

Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, June 10, 2013 4:45 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FR notice re SUPPORT public meeting

Thanks, Kathy. It's great to hear that. And if the briefing helps, we can see what else we can do to help people better understand the NPRM (and to revise it to make it clearer!).

Jerry

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Monday, June 10, 2013 4:21 PM
To: Menikoff, Jerry (HHS/OASH)
Subject: RE: FR notice re SUPPORT public meeting

Great. Thanks.

Just finished reading the draft nprm. It looks terrific. thanks for doing the brfing tomorrow. I hope that will help smooth the final clearances.

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, June 10, 2013 4:07 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: FR notice re SUPPORT public meeting

Kathy,

The date selected is August 28th, and yes, the notice has been put into the federal register process.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Monday, June 10, 2013 2:30 PM
To: Menikoff, Jerry (HHS/OASH)
Subject: FW: FR notice re SUPPORT public meeting

Hi Jerry

Caya forwarded this version of the fed reg notice. Do you know if a date has been selected and if the notice has been put into the fed reg process?

Thanks
kathy

From: Lewis, Caya (HHS/IOS)
Sent: Monday, June 10, 2013 2:14 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FR notice re SUPPORT public meeting

This is the final sent to OHRP

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Bartok, Lauren (NIH/OD) [C]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Friday, June 07, 2013 3:41 PM
To: Lewis, Caya (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Lee, Noelle C. (HHS/IOS)
Subject: Media on SUPPORT
Attachments: Press Coverage on SUPPORT - June 2013.doc

Hi Caya and Noelle –

Attached are the major media pieces that followed the SUPPORT announcements on Wednesday. There are stories from: NYT, WSJ, NPR, Science Insider, and Chronicle of Higher Education.

Best,
Steph

Stephanie Devaney, Ph.D.
Science Policy Analyst
Special Assistant to the Deputy Director for Science, Outreach, and Policy
Office of the Director
National Institutes of Health
1 Center Drive, Building 1/103
Bethesda, MD 20892
Phone: 301-402-1994
stephanie.devaney@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

Wall Street Journal

U.S. NEWS June 5, 2013, 7:38 p.m. ET

Sanction on Study Eased

By THOMAS M. BURTON

A federal agency that had criticized a study of oxygen given to premature infants said it was putting on hold any regulatory action against hospitals involved, saying that its rules could be misunderstood.

Hospitals and doctors had challenged the determination by the Office for Human Research Protections and defended the ethical standards of the study.

In a letter dated Tuesday to the University of Alabama at Birmingham, where the research was centered, Lisa R. Buchanan of the research office said that her agency was correct when it concluded in March that researchers didn't adequately notify parents of the possible risks in the study.

Related

Letter to the University of Alabama at Birmingham

But she said the office had an "obligation to provide clear guidance on what the rules are" and nodded to the views of those who disagreed with the office's initial finding.

At issue is a study of 1,300 premature babies, conducted between 2004 and 2009, that looked at the levels of oxygen they should receive. Too much oxygen could result in blindness, but too little, it turned out in the research, could result in excessive deaths.

About 28,000 infants weighing less than 2.75 pounds are born prematurely in the U.S. each year, and more than half develop a condition called retinopathy of prematurity, which often leads to blindness.

Many doctors in the study have said that they were surprised that babies on lower levels of oxygen had a higher death rate, and that they couldn't have warned of such an unexpected result.

Ms. Buchanan disagreed, writing: "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."

On Wednesday, more than 30 senior physicians—including the director of the National Institutes of Health—spoke out in favor of the researchers.

In an opinion piece in the *New England Journal of Medicine*, NIH Director Francis Collins, along with NIH colleagues Kathy L. Hudson and Alan E. Guttmacher, wrote in support of the pediatricians' study. They said researchers "had no scientific evidence to expect a difference in mortality" between the two groups of babies. Both levels of oxygen at the time were considered within the standard of medical care.

In the study, among infants getting low oxygen, there was a higher percentage of deaths before discharge, 19.9%, compared with the 16.2% who died in the high oxygen group. The federal agency said this finding was "statistically significant." Among babies getting high oxygen levels, 17.9% got the severe eye disease, compared with 8.6% who were treated with low oxygen.

Write to Thomas M. Burton at tom.burton@wsj.com

New York Times

June 5, 2013

Watchdog Halts Action on Researchers

By JAN HOFFMAN

The federal Office for Human Research Protections announced on Wednesday that it would suspend action against the University of Alabama at Birmingham, which it said in March did not adequately inform parents about the risks to their premature infants of enrollment in a large research trial.

In a letter dated Tuesday, the watchdog office still maintained that researchers had not properly informed parents, and that it could still require that the university and 22 other trial sites, which include many of the country's top research universities, take corrective action. But it also acknowledged that federal guidelines about a researcher's obligations needed to be clarified and issued. On the office's Web site, the federal Department of Health and Human Services announced that a public meeting to debate such guidelines was forthcoming.

The timing of the letter coincided with the publication on the Web site of The New England Journal of Medicine of an opinion article by leaders of the National Institutes of Health that took issue with the agency's initial condemnation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial, widely known as Support. Both the agency and the N.I.H. are branches of Health and Human Services.

The Journal also published a letter, signed by 46 doctors and scholars, that criticized the office's initial action as overreaching and having a potentially chilling effect on essential research.

At the center of the uproar, which has engendered commentary from scientists, is whether researchers needed to disclose to parents the risks of a randomized trial of higher and lower oxygen levels administered to premature infants. The levels of oxygen concentration given to the infants were within the range of 85 percent to 95 percent, the standard treatment recommended by the American Academy of Pediatrics. Researchers wanted to pinpoint more precisely the level at which the risks of eye damage or neurological damage, or even death, were abated.

There were risks to the infants at either end of the narrow band. The results, published in The New England Journal of Medicine in 2010, showed that lowering the oxygen levels led to greater mortality rates than expected.

But as the office wrote, "Some physicians, recognizing the particular concerns about risks near the low (85 percent) and high (95 percent) ends of that range, might choose to avoid one or both of those regions."

Dr. Joel E. Frader, a pediatrician and professor of medical humanities and bioethics at Northwestern, who signed the letter in *The Journal*, felt that the office initially did overreach, but also that the researchers did not properly inform parents of all risks. Because there was a band of oxygen saturation levels, he said, there was no clear standard of care for these infants, only an "acceptable range." And parents should have been told that, he said.

"It's the obligation of investigators to say, 'Here's the debate, here's how we're trying to answer the question, and that involves the possibility that there is an additional risk with being a research subject,' " he said.

He applauded the effort to clarify guidelines for disclosure, even in standard-of-care trials. Researchers should not shy away from fully informing subjects, he said. "There is no empirical evidence that transparency and clarity decreases participation in clinical research," he said.

NPR

Policy-ish

NIH Chief Rejects Ethics Critique Of Preemie Study

by Richard Knox
June 06, 2013 8:58 AM

National Institutes of Health Director Dr. Francis Collins contested criticism that researchers running a study of premature infants didn't adequately advise parents about the risks.

Charles Dharapak/AP

The chief of the National Institutes of Health is disavowing a ruling from the government office that oversees the ethics of human research.

At issue is a controversial study of more than 1,300 severely premature infants. This spring, the federal Office for Human Research Protections criticized the scientists who ran the study for failing to tell parents about the risks their newborn children might face.

"We respectfully disagree," NIH director Dr. Francis Collins and two colleagues say, in an unusual public disagreement within the government over research ethics.

At the same time, the Office for Human Research Protections or OHRP told the University of Alabama at Birmingham, one of the study sites, that it was suspending disciplinary action on the matter until ethics guidelines on such studies are clarified.

The watchdog office also says it won't proceed against sponsors of similar studies for now. But it held open the possibility that the Alabama medical center and 22 other trial sites could still face

sanctions. The OHRP is an arm of the Department of Health and Human Services, the NIH's parent agency.

In a commentary published by the *New England Journal of Medicine*, Collins and company write that "this controversy has alarmed some of the parents of infants who were in the study, confused the biomedical research community, and befuddled IRBs," the Institutional Review Boards that oversee human research at every clinical center.

Collins' coauthors are Kathy Hudson, NIH's deputy director for science, outreach and policy, and Dr. Alan Guttmacher, director of the National Institute of Child Health and Human Development.

The three say they have "a fundamental difference in interpretations" over what doctors knew about how to treat preemies at the time the multicenter study was launched, back in 2004.

The government's research watchdogs say the study's authors should have warned patients that children receiving lower doses of oxygen might be at higher risk of nerve damage and death.

But Collins and other defenders of the study, called SUPPORT, say data available back in 2004 gave "no reason to foresee that infants in one study group would have a higher risk of death that would those in the other group."

The commentary is accompanied by a letter roundly supporting the disputed study that is signed by 46 ethicists and pediatricians.

The ruling of the OHRP is "unfair to the investigators and institutions involved in SUPPORT," the letter says. Allowing it to stand "would...set a precedent that would impede ongoing and future...outcomes studies."

While the letter's signatories say the OHRP "overreaches" in concluding that the study violated federal ethics guidelines, they "acknowledge that the permission forms could have been improved" and "the consent process for clinical research can no doubt be improved."

They did not specify how the SUPPORT study's consent process fell short.

Collins and his colleagues also say the controversy serves as an occasion for "a substantive national dialogue" about "how best to respect and protect participants in research studies conducted within the standard of care and how to define 'reasonably foreseeable risks' in this setting."

The phrase "standard of care" is at the heart of the matter. Basically, the NIH leaders say the SUPPORT controversy raises issues that apply to any research that aims to test and improve accepted medical practice.

Thus, the case could turn out to have far-reaching effects on future clinical research.

To underscore that, HHS announced Wednesday that it plans to hold a public meeting to discuss how federal regulations designed to protect human research subjects should be applied to studies that probe "standard of care treatment."

The upcoming meeting, whose date has not been set, will address how Institutional Review Boards should assess the risks of studies looking at current clinical practice and what "reasonably foreseeable risks" should be disclosed to study volunteers.

OHRP's six-page [letter](#) sent Tuesday to Alabama researchers suggests how complicated and subtle an issue this is.

The letter acknowledges that some doctors treating a premature infant might avoid giving oxygen at levels at either end of the range used in the SUPPORT study. But by enrolling their infants in the study, parents were waiving their children's right to such individualized treatment.

"Ultimately, the issues in this case come down to a fundamental difference between the obligations of clinicians and researchers," the OHRP's Lisa Buchanan writes. "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."

