more likely that they would be within the range in which there were significant concerns about increased mortality.

And this circumstance is likely not unique to that site. As another of the consent forms noted, the "aim in many units is to keep oxygen saturations between 88 and 92%."[6] For institutions with those clinical care policies, participating in the study would have significantly increased the chance of an infant being assigned to oxygen levels at both the very low (85 to 88%) and the very high ends (92 to 95%), as opposed to the level they would have received, had they not been in the study.[7]

Unless, as is extraordinarily unlikely, an institution used for clinical purposes exactly the same randomization assignment procedure that was used in the SUPPORT trial, every child in the SUPPORT trial experienced some change in the likelihood of being assigned to the various oxygen levels. And as the above discussion demonstrates, for at least some of the children participating in the SUPPORT trial, the effect of such participation was to specifically increase their likelihood of being assigned to oxygen levels close to either end of the range of standard care – and thus to oxygen levels at which, as a clinical matter, they would not have been assigned by their individual physicians, had they not been in the study.

Ultimately, the issues in this case come down to a fundamental difference between the obligations of clinicians and those of researchers. Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation: Our society relaxes that requirement because of the need to conduct research, the results of which are important to us all. As a modest but crucial trade-off in allowing researchers such flexibility, society requires that researchers tell subjects how participating in the study might alter the risks to which they are exposed. For some if not many of the subjects in the SUPPORT study, research participation increased the chance that they were treated at one or another end of the standard of care range. Given the requirement that subjects be apprised of "reasonably foreseeable risks," it would seem appropriate that the parents of the infants should have been informed of the real concerns within the medical community regarding those oxygen levels. [8]

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[6] SUPPORT consent form, Duke University Health System, available at http://www.citizen.org/documents/support-study-consent-form.pdf .

[7] Imagine, for example, an institution whose clinical standard allowed the full range of standard care to be used, with the pulse oximeter alarm set to go off at the levels of 85% and 95%, and with the goal of trying to keep the infant in the middle of that range (near 90%). Even under that scenario, by participating in the trial, the likelihood of the infant ending up in the more extreme values (85 to 87% or 93 to 95%) would, under some plausible assumptions, have nearly doubled.

[8] As noted above, the UAB consent form mentioned no risks with regard to the use of lower oxygen levels. In contrast, a 2005 version of the consent form used in the New Zealand BOOST study included this language: "Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . . The aim of this study is to determine, *within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%)*, whether targeting the lower end of

OHRP recognizes that applying the "reasonably foreseeable risk" concept to randomized studies of standard of care treatments is a complex undertaking. We want to be clear, however, that it is not necessary to disclose all theoretical risks present at the outset of every study. Moreover, disclosure of a risk is unnecessary when study participation has no potential to increase or modify that risk compared to what would have happened had the subject not been in the study.

The facts regarding the SUPPORT study and what was known about the use of oxygen to treat premature infants also are complicated. Accordingly, we appreciate that there is justification for an incomplete understanding of how those rules might apply to this study. In addition, there are some who disagree with OHRP's analysis of how the regulations should apply to such studies. Indeed, some of the researchers involved in the SUPPORT study and others have argued that there was no need for researchers to have obtained any consent from parents before placing their children in this study.[9] This discussion takes place in the midst of a much broader discussion regarding a proposal from a distinguished group of scholars that is receiving prominent attention, which argues for completely eliminating the need for any consent in similar studies – a change that would involve a major reframing of the rules for protecting research subjects.[10]

These are crucially important issues, not just with regard to our ability to be able to conduct research with appropriate oversight, but also with regard to fundamental questions about the obligations owed by doctors to patients. Given their importance, we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly. Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing such guidance is as open as possible, to allow input from all interested parties. Thus, not only will we engage in the usual notice and comment process with regard to draft guidance, we will also conduct an open public meeting on this topic.

In addition, in further recognition of the concerns noted above, we have put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further

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this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision (ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability." (BOOST-NZ consent form, July 2005, personal communication from Brian Darlow, principal investigator of BOOST-NZ) Had such language been in the UAB consent form, there would likely have been no OHRP finding with regard to non-disclosure of the risks relating to mortality and neurodevelopmental problems. And the NeOProM 2011 write-up, mentioned in note 2 above, using only pre-2005 references, describes the risks issue as follows: "There are two opposing concerns. Less inspired oxygen [under 90%] may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development. More inspired oxygen [greater than 90%] may increase severe [retinopathy] and chronic lung disease."

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

[10] Faden RR et al. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. Hastings Center Report Special Report 2013;43(1):S16.

action in studies involving similar designs until the process of producing appropriate guidance is completed.

OHRP's top priority remains that of protecting research participants. For this reason, we look forward to the forthcoming public discussion, and assuring that important research can proceed both with appropriate protection of subjects and without confusion about which risks must be disclosed.

We appreciate the continued commitment of your institutions 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:
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