As a "crucial trade-off" in doing clinical research, Buchanan writes, "society requires that researchers tell subjects how participating in the study might alter the risks to which they are exposed."

Another effect of the controversy: HHS plans to set up a process for researchers and institutions to appeal the rulings of the Office of Human Research Protections "in those situations in which reasonable people disagree about the actions taken."

Currently, there is no appeal from the Office's rulings. [Dr. Michael Carome](#) of Public Citizen, an advocacy group that first complained about the SUPPORT study, says the OHRP letter is "an important step toward addressing a highly unethical trial."

But Carome said HHS's decision to allow "current similar trials to continue ... is an abject and unacceptable failure to protect human subjects in clinical trials."

Science Insider

U.S. Patient Protection Agency Drops Plan to Sanction Leaders of Infant Study

by David Malakoff on 6 June 2013, 1:10 PM

Breath of life. Controversial study looked at how much oxygen premature infants should receive.

Credit: Wikimedia

Under fire from researchers and ethicists, the U.S. government agency responsible for protecting patients involved in scientific studies is backing away from a decision to sanction the leaders of a clinical trial involving premature infants after finding that the researchers failed to disclose the trial's full risks. "We have put on hold all compliance actions," the U.S. Office for Human Research Protections (OHRP) announced in a [4 June letter to the University of Alabama, Birmingham \(UAB\)](#), which led the trial. OHRP also says that it plans to hold a public meeting to discuss the controversy, with an eye toward clarifying the rules for providing informed consent.

OHRP's move came a day before *The New England Journal of Medicine* published two pieces urging OHRP to reconsider the sanctions and expressing support for the researchers who

designed and carried out the trial. "[W]e respectfully disagree with the conclusions of the OHRP," wrote three senior officials from the National Institutes of Health (NIH), which funded the study, including NIH Director Francis Collins. "Allowing the decision to stand would be unfair to the investigators and institutions involved," wrote a group of several dozen prominent bioethicists and pediatric researchers.

The controversy came to public light in early April, after the nonprofit group Public Citizen alerted reporters to a 7 March letter from OHRP to UAB. It concluded that the 23 institutions involved in the trial, known as SUPPORT, had failed to fully disclose its risks. The letter also asked UAB to prepare a "corrective action plan." The trial, which ran from 2005 to 2009, provided 1316 extremely premature infants with different oxygen concentrations to better understand how to prevent the blindness that sometimes accompanies the treatment. The trial's results, published in 2010 in *The New England Journal of Medicine*, indicated that infants receiving lower oxygen levels were more likely to die, but less likely to become blind, than babies receiving higher levels. All of the babies received oxygen levels that were within then-accepted standards of medical care. OHRP concluded, however, that consent forms didn't adequately spell out the possible consequences, including death, of being at one end of the range or the other. And Public Citizen argued that parents would not have signed their children up for the trial if the risks had been fully explained.

The controversy sparked extensive discussion in biomedical research circles, and the trial got harsh ethical reviews in public forums such as websites. But OHRP's 4 June letter seeks to calm the waters. "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," the letter states, adding that "we wish to emphasize that OHRP does not and has never questioned whether the design of the SUPPORT study was ethical."

But the issues involved are complex, the letter notes, and "[g]iven 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." Not only will the agency "engage in the usual notice and comment process with regard to draft guidance," it says, "we will also conduct an open public meeting on this topic."

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Chronicle of Higher Education

June 6, 2013

U.S. Agency Backs Away From Penalties in Controversial Study Involving Infants

By Paul Basken

Federal research-ethics regulators have retreated from their consideration of punitive action over a medical trial at 23 universities in which premature babies faced potentially lethal oxygen levels, saying government rules may have been unclear.

The federal Office for Human Research Protections, in a letter to the University of Alabama at Birmingham, the lead institution in the "Support" study, cited a series of problems with the research project, including the failure to properly notify parents of the risks that infants enrolled in the study might face.

The agency then blamed itself, saying it had an "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."

The human-research-protections office therefore will "put on hold all compliance actions against UAB relating to the Support case," Lisa R. Buchanan, a compliance-oversight coordinator at the agency, said in a letter on Tuesday to Richard B. Marchese, vice president for research and economic development at Birmingham.

The study—"Support" is an abbreviation of its full title, the "Surfactant, Positive Pressure, and Oxygenation Randomized Trial"—involved some 1,300 premature infants at two dozen hospitals. It was designed to determine the optimal levels of oxygen to give to the babies in the neonatal unit.

All of the oxygen levels that were used in the study were considered as being within a commonly used range, but previous research and clinical experience had suggested that too little oxygen could increase the risk of death, and too much could lead to blindness.

Ms. Buchanan issued her letter less than two months after the director of the research-protections office, Jerry A. Menikoff, in response to public revelations of the study's handling, criticized the consent form given to parents. The form "was written in a slanted way," describing the benefits but not all of the risks, he said.

Implications for Researchers

The agency's retreat was endorsed on Wednesday both by the [National Institutes of Health](#), which financed the study, and by a group of [46 university experts](#) in medicine and ethics, writing in *The New England Journal of Medicine*.

The university experts, led by Benjamin S. Wilfond, a professor of bioethics in the pediatrics department at the University of Washington, said the original position of Dr. Menikoff's agency "was a substantive error and will have adverse implications for future research."

Writing in the same journal, the NIH's director, Francis S. Collins, and two other top NIH officials also urged a pullback, saying the controversy had "alarmed some of the parents of infants who were in the study, confused the biomedical-research community, and befuddled IRBs," the institutional review boards that approve study protocols.

The reversal nevertheless is likely to generate its own pushback among both parents of the infants and university bioethics experts who regard the case as a clear-cut violation of the right of patients to informed consent, said Alice D. Dreger, a professor of clinical medical humanities and bioethics at Northwestern University.

Ms. Buchanan's letter "did a beautiful job" of reiterating the specific risks faced by babies in the trial and making clear that the parental consent forms did not convey those risks, Ms. Dreger said. In her letter, therefore, "the OHRP has said, 'You're guilty, but we're not going to do anything about it,'" she said.

At least one lawsuit has been filed against the University of Alabama at Birmingham and its institutional review board over the matter. The case, filed in April in a federal court in Alabama, names 11 families as plaintiffs and contends that infants in the research "suffered permanent neurological and vision issues, among other catastrophic injuries."

Other institutions that were involved in the research, which took place from 2004 to 2009, include Duke, Stanford, and Yale Universities.

The NIH agrees that the federal government needs to do a better job of setting rules in such cases, and it plans a process to accomplish that, including a public hearing, said Kathy L. Hudson, the NIH's deputy director for science, outreach, and policy.

But the NIH does not accept Ms. Buchanan's conclusion that there was a reasonably foreseeable increased risk of death from the lower oxygen levels provided to some of the infants in the trial, Ms. Hudson said. "That's where NIH and OHRP disagree," she said.

Although the research-protections office took issue with the consent form, Ms. Buchanan emphasized her agency's belief that the study itself was fundamentally ethical and designed to gain important information.

She was less clear on whether the state of scientific knowledge at the outset of the trial could have reasonably justified a warning to parents of heightened risk.

At one point in her letter, she said 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. Yet she also wrote that many researchers and clinicians were worried that low oxygen levels could lead to increased mortality and neurodevelopmental problems. Those concerns, she said, were a prime reason for the study.

Bartok, Lauren (NIH/OD) [C]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 5:02 PM
To: Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: DCOI U Ala Birmingham 060413 signed--Scanned document from Borrer, Kristina C (HHS/OASH) (Kristina.Borrer@hhs.gov)
Attachments: DCOI U Ala Birmingham 060413 signed .pdf; ATT00001.htm

FYI.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

Begin forwarded message:

From: "Buchanan, Lisa (HHS/OASH)" <Lisa.Buchanan@hhs.gov>
To: "marchase@uab.edu" <marchase@uab.edu>
Cc: "jonathanm@uab.edu" <jonathanm@uab.edu>, "furthaler@uab.edu" <furthaler@uab.edu>, "wsax@rti.org" <wsax@rti.org>, "jmc@rti.org" <jmc@rti.org>, "dborasky@rti.org" <dborasky@rti.org>, "amg@rti.org" <amg@rti.org>, "Hamburg, Margaret A. (FDA)" <margaret.hamburg@fda.hhs.gov>, "Less, Joanne (FDA/OC)" <Joanne.Less@fda.hhs.gov>, "Mills, Sherry (NIH/OD) [E]" <millsshe@od.nih.gov>, "Ellis, Joe (NIH/OD) [E]" <ellisj1@od.nih.gov>, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>, "Maddox, Yvonne (NIH/NICHD) [E]" <maddoxy@exchange.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Patterson, Amy (NIH/OD) [E]" <PattersA@OD.NIH.GOV>, "rhm3@case.edu" <rhm3@case.edu>, "rhm3@case.edu" <rhm3@case.edu>, "jwagner@wfubmc.edu" <jwagner@wfubmc.edu>, "Thughes@wihri.org" <Thughes@wihri.org>, "clyde_briant@Brown.EDU" <clyde_briant@Brown.EDU>, "thomas.parks@neuro.utah.edu" <thomas.parks@neuro.utah.edu>, "jane.strasser@uc.edu" <jane.strasser@uc.edu>, "sblanchard1@tuftsmedicalcenter.org" <sblanchard1@tuftsmedicalcenter.org>, "angela.wishon@UTSouthwestern.edu" <angela.wishon@UTSouthwestern.edu>, "david.wynes@emory.edu" <david.wynes@emory.edu>, "gary_chadwick@urmc.rochester.edu" <gary_chadwick@urmc.rochester.edu>, "vpr@iu.edu" <vpr@iu.edu>, "NanLee@stanfordmed.org" <NanLee@stanfordmed.org>, "jbixby@med.miami.edu" <jbixby@med.miami.edu>, "hilary.ratner@wayne.edu" <hilary.ratner@wayne.edu>, "james-walker@uiowa.edu" <james-walker@uiowa.edu>, "andrew.rudczynski@yale.edu" <andrew.rudczynski@yale.edu>, "Firestein, Gary Steven" <gfirestein@ucsd.edu>, "dan.gross@sharp.com" <dan.gross@sharp.com>, "proth@salud.unm.edu" <proth@salud.unm.edu>
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borrer, Kristina C (HHS/OASH) (Kristina.Borrer@hhs.gov)

Dear Dr. Marchase:

Attached is OHRP's letter regarding our evaluation of the SUPPORT trial. Please do not

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hesitate to contact me should you have any questions regarding this matter.

Thank you,

Lisa Buchanan, MAOM
Public Health Analyst
Division of Compliance Oversight
DHHS, Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Ph: 240-453 (b) (6)



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of the Assistant Secretary for Health

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June 4, 2013

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

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

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

Dear Dr. Marchase:

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

Richard B. Marchase, Ph.D. --University of Alabama at Birmingham
Page 2 of 7
June 4, 2013

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.

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

Richard B. Marchase, Ph.D. --University of Alabama at Birmingham
Page 3 of 7
June 4, 2013

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

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>.

Richard B. Marchase, Ph.D. --University of Alabama at Birmingham
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June 4, 2013

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

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

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

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.

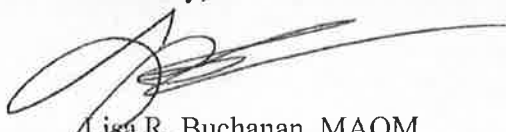
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June 4, 2013

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

OIRP'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:

Ms. Sheila D. Moore, Director, Office of the IRB, UAB
Dr. Ferdinand Urthaler, Chair, UAB IRBs
Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI
Mr. David Borasky, Chair IRB#1, RTI
Ms. Angela Greene, Chair IRB#2, RTI
Dr. Juesta M. Caddell, Chair IRB#3, RTI
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Dr. Yvonne Maddox, Deputy Director, NICHD
Dr. Rosemary Higgins, Program Scientist, NICHD
Dr. Robert H. Miller, Case Western Reserve University
Dr. Nancy C. Andrews, Duke University
Dr. Janice D. Wagner, Wake Forest University School of Medicine
Mr. Thomas Hughes, Women and Infants Hospital of Rhode Island
Dr. Clyde L. Briant, Brown University
Dr. Thomas N. Parks, University of Utah, School of Medicine
Dr. Jane Strasser, University of Cincinnati
Ms. Susan Blanchard, BBA, Tufts Medical Center
Ms. Angela Wishon, University of Texas Southwestern Medical Center

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

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Dr. David Wynes, Emory University School of Medicine
Dr. Gary Chadwick, MPH, University of Rochester, School of Medicine and Dentistry
Dr. Jorge Jose, Indiana University School of Medicine
Ms. Nancy J. Lee, Stanford University School of Medicine
Dr. John L. Bixby, University of Miami, Miller School of Medicine
Dr. Hilary H. Ratner, Wayne State University
Dr. James C. Walker, University of Iowa
Dr. Andrew Rudczynski, Yale University School of Medicine
Dr. Gary S. Firestein, University of California, San Diego
Dr. Daniel L. Gross, Sharp Mary Birch Hospital for Women and Newborns
Dr. Paul B. Roth, University of New Mexico Health Sciences Center

Blansfield, Earl (NIH/NICHD) [E]

From: Sye, Tait (OS/ASPA)
Sent: Tuesday, June 04, 2013 3:49 PM
To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]; Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) -Attorney Client privilege

From: Koh, Howard (HHS/OASH)
Sent: Tuesday, June 04, 2013 3:44 PM
To: Collins, Francis (NIH/OD) [E]; Lewis, Caya (HHS/IOS); Sye, Tait (OS/ASPA); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

Thanks everyone, to recap then:

- 1) OHRP Letter to UAB
 - a) Will send now
 - b) Post Letter on OHRP Website tomorrow Wednesday at 5PM
- 2) NIH NEJM Perspective- Post tomorrow Wednesday 5PM
- 3) OHRP Web Posting Announcing the Public Meeting
Will Post at 3-4PM tomorrow Wednesday, with the one word change noted
- 4) Continued coordination with ASPA, based on the above timetable

Howard

From: Collins, Francis (NIH/OD) [E] [mailto:collinsf@od.nih.gov]
Sent: Tuesday, June 04, 2013 3:26 PM
To: Lewis, Caya (HHS/IOS); Sye, Tait (OS/ASPA); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

Hi all,

Sorry, I have been off line for a few hours at Princeton commencement. This all seems to be coming together well -- thanks for everyone's hard work. NEJM has confirmed that they will post the NIH essay at 5 PM on Wednesday. (b) (5)

(b) (5)

Thanks, everyone,

Francis

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 3:01 PM
To: Sye, Tait (OS/ASPA); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Sye, Tait (OS/ASPA)
Sent: Tuesday, June 04, 2013 2:49 PM
To: Koh, Howard (HHS/OASH); Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Koh, Howard (HHS/OASH)
Sent: Tuesday, June 04, 2013 2:42 PM
To: Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: RE: Last minute logistical challenges

OK. Putting up the OHRP Web Posting Announcing the Public Meeting(#3A below) today may invite press calls today, so ASPA should be ready.

Let us know about the proposed word change (#3B below) and then OHRP can proceed.

Let us know if #1A is ok w everyone and OHRP will do that today as well. Thanks Howard

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 2:28 PM
To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Koh, Howard (HHS/OASH)
Sent: Tuesday, June 04, 2013 02:22 PM
To: Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: RE: Last minute logistical challenges

Hi, here are the next steps, as we see them:

- 5) OHRP Letter to UAB-
 - c) Send today Tuesday afternoon
 - d) Post Letter on OHRP Website tomorrow Wednesday at 5PM

- 6) NIH NEJM Perspective- Post tomorrow Wednesday 5PM
- 7) OHRP Web Posting Announcing the Public Meeting
 - a) Post at 5PM tomorrow Wednesday
 - b) In the post, we suggest a one word change for clarity—right now, the first sentence refers to “research studying one or more interventions which are used as standard of care treatment in the (b) (5) which is a bit confusing. We would recommend changing (b) (5). Another alternative is to change it to (b) (5)

- 8) Continued coordination with ASPA, based on the above timetable

Let us know if this timetable works and that one word change is ok.

If so, OHRP will then proceed with Step 1A, ie, to send the OHRP Letter to UAB today. Howard

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 1:55 PM
To: Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 11:55 AM
To: Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: RE: Last minute logistical challenges

Adding Tait in here. Thanks.

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 11:38 AM
To: Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

OHRP web posting

The Department of Health and Human Services (HHS) plans to announce a public meeting to discuss how certain provisions of the HHS protection of human subjects regulations, 45 CFR part 46, should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically will request input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process. A meeting notice providing more detail will be published in the Federal Register shortly.

From: Menikoff, Jerry (HHS/OASH)

Sent: Tuesday, June 04, 2013 11:14 AM

To: Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC); Lewis, Caya (HHS/IOS)

Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: RE: Last minute logistical challenges

On the OHRP end, the only point I would clarify relates to the web posting of our letter. Assuming the letter is sent out today, we would not plan to do the posting until late tomorrow (around 5:00). That would give the institutions at least some minimal amount of time to look at the letter, before having to deal with the media. Normally we give them much more time, usually two weeks (even when there isn't any concern regarding a media blitz). Kathy had in fact raised this issue with us a while ago, wanting to make sure that the institutions were given at least some time to digest the letter, and we fully agreed.

From: Palm, Andrea (HHS/IOS)

Sent: Tuesday, June 04, 2013 11:08 AM

To: Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS)

Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Corr, Bill (HHS/IOS)

Sent: Tuesday, June 04, 2013 10:59 AM

To: Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS)

Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: RE: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, June 04, 2013 10:49 AM
To: Dotzel, Peggy (HHS/OGC); Lewis, Caya (HHS/IOS)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

Peggy,

When would you want this posted on our website? There are only a couple of times a day that we can get something posted, and we need to provide some lead time to the web people.

Thanks,
Jerry

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 9:53 AM
To: Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

Sent from my iPhone

On Jun 4, 2013, at 6:59 AM, "Menikoff, Jerry (HHS/OASH)" <Jerry.Menikoff@hhs.gov> wrote:

We are looking into this on the OHRP end. I am hopeful that the letter can be released and posted consistent with the described timing. I will let everyone know when I have more information.

Jerry

From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Monday, June 03, 2013 10:38 PM
To: Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Last minute logistical challenges

Dear Colleagues,

We submitted the revised essay to NEJM this evening, and the editors are excited and gratified about the progress reflected in the changes. (b) (5)

(b) (5)

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Would this be possible?

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Can this plan work for all parties?

Thanks again, for everyone's hard work and flexibility in getting this information in front of the public as soon as possible.

Francis

(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



Blansfield, Earl (NIH/NICHD) [E]

From: Sye, Tait (OS/ASPA)
Sent: Tuesday, June 04, 2013 2:19 PM
To: Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

I'll loop with OASH comms, to post on OHRP website this blurb about the public meeting.

OHRP web posting

The Department of Health and Human Services (HHS) plans to announce a public meeting to discuss how certain provisions of the HHS protection of human subjects regulations, 45 CFR part 46, should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically will request input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process. A meeting notice providing more detail will be published in the Federal Register shortly.

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 1:55 PM
To: Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 11:55 AM
To: Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: RE: Last minute logistical challenges

Adding Tait in here. Thanks.

From: Lewis, Caya (HHS/IOS)

Sent: Tuesday, June 04, 2013 11:38 AM

To: Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC)

Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: RE: Last minute logistical challenges

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From: Menikoff, Jerry (HHS/OASH)

Sent: Tuesday, June 04, 2013 11:14 AM

To: Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC); Lewis, Caya (HHS/IOS)

Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: RE: Last minute logistical challenges

On the OHRP end, the only point I would clarify relates to the web posting of our letter. Assuming the letter is sent out today, we would not plan to do the posting until late tomorrow (around 5:00). That would give the institutions at least some minimal amount of time to look at the letter, before having to deal with the media. Normally we give them much more time, usually two weeks (even when there isn't any concern regarding a media blitz). Kathy had in fact raised this issue with us a while ago, wanting to make sure that the institutions were given at least some time to digest the letter, and we fully agreed.

From: Palm, Andrea (HHS/IOS)
Sent: Tuesday, June 04, 2013 11:08 AM
To: Corr, Bill (HHS/IOS); Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Corr, Bill (HHS/IOS)
Sent: Tuesday, June 04, 2013 10:59 AM
To: Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, June 04, 2013 10:49 AM
To: Dotzel, Peggy (HHS/OGC); Lewis, Caya (HHS/IOS)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Last minute logistical challenges

Peggy,

When would you want this posted on our website? There are only a couple of times a day that we can get something posted, and we need to provide some lead time to the web people.

Thanks,
Jerry

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

From: Lewis, Caya (HHS/IOS)

Sent: Tuesday, June 04, 2013 9:53 AM

To: Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH)

Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

Sent from my iPhone

On Jun 4, 2013, at 6:59 AM, "Menikoff, Jerry (HHS/OASH)" <Jerry.Menikoff@hhs.gov> wrote:

We are looking into this on the OHRP end. I am hopeful that the letter can be released and posted consistent with the described timing. I will let everyone know when I have more information.

Jerry

From: Collins, Francis (NIH/OD) [E] [mailto:collinsf@od.nih.gov]
Sent: Monday, June 03, 2013 10:38 PM
To: Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Last minute logistical challenges

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Francis

Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, June 04, 2013 10:45 AM
To: Lewis, Caya (HHS/IOS); Dotzel, Peggy (HHS/OGC)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Last minute logistical challenges
Attachments: DCOI U Alabama Birminham 060413 draft.docx

Here is a clean copy of what we would expect to be the final version of our letter. We await hearing when we can go ahead and release it. Ideally we'd want to do that as soon as possible.

Jerry

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, June 04, 2013 9:53 AM
To: Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH)
Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege

Sent from my iPhone

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From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Monday, June 03, 2013 10:38 PM
To: Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)

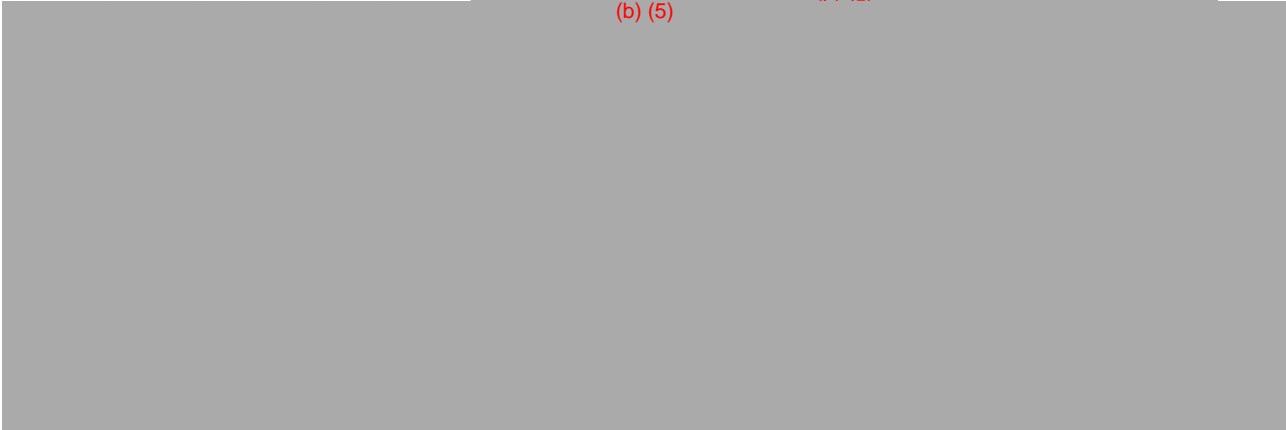
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: Last minute logistical challenges

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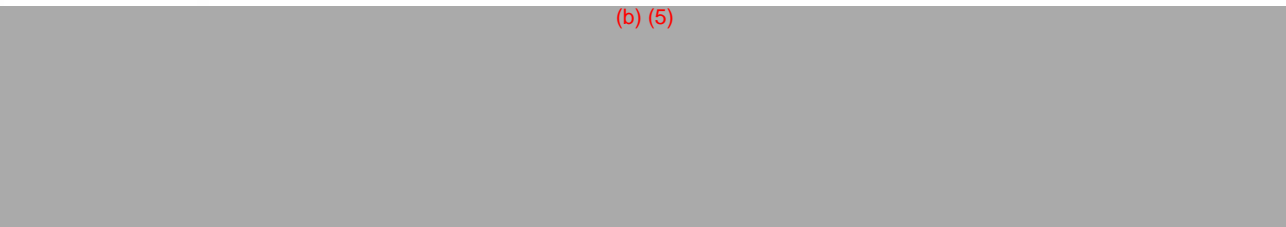
(b) (5)



(b) (5)

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Francis

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Bartok, Lauren (NIH/OD) [C]

(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege



From: Lewis, Caya (HHS/IOS)

Sent: Tuesday, June 04, 2013 9:53 AM

To: Dotzel, Peggy (HHS/OGC); Menikoff, Jerry (HHS/OASH)

Cc: Collins, Francis (NIH/OD) [E]; Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: Re: Last minute logistical challenges

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



(b)(5) - deliberative process, (b)(5) - Attorney work product privilege, (b)(5) - Attorney Client privilege



Sent from my iPhone

On Jun 4, 2013, at 6:59 AM, "Menikoff, Jerry (HHS/OASH)" <Jerry.Menikoff@hhs.gov> wrote:

(b)(5) - deliberative process

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From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Monday, June 03, 2013 10:38 PM
To: Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Last minute logistical challenges

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Francis

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, June 03, 2013 6:13 PM
To: Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Gutmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: NIH comments on docs for SUPPORT
Attachments: NEJM SUPPORT_060313_Final.docx

Hi everyone,

Thanks to Caya for summarizing the status of the FRN. (b) (5)

(b) (5)

We very much appreciate the edits (b) (5) provided by Howard Koh earlier today.

(b) (5)

It will be great to get this all launched on Wednesday! Thanks to all of our HHS colleagues for the hard work it has taken to get us here.

Francis

From: Lewis, Caya (HHS/IOS)
Sent: Monday, June 03, 2013 4:26 PM
To: Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Collins, Francis (NIH/OD) [E]; Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Subject: RE: Draft FR Notice regarding Support Study
Importance: High

All,

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

Thank you,

Caya

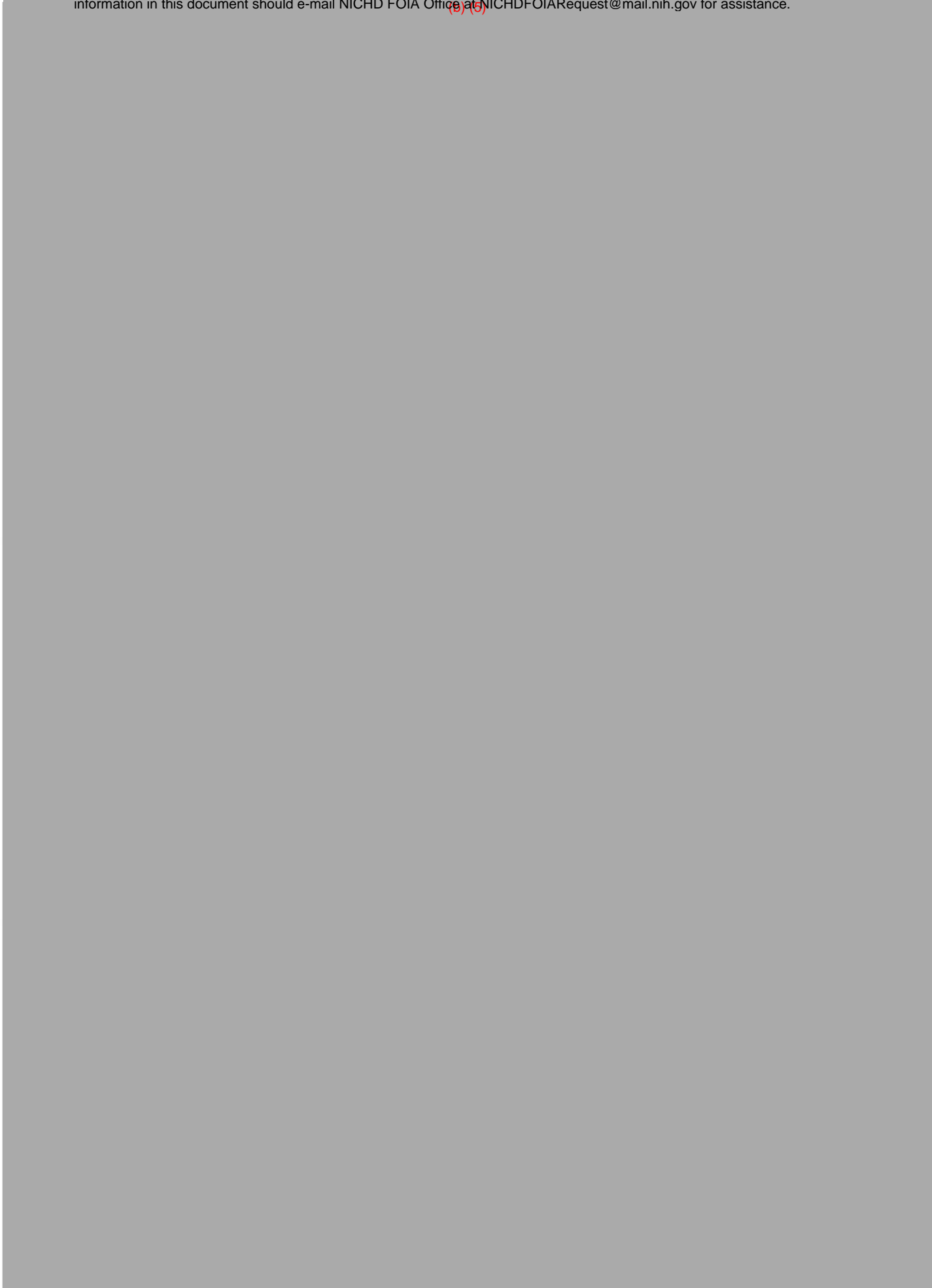
(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Koh, Howard (HHS/OASH)
Sent: Monday, June 03, 2013 8:28 AM
To: Collins, Francis (NIH/OD) [E]; Corr, Bill (HHS/IOS); Palm, Andrea (HHS/IOS); Schultz, William B (HHS/OGC); Horowitz, David (HHS/OGC); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Lewis, Caya (HHS/IOS); LaPan, Jarel (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Koh, Howard (HHS/OASH)
Subject: Comments on UAB letter and FRN; Text of NEJM essay
Attachments: 06 03 13 SUPPORT Letter Draft.docx

Colleagues

We now enclose comments/updates on 1) OHRP letter to UAB , 2) the FRN and 3) the proposed NEJM Perspective.

1) Regarding the **OHRP Letter**, attached is the updated version. There are some slight changes that accent and implement NIH's first suggestion. (b) (5)

2) Regarding the **Draft Federal Register Notice**:

- a. **Deadline:** We agree with your desire to make it as flexible as possible for people to attend or present at the meeting, and would be fine with extending the deadline to a week before the meeting.
- b. **Location:** We believe this should represent a HHS meeting and therefore would recommend the location as provided in the draft notice be retained.
- c. **Public Meeting versus Town Hall:** Thank you for pointing out the inconsistencies in the description of the meeting. The terminology "public meeting" throughout sounds fine
- d. **Meeting Format:** We think it is preferable to resolve the format issues as early as possible, so there will not be future disagreements about the format. Accordingly, we believe the existing level of detail is appropriate.
- e. **Issues for Discussion:** We agree that there is substantial information in the rest of the document indicating the scope of the discussion, and (b) (5)

Small point: There is some question about the conditions for using the phone line here- that may need more detail

3). **NEJM piece**

We are appreciative of the professional tone of this piece, and NIH has written this carefully and professionally.

We have 2 quick suggestions. We would like to raise (b) (5)

(b) (5)

Thank you for the opportunity for this dialogue. Howard

From: Collins, Francis (NIH/OD) [E] [collinsf@od.nih.gov]

Sent: Sunday, June 02, 2013 3:30 PM

To: Corr, Bill (HHS/IOS); Palm, Andrea (HHS/IOS); Koh, Howard (HHS/OASH); Schultz, William B (HHS/OGC); Horowitz, David (HHS/OGC); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Lewis, Caya (HHS/IOS); LaPan, Jarel (HHS/IOS)

Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: Comments on UAB letter and FRN; Text of NEJM essay

Hello all,

Thank you for the opportunity to weigh in on OHRP's letter to UAB and the Federal Register Notice related to SUPPORT. I have pasted NIH's comments on each of those documents below. (b) (5)

(b) (5)

We at NIH are grateful for the opportunity to work with such a dedicated team within HHS. We have come a long way, and the outcomes that will be announced on Wednesday will help a great deal.

Best regards, Francis

Comments on UAB letter

(b) (5)

(b) (5)



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(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Sunday, June 02, 2013 3:30 PM
To: Corr, Bill (HHS/IOS); Palm, Andrea (HHS/IOS); Koh, Howard (HHS/OASH); Schultz, William B (HHS/OGC); Horowitz, David (HHS/OGC); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Lewis, Caya (HHS/IOS); LaPan, Jarel (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Comments on UAB letter and FRN; Text of NEJM essay
Attachments: 05 31 13 SUPPORT E clean NIH.DOCX; BOOST NZ PI Form-Final-Chch.doc; NEJM SUPPORT_060213.docx

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(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



INFORMATION SHEET

What oxygen saturation level should we target in very preterm infants? – a randomised controlled trial (RCT). The BOOST (Benefits Of Oxygen Saturation Targeting) – NZ study.

Thank you for taking time to read this when so much is happening to your baby. We know it is a difficult time for you. We would like to invite you and your baby to take part in the BOOST - NZ study.

Summary

- **You may either be at risk of delivering more than 12 weeks early; or Your baby has already been born less than 28 weeks gestation and is less than one day old**
- **Very premature babies need treatment with oxygen because their lungs are not fully developed**
- **We want to understand whether it's better for a baby's long term health to aim to keep the blood oxygen level at either 85-89% or 91-95% saturation.**

Background to the study

Modern intensive care now enables many very preterm babies to survive who otherwise may not do so. One of the most important aspects of this care is help with breathing and treatment with oxygen because the baby's lungs are very immature. It is important to monitor the blood oxygen level (oxygen saturation) to try to make sure they do not have either too much or too little.

Too high oxygen in the blood for long periods may

- contribute to abnormal development of the retina (a condition called retinopathy of prematurity – ROP) and affect vision – it even is possible for some babies with ROP to become blind
- contribute to changes in the lungs that mean the baby needs ongoing help with breathing for weeks or months (a condition called bronchopulmonary dysplasia - BPD)
- be one cause of damage to brain cells and lead to developmental problems

Too low oxygen in the blood for long periods may

- increase the risk the baby will not survive or contribute to poor growth
- raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia
- damage the brain cells and lead to developmental problems

Blood oxygen changes every few seconds and cannot be controlled exactly. But most doctors who care for very preterm babies around the world target an oxygen saturation between 85% and 95%. But this range is based upon opinion and exactly what is the optimal range is unknown.

What is the purpose of the study?

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 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.

This is the New Zealand arm of an international study that will involve 5,000 very preterm infants in Australia, the United Kingdom, Scandinavia, Germany, Spain, Canada, and the United States. *In this country the study has been funded by the New Zealand Health Research Council*

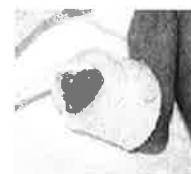
WHAT THE RESEARCH INVOLVES FOR YOU OR YOUR CHILD

Babies are eligible for the study if they are

- born at less than 28 completed weeks
- and are less than 24 hours old when the study starts

All very preterm babies, whether in this study or not, have their blood oxygen saturation monitored continuously. The monitor we use for this is called an "oximeter" and it works via a small probe attached to the hand or the foot. The probe shines a light through the tissues and from the return signal the oxygen saturation of the blood can be measured.

This picture shows an oxygen sensor, which has been placed on the baby's foot and covered to keep out the light. The sensor lead is connected to an oximeter, which is not shown.



For all babies who need supplementary oxygen the doctors and nurses will aim for a displayed target range of 88%-92%. If you agree to your baby joining the study, the only difference will be that your baby will be allocated a study oximeter at random (like tossing a coin), which has been altered to read either slightly higher or slightly lower than the actual saturation.

- One type reads 88% - 92% when the oxygen saturation is actually 3% lower at 85% - 89%.
- The other type reads 88% - 92% when the saturation is actually 3% higher at 91% - 95%.

The doctors and nurses will aim for an oxygen saturation of 88% - 92%, with both types of oximeter.

- Neither you nor the doctors or nurses can choose or know which type of oximeter your baby gets
- Above and below the range of 85%-95% each oximeter will always show the true oxygen saturation
- For babies who do not need extra oxygen, the study oximeter will often read up to 100%. That is quite normal
- All babies (whether in the study or not) will need occasional blood tests as part of routine care to check other things such as carbon dioxide

The pulse oximeter is a machine about the same size as a DVD player. It is kept on a shelf near the baby. This picture shows a display from a pulse oximeter. The baby's oxygen saturation reading is 91% and heart rate is 144



- Information will also be collected on your baby's antenatal and neonatal course and kept in a confidential way using code numbers. No reports from the study will identify you or your baby in any way.
- It's very important that we find out how your baby is doing at 2 years of age. When you go home, we'd like to keep in touch, so we will record your contact details. It's important to tell us if they change.
- When your baby is 2 years old (corrected for prematurity) he/she will be invited to be assessed by a paediatrician and have a formal test of development (the Bayley Test) and of vision.
- Most children will still be in routine paediatric follow-up at this time so the paediatric assessment will be at the time of a normal out-patient visit. The Bayley Test and vision assessment may require one or two extra visits and take 45 minutes and 30 minutes each.

DESCRIPTION OF INCONVENIENCES OR HAZARDS WHICH MIGHT BE EXPECTED:

We do not expect any difficulties at all with this study for your baby.

- Too much or too little blood oxygen might affect long term health and development. These risks exist whether or not your baby is in the study.
- The main benefit is to help improve the care of future very premature babies.
- As noted the Bayley Test and vision assessment might require two extra visits. We can help with the expense of this, for example by providing a petrol voucher, if necessary

Participation:

Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part your baby will receive the usual care. If you do agree to take part you are free to withdraw your baby from this study at any time, without having to give a reason, and this will in no way affect your baby's care.

Compensation:

In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2001 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually only provides partial reimbursement of costs and expenses and there may be no lump sum compensation. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

Ethical approval:

This study has been approved by the Multi-Region Ethics Committee, which reviews national and multiregional studies.

IF YOU WANT TO KNOW MORE:

If you want to know anything further about this study (either now or at any later date) please feel free to ask.

Prof Brian Darlow

Principal investigator BOOST-NZ
Paediatrician, Christchurch Women's Neonatal Unit
Phone: 3644-699 : carries pager

Dr Glynn Russell

Paediatrician, Christchurch Women's Neonatal Unit
Phone: 3644-699 : carries pager

Nicki McNeill/Trish Graham

Research Nurses BOOST-NZ
Christchurch Women's Neonatal Unit
Phone: 3644-742: has answerphone

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate: phone 3777 501
Or free phone if residing out of town: 0800 377 766

CONSENT FORM

PROJECT TITLE: What oxygen saturation level should we target in very preterm infants? – a randomised controlled trial (RCT). The BOOST-NZ study

INVESTIGATORS: Professor Brian Darlow, Department of Paediatrics,
Christchurch School of Medicine and Health Sciences.
Dr Carl Kuschel, National Women's Health, Auckland City Hospital
Dr Michael Meyer, Middlemore Hospital
Dr Michael Hewson, Wellington Hospital
Dr Roland Broadbent, Dunedin Hospital
Dr Cynthia Cole, Harvard University, Boston

VENUE: Christchurch Women's Hospital, Christchurch; National Women's Health, Auckland; Middlemore Hospital; Wellington Women's Hospital; Dunedin Hospital

STATEMENT BY PARENT:

I/we have read and understood the attached information sheets and have had the opportunity for discussion with a doctor. I/we am/are satisfied with answers I/we have been given. I/we understand that taking part in this study is voluntary (my/our choice) and that I/we may withdraw my baby from this study at any time, and this will in no way affect my baby's or my family's continuing or future health care in any way.

I/we understand that participation in this study is confidential and that no material which could identify me/us, or my/our child, will be used in any reports on this study.

I/we understand the compensation provisions for this study.

I/we have had time to consider whether to take part.

I/we know whom to contact if I have any questions about the study.

I/we wish to receive a summary of the results of the research. **Yes / No**

I/we give consent for my midwife / GP to be notified of my baby's participation in this research. **Yes / No**

I consent to my baby _____ (baby's name) taking part in this study.

Signed:-----Print----- Date: / /

-----Print----- Date: / /

Doctor:-----Print----- Date: / /

Request for Interpreter

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoaan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
	Other languages to be added following consultation with relevant communities.		

2001 Census question about ethnicity:

<p>Which ethnic group do you belong to? <i>Mark the space or spaces which apply to you.</i></p> <p><input type="radio"/> NZ European</p> <p><input type="radio"/> Māori</p> <p><input type="radio"/> Samoan</p> <p><input type="radio"/> Cook Island Maori</p> <p><input type="radio"/> Tongan</p> <p><input type="radio"/> Niuean</p> <p><input type="radio"/> Chinese</p> <p><input type="radio"/> Indian</p> <p><input type="radio"/> other (such as <i>DUTCH, JAPANESE, TOKELAUAN</i>). <i>Please state:</i></p> <p><input type="text"/></p> <p><input type="text"/></p>	<p>Ko tēhea momo tāngata e whai pānga atu ana koe? <i>Tohua te katoa o raro nei e hāngai ana ki a koe.</i></p> <p><input type="radio"/> Pākehā</p> <p><input type="radio"/> Māori</p> <p><input type="radio"/> Hāmoa</p> <p><input type="radio"/> Māori Kuki Airani</p> <p><input type="radio"/> Tonga</p> <p><input type="radio"/> Niue</p> <p><input type="radio"/> Hainamana</p> <p><input type="radio"/> Īnia</p> <p><input type="radio"/> tētahi atu (pērā i <i>TATIMANA, HAPANĪHI, TOKELAU</i>). <i>Tuhia mai:</i></p> <p><input type="text"/></p> <p><input type="text"/></p>
--	--

(b) (5)



(b) (5)



(b) (5)



(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 31, 2013 6:04 PM
To: Corr, Bill (HHS/IOS); Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Collins, Francis (NIH/OD) [E]; Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Wolters, Bradley (OS/OPHS); Bumpus, Kirby (HHS/OASH)
Subject: Draft letter to UAB
Attachments: 05 31 13 SUPPORT E clean.docx

All,

Here is the latest version of the letter to UAB.

Best,
Jerry

(b) (5)

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(b) (5)



(b) (5)



(b) (5)



(b) (5)



DRAFT

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, May 29, 2013 5:39 AM
To: Corr, Bill (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: Letter from bioethicists on SUPPORT
Attachments: BioethicistsSUPPORT.pdf

Hi Bill and Andrea,

I mentioned yesterday having just received a copy of a letter about SUPPORT, addressed to Jerry Menikoff and signed by a large group of senior bioethicists. Since the letter was also cc'd to KGS and Howard Koh, I am sure it will reach you soon anyway – but thought it might be useful for you to see this now.

Thanks for your leadership in helping identify a path forward.

Francis



1900 9th Avenue
M/S: C9S-6
Seattle, WA 98101
www.bioethicsdirectors.net

May 27, 2013

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
Department of Health and Human Services
Suite 200
1101 Wootton Parkway
Rockville, MD 20852

Dear Dr Menikoff,

We are a group of scholars and leaders in bioethics with extensive experience in ethical and regulatory issues in pediatrics and human subjects research. We urge you to reconsider OHRP's finding that the institutions involved with the Surfactant, Positive Pressure, Oxygenation Randomized Trial (SUPPORT) failed to meet regulatory informed consent requirements, in particular regarding reasonably foreseeable risks of enrollment in the study. We believe this conclusion was a substantive error that will have adverse implications for future research.

SUPPORT was undertaken because there was no reliable scientific evidence as to which blood oxygen saturation levels were optimum for extremely premature babies. The infants in the study were randomized to oxygen saturation targets that were consistent with standard clinical care at the participating institutions. OHRP's conclusion that the study's experimental evaluation of these otherwise routinely used oxygen saturation levels exposed subjects to additional risk (above the risks of routine clinical treatment) is not supported by evidence.

Furthermore, OHRP's conclusion that the SUPPORT investigators violated federal regulations in failing to include specific information elements in the parental permission documents regarding risks of the study interventions is without substantive merit. While the permission forms conceivably could have been improved, the risks of retinopathy of prematurity and death during participation in this factorial design study were noted. There is nothing to indicate that the institutional bodies responsible for reviewing the SUPPORT study failed to exercise appropriate care and judgment as to all the factors required by the Common Rule in approving the study. OHRP should not sanction research institutions simply because it disagrees with their assessment of the risks of research, absent a finding that an institution has failed to meet the terms of its federal-wide assurance, such as in the manner in which its IRB is constituted or

operates. Accordingly, a finding by OHRP that the institutions conducting the SUPPORT study failed to meet applicable regulatory requirements, when unsupported by substantial evidence, would be arbitrary and capricious.

In the absence of a formal mechanism for appeal, we urge you to regard this expression of disagreement by signatories representing leaders in research ethics as an appropriate basis for OHRP to reconsider this decision. Allowing the decision to stand would be unfair to the investigators and institutions involved in SUPPORT. It would also set a precedent that will impede ongoing and future patient-centered outcomes studies. Such studies are crucial to advance medical practice, reduce risks, improve outcomes, and enhance cost effectiveness, particularly in pediatrics.

The consent process for clinical research can no doubt be improved. The recent scrutiny of SUPPORT highlights the challenges faced in clinical research. We believe that these challenges can best be addressed through open discussions among the full range of relevant stakeholders. We stand ready to participate in any such discussions to assist OHRP and the Department in their efforts to assure the highest standards of ethics in research.

Sincerely,

Benjamin Wilfond, MD, Professor of Pediatrics, University of Washington; Director, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute

David Magnus, PhD, Thomas A. Raffin Professor of Medicine and Biomedical Ethics and Professor of Pediatrics, Director, Center for Biomedical Ethics, Stanford University*

Armand Antommaria, MD, PhD, Associate Professor of Pediatrics, University of Cincinnati; Director, Ethics Center, Cincinnati Children's Hospital Medical Center*

Paul Appelbaum, PhD, Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law, Columbia University

Renee D. Boss, MD, MHS, Division of Neonatology, Department of Pediatrics, Johns Hopkins School of Medicine; Johns Hopkins Berman Institute of Bioethics

Arthur L. Caplan, PhD, Drs. William F. and Virginia Connolly Mitty Chair, Director, Division of Medical Ethics, New York University Langone Medical Center

Alexander M. Capron, University Professor, Scott H. Bice Chair in Healthcare Law, Policy and Ethics, Co-Director, Pacific Center for Health Policy and Ethics, University of Southern California

Ellen Wright Clayton, MD, JD, Professor of Law, Vanderbilt Law School; Craig-Weaver Professor of Pediatrics, Vanderbilt University School of Medicine

Mildred Cho, PhD, Professor of Pediatrics, Stanford University; Associate Director, Stanford Center for Biomedical Ethics, Stanford University*

Douglas Diekema, MD MPH, Professor of Pediatrics, University of Washington; Director of Education, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute

- Joel Frader MD MA, Professor of Pediatrics and Medical Humanities & Bioethics, Northwestern University
- Ruth R. Faden, PhD, MPH, Philip Franklin Wagley Professor of Biomedical Ethics; Director, Johns Hopkins Berman Institute of Bioethics
- Chris Feudtner, MD, PhD, Associate Professor of Pediatrics, Perelman School of Medicine, University of Pennsylvania; Steven D. Handler Endowed Chair of Medical Ethics, Director Department of Medical Ethics, Children's Hospital of Philadelphia
- Joseph J. Fins, MD, E. William Davis, Jr., MD Professor of Medical Ethics, Chief, Division of Medical Ethics, Professor of Medicine, Weill Medical College of Cornell University and Director of Medical Ethics, New York Presbyterian Hospital-Weill Cornell Medical Center
- Norman Fost, MD, MPH, Professor, Pediatrics and Bioethics, University of Wisconsin School of Medicine and Public Health
- D. Micah Hester, PhD, Chief, Division of Medical Humanities, University of Arkansas for Medical Sciences; Clinical Ethicist, Arkansas Children's Hospital
- Steven Joffe, MD, MPH, Associate Professor of Pediatrics, Global Health and Social Medicine, Harvard Medical School; Hospital Ethicist, Dana-Farber Cancer Institute
- Jeffrey Kahn, PhD, MPH, Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy, Deputy Director for Policy and Administration, Johns Hopkins Berman Institute of Bioethics
- Nancy E. Kass, ScD, Phoebe R. Berman Professor of Bioethics and Public Health, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; Deputy Director for Public Health, Johns Hopkins Berman Institute of Bioethics
- Eric Kodish MD, FJ O'Neill Professor and Chair, Department of Bioethics, Professor of Pediatrics, Lerner College of Medicine, Cleveland Clinic
- John D. Lantos MD, Professor of Pediatrics, University of Missouri at Kansas City; Director, Children's Mercy Hospital Bioethics Center
- Laurence McCullough, PhD, Dalton Tomlin Chair in Medical Ethics and Health Policy, Professor of Medicine and Medical Ethics; Associate Director for Education, Center for Medical Ethics and Health Policy, Baylor College of Medicine
- Ross McKinney, Jr., MD, Professor of Pediatric Infectious Diseases; Director, Trent Center for Bioethics, Humanities and History of Medicine, Duke University and School of Medicine
- P. Pearl O'Rourke, MD, Director, Human Research Affairs, Partners HealthCare
- Kathleen E. Powderly, CNM, PhD, Director, John Conley Division of Medical Ethics and Humanities, SUNY Downstate Medical Center
- Lainie Friedman Ross, MD, PhD, Carolyn and Matthew Bucksbaum Professor of Clinical Ethics, Professor, Departments of Pediatrics, Medicine, and Surgery, Co-Director, Institute for Translational Medicine, Associate Director, MacLean Center for Clinical Medical Ethics, University of Chicago*
- Richard Sharp, PhD Director of Research Center for Ethics, Humanities and Spiritual Care, Cleveland Clinic

Sadath Sayeed, MD, JD, Assistant Professor of Global Health and Social Medicine, Harvard University

Jeremy Sugarman, MD, MPH, MA, Harvey M. Meyerhoff Professor of Bioethics and Medicine, Deputy Director for Medicine, Johns Hopkins Berman Institute of Bioethics

Tom Tomlinson, PhD, Director, Center for Ethics and Humanities in the Life Sciences, College of Human Medicine, Michigan State University

Robert D. Truog, MD, Professor of Medical Ethics, Anesthesiology, & Pediatrics, Director of Clinical Ethics, Harvard Medical School; Senior Associate in Critical Care Medicine, Children's Hospital Boston

Yoram T. Unguru, MD, MS, MA, Division of Pediatric Hematology/Oncology, The Herman and Walter Samuelson Children's Hospital at Sinai; Johns Hopkins Berman Institute of Bioethics

Kathryn L. Weise, MD, MA, Program Director, Cleveland Fellowship in Advanced Bioethics, Department of Bioethics, Cleveland Clinic

Stuart Youngner, MD, Professor of Psychiatry and Cognitive Science, Susan E. Watson Professor of Bioethics, Chair, Department of Bioethics, Case Western Reserve University*

*[*individuals who work at the same institutions as the SUPPORT Investigators]*

cc:

The Honorable Kathleen Sibelius, Secretary, Department of Health and Human Services (HHS)

The Honorable Howard K. Koh, Assistant Secretary for Health, HHS

Dr. Francis Collins, Director, National Institutes of Health

Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Development

Dr. Christopher Austin, Director, National Center for Advancing Clinical and Translational Sciences

Dr Richard B. Marchase, Vice President, Research, University of Alabama at Birmingham

Dr Jeffrey R Botkin, Chair, Secretary's Advisory Committee on Human Research Protections

Blansfield, Earl (NIH/NICHD) [E]

From: Corr, Bill (HHS/IOS)
Sent: Monday, May 27, 2013 9:42 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Palm, Andrea (HHS/IOS)
Subject: Re: possible next steps for HHS in standard of care research

(b)(5) - deliberative process,

From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Monday, May 27, 2013 06:05 PM
To: Corr, Bill (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: possible next steps for HHS in standard of care research

Hi Bill,

Kathy Hudson, Alan Guttmacher, and I gave some thought to options of next steps to follow up on the current controversy about standard of care research, as triggered by the SUPPORT study. (b) (5)

(b) (5)

I hope you are having a restful Memorial Day weekend.

Francis

(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, May 23, 2013 8:46 AM
To: Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: Draft of essay for NEJM on SUPPORT
Attachments: NEJM draft - support statement 5-23-13.docx

Hi Andrea and Bill,

It was very helpful to speak with Andrea last night about the next steps in the debate about the SUPPORT study, and the larger implications for studies that investigate variations of the standard of care.

(b) (5)



Many thanks, Francis

(b) (5)



(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 2:29 PM
To: Lewis, Caya (HHS/IOS)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH); Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: DRAFT outline- HHS stmt on SUPPORT
Attachments: HHSStatementonSUPPORTocpledits 5-21-13.docx

All,

(b) (5)

Thanks.

kathy

From: Lewis, Caya (HHS/IOS)
Sent: Monday, May 20, 2013 5:43 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Subject: RE: DRAFT outline- HHS stmt on SUPPORT

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, May 20, 2013 5:21 PM
To: Lewis, Caya (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Subject: RE: DRAFT outline- HHS stmt on SUPPORT

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Lewis, Caya (HHS/IOS)
Sent: Monday, May 20, 2013 5:02 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Subject: RE: DRAFT outline- HHS stmt on SUPPORT

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

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(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Jones, Wanda K. (DHHS/OS/OASH)

Sent: Monday, May 20, 2013 4:54 PM

To: Lewis, Caya (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)

Cc: Sye, Tait (OS/ASPAs); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)

Subject: RE: DRAFT outline- HHS stmt on SUPPORT

(b) (5)

From: Lewis, Caya (HHS/IOS)

Sent: Monday, May 20, 2013 4:39 PM

To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)

Cc: Sye, Tait (OS/ASPAs); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)

Subject: DRAFT outline- HHS stmt on SUPPORT

Importance: High

All,

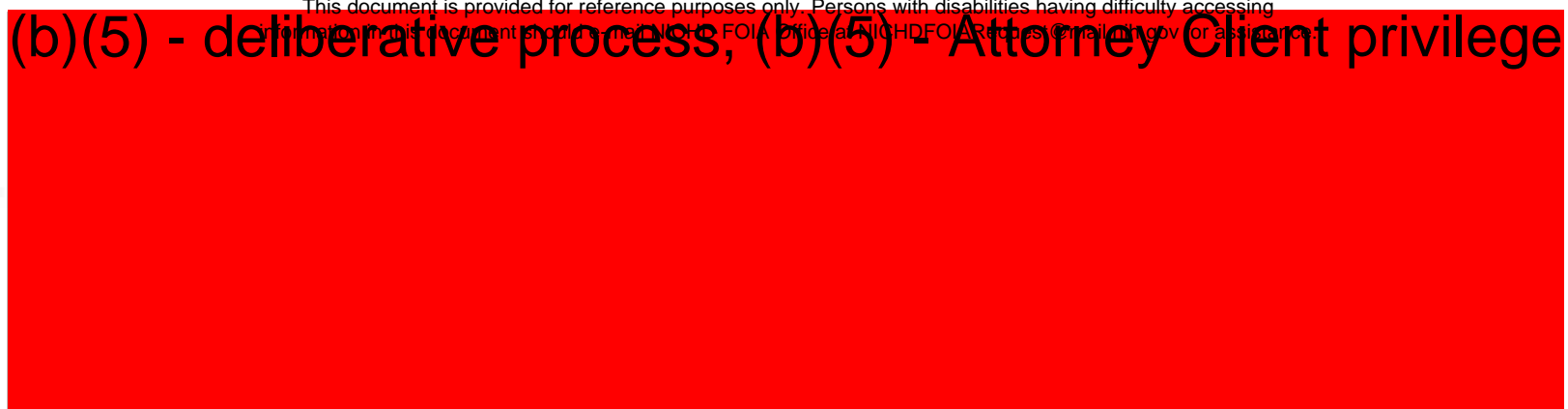
(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

Thanks,

Caya

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 17, 2013 4:58 PM
To: Koh, Howard (HHS/OASH)
Cc: LaPan, Jarel (HHS/IOS); Sye, Tait (OS/ASPA); Bumpus, Kirby (HHS/OASH); Lewis, Caya (HHS/IOS); Corr, Bill (HHS/IOS); Palm, Andrea (HHS/IOS); Schultz, William B (HHS/OGC); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Guttmacher, Alan (NIH/NICHHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: Next steps on SUPPORT Study
Attachments: RE: SUPPORT study

Thanks for sharing this. We are happy to work with ASPA to review comments.

(b) (5)

-----Original Message-----

From: Koh, Howard (HHS/OASH)
Sent: Friday, May 17, 2013 4:17 PM
To: Lewis, Caya (HHS/IOS); Corr, Bill (HHS/IOS); Palm, Andrea (HHS/IOS); Schultz, William B (HHS/OGC); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)
Cc: LaPan, Jarel (HHS/IOS); Sye, Tait (OS/ASPA); Hudson, Kathy (NIH/OD) [E]; Bumpus, Kirby (HHS/OASH)
Subject: RE: Next steps on SUPPORT Study

Caya and colleagues

Attached is the final updated draft letter from OHRP.

It accepts all the changes communicated from you in the earlier message/draft this morning, and in addition, makes one slight change in the direct citation for footnote 2, as was recommended by you.

The proposed next steps then would be:

- 1) To send this letter to UAB early next week- Monday or Tuesday.
- 2) To post this letter on the OHRP website one day after sending (usually the interval between sending and posting is longer, but a shorter interval is recommended here).

In the meantime, OASH/OHRP Communications is working w ASPA Communications on tps.

I am leaving for Geneva/World Health Assembly tomorrow so Wanda Jones will be the main point of direct contact till I return Friday AM. However I will be checking email regularly and could also join a call, if the timing were right.

Many thanks everyone for your help. Howard

-----Original Message-----

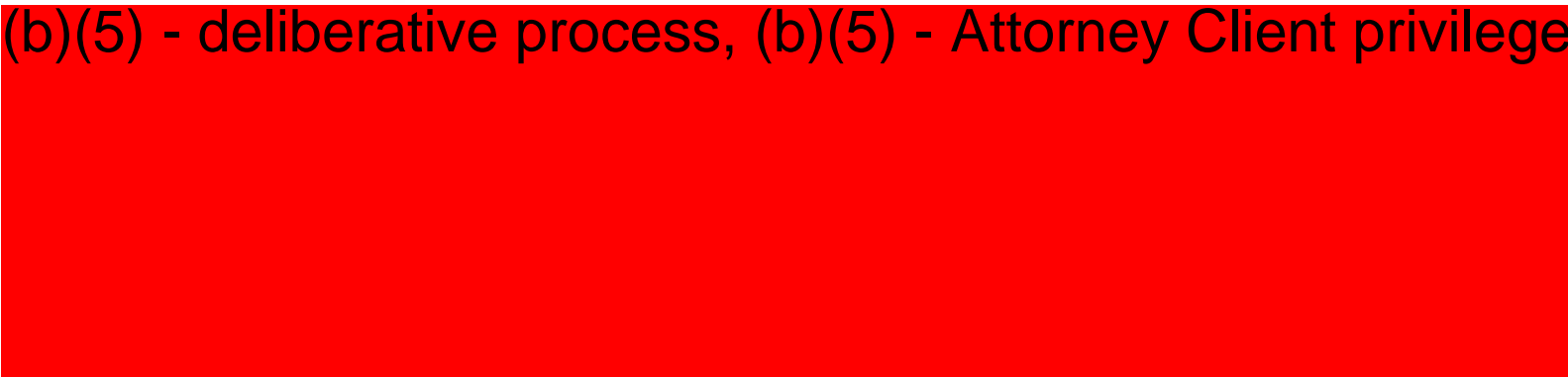
From: Lewis, Caya (HHS/IOS)
Sent: Friday, May 17, 2013 1:53 PM
To: Corr, Bill (HHS/IOS); Palm, Andrea (HHS/IOS); Schultz, William B (HHS/OGC); Koh, Howard (HHS/OASH); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)

Cc: LaPan, Jarel (HHS/IOS); Sye, Tait (OS/ASPA); Hudson, Kathy (NIH/OD) [E]; Bumpus, Kirby (HHS/OASH)

Subject: Next steps on SUPPORT Study

All,

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



Thanks and please let me know if you have questions.

Caya

(b) (5)



(b) (5)



(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, May 16, 2013 9:51 PM
To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Jones, Wanda K. (DHHS/OS/OASH)
Cc: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Horowitz, David (HHS/OGC); McGarey, Barbara (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: SUPPORT new articles/discussions
Attachments: DrazenEditorialSUPPORT.pdf; MagnusCaplanSUPPORT.pdf; SHELBY-COLLINS 5-15-13.docx

Hello everyone,

I wanted to make sure you all had the latest information on the SUPPORT study.

1. The two attached articles were published today in the New England Journal of Medicine (NEJM). The first is written by a NEJM editor, Dr. Drazen, who has considerable expertise in clinical trials. He is, for example, the co chair of the IOM Forum on Drug Discovery, Development, and Translation. The second article is written by Art Caplan and Dave Magnus, two prominent bioethicists. Both are supportive of the SUPPORT study and raise questions about OHRP determinations.

2. I wanted also to make sure folks were aware that Francis got a couple of questions from Senator Shelby in the hearing yesterday. That transcript is attached. Basically, FC said that studies to improve the standard of care are vital. He also said that he did not believe that babies in the SUPPORT study were placed at increased risk over babies not enrolled. (b) (5)

3. I have heard that a letter to the Secretary is being generated by the directors of all the US bioethics departments. I (b) (5)

4. In response to multiple requests from Public Citizen, Dr. Alan Guttmacher and I will be meeting with Sid Wolfe and his deputy tomorrow. We will largely be in "listen only" mode.

5. Finally, I wanted to make sure everyone had seen this article by the pediatrician and bioethicist, John Lantos. <http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blogid=140> It outlines beautifully the debate before us.

(b) (5) Studies in the newborn research network have been suspended (tragic) and investigators in large clinical trials to examine and improve the standard of care are weary. We look forward to engaging them in a discussion about the broad issues in CER studies. (b) (5)

Please let us know if we can provide any information. And, while we have said it a million times, it is worth repeating – we could not have picked a finer team for this scientific and ethical debate. NIH continues to work on a zillion issues collaboratively with OASH and OHRP. (b) (5)

Thanks
kathy

EDITORIALS



Informed Consent and SUPPORT

Jeffrey M. Drazen, M.D., Caren G. Solomon, M.D., M.P.H., and Michael F. Greene, M.D.

In the summer of 1963, the nation watched in sadness as Patrick Bouvier Kennedy, the youngest child of President John F. Kennedy and First Lady Jacqueline Bouvier Kennedy, was born prematurely and then died of lung disease 2 days later at Children's Hospital in Boston. Even now, it is common knowledge that children born prematurely are at high risk for death.

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. Decades of study and refining practice have resulted in major improvements in the care of premature infants; now most babies weighing a kilogram or more, and many weighing less than this, survive. This progress has come through careful research in multiple aspects of neonatal care, but many questions remain regarding practice that will maximize survival and minimize the long-term sequelae resulting from surviving severe prematurity. Without research studies, your neonatologist would simply be guessing about what is best rather than knowing what is best for your child.

The physicians in the nursery ask you to allow your very premature baby to participate in a research study, called the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), part of which is focused on the amount of supplemental oxygen they will give to your baby. They orally explain the study to you and ask you to sign an informed-consent

document; it is six pages of single-spaced type-script.

Premature babies often require supplemental oxygen; what was not known in 2005 was exactly how much oxygen to give. The doctors knew that maintaining very high oxygen levels in the blood might cause retinopathy of prematurity (ROP), or abnormal growth of blood vessels in the eyes, which can damage the retinas and impair vision. The informed-consent form notes the higher risk of ROP that is associated with prolonged exposure to supplemental oxygen but states that "the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known" and also notes that "the use of lower saturation ranges may result in a lower incidence of severe ROP." Clinical practice at the time (and that recommended in the 2002 and 2007 guidelines of the American Academy of Pediatrics,^{1,2} on whose guidelines committee one of us served) was to target values for the partial pressure of arterial oxygen anywhere between 50 and 80 mm Hg, consistent with oxygen saturations measured by pulse oximetry between 85% and 95%. Among the clinical questions addressed by SUPPORT was whether targeting the upper or lower end of this range might result in better outcomes for very preterm infants.

The study was conceived in 2003, initiated in 2005, and completed in 2009. Trials addressing the same clinical question were initiated in 2006 in the United Kingdom, Australia, and New Zealand (Benefits of Oxygen Saturation Targeting [BOOST II]), indicating the importance of the question.³ 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.

The consent document for SUPPORT that you have been handed spells this out clearly and succinctly: "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." You sign the form, and your child enters the study. The same process was also taking place with parents of newborn extremely premature infants at multiple centers across the country.

After 5 years and more than 1300 babies studied, the data from SUPPORT are published in 2010 in the *Journal*.⁴ The data show that, even within the recommended oxygen saturation range, babies with a higher oxygen saturation target had a higher risk of ROP, and those with a lower saturation target had a higher risk of death. With this new information, the investigators in the BOOST II trials in the United Kingdom and Australia review their preliminary data and discover that lower oxygen saturations in their trials are also associated with a higher rate of death.³ These findings changed medical practice at many centers.

There was no way for you as a parent of a child in SUPPORT to know what the answer would be before your child participated. The study made clear that higher oxygen saturations within the then-recommended range increased the risk of retinopathy but decreased the risk of death. This is how new medical knowledge is gained. The story should have ended there, but it didn't.

In 2011, the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services began an investigation into the informed-consent process used when newborns were enrolled in SUPPORT. Their investigation concluded with a 13-page letter of determination sent to the SUPPORT lead center on March 7, 2013 (provided with a sample informed-consent form in the Supplementary Appendix, available with the full text of this article at NEJM.org). The OHRP reached the following conclusion: "It was alleged, and we determine, that the IRB [institutional review board] approved informed consent documents for this study failed to include or adequately address the following basic element required by

HHS [Health and Human Services] regulations at 45 CFR 46.116(a): Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts."

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. At the time, as explained in the principal investigator's response to the allegations and in a related letter to the editor in the *Journal*,⁵ there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent from parents of participating infants. Through hindsight (and essentially faulting investigators for not informing parents up front of a risk later uncovered by the trial itself), the OHRP investigation has had the effect of damaging the reputation of the investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice.

Clinical research is crucial if we are to advance medical science. Clinical investigators acted in good faith to design a trial to address an important question. An informed-consent document was drafted and approved by institutional review boards of participating centers before the work was begun. The OHRP has a duty to investigate questions of research impropriety, but we strongly disagree with their determination of inadequate informed consent in this case.

The results of SUPPORT have been critical in informing treatment decisions for extremely preterm infants. When babies like Patrick Bouvier Kennedy are born today, their chances of survival to adulthood are greatly improved, thanks to research made possible by thousands of parents and their children. We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Massachusetts General Hospital, Boston (M.F.G.).

This article was published on April 17, 2013, at NEJM.org.

1. American Academy of Pediatrics, American College of Ob-

stetricians and Gynecologists. Guidelines for perinatal care. 5th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2002.

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NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010; 362:1959-69.

5. Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely preterm infants. *N Engl J Med* 2013;368:1949-50.

DOI: 10.1056/NEJMe1304996

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HCV Treatment — No More Room for Interferonologists?

Joost P.H. Drenth, M.D., Ph.D.

The landscape of therapy for hepatitis C virus (HCV) infection is changing rapidly. Until recently, the standard of care for HCV infection was a combination of peginterferon and ribavirin. Our increased understanding of the basic biology of HCV led to the identification of specific proteins involved in the replication of the virus. These proteins can be targeted by protease and polymerase inhibitors.

Two years ago, the advent of protease inhibitors, such as telaprevir and boceprevir, profoundly affected the field.^{1,2} These agents improved the likelihood of cure but came with a number of inherent limitations. Protease inhibitors do not have antiviral activity in HCV genotypes other than the predominant genotype 1, which leaves at least five other HCV genotypes without coverage. Moreover, protease inhibitors can promote viral resistance, which usually signals therapeutic failure, and have multiple pharmacokinetic interactions with other drugs. Finally, protease inhibitors need to be administered with peginterferon and ribavirin, two drugs with extensive and well-established side-effect profiles that are aggravated by the addition of telaprevir or boceprevir.

Clinicians who treat patients with HCV infection have learned to accept and treat adverse effects as an integral part of patient care, but the inclusion of protease inhibitors in the therapeutic arsenal has added a layer of complexity. Indeed, the major challenge of contemporary interferon therapy is adequate management of side effects. Physicians and patients are ready for less toxic therapeutic options.

Two groups of investigators (Jacobson et al.³ and Lawitz et al.⁴) now suggest in the *Journal* that change is about to happen. They describe the use of sofosbuvir, a novel polymerase inhibitor, in a series of four experimental studies targeting patients with HCV infection. In three random-

ized trials — FISSION, POSITRON, and FUSION — investigators focused on patients with HCV genotype 2 or 3, as seen in everyday clinical practice, including patients who had received no previous treatment, those who were unwilling to take interferon or had unacceptable side effects, and those who did not have a response to previous therapy. All the studies had a similar end point: a sustained virologic response at 12 weeks after the end of therapy. In addition, in the single-group, open-label NEUTRINO study, investigators studied the use of a sofosbuvir-based regimen in patients with genotype 1, 4, 5, or 6 infection.

The FISSION study examined the efficacy of 12 weeks of sofosbuvir plus ribavirin, as compared with the standard of care, peginterferon alfa-2a plus ribavirin, administered for 24 weeks. Standard therapy was successful in 78% of patients with genotype 2 infection and 63% of those with genotype 3 infection, as compared with rates of 97% and 56%, respectively, with the sofosbuvir-based regimen.

The POSITRON study evaluated a population that was not deemed to be eligible for interferon-based therapy and compared 12 weeks of sofosbuvir plus ribavirin with placebo. The primary reasons for ineligibility were a preexisting psychiatric disorder (57%) or autoimmune disorder (19%). None of the patients in the placebo group achieved the end point, but 93% of those with genotype 2 infection and 61% of those with genotype 3 infection had a sustained virologic response with sofosbuvir plus ribavirin.

The FUSION study, which targeted patients without a sustained response to interferon-based therapy, compared a 12-week regimen of sofosbuvir-ribavirin with a 16-week regimen. Four additional weeks of treatment made a difference, with an increase in the rate of sustained virologic response from 86% to 94% in patients with

critical in implementing successful prevention and control activities. The detection of human H7N9 virus infections is yet another reminder that we must continue to prepare for the next influenza pandemic. The coming weeks will reveal whether the epidemiology reflects only a widespread zoonosis, whether an H7N9 pandemic is beginning, or something in between. The key is intensified surveillance for H7N9 virus in humans and animals to help answer important questions. We cannot rest our guard.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta.

This article was published on April 11, 2013, at NEJM.org.

1. Matrosovich MN, Matrosovich TY, Gray T, Roberts NA, Klenk HD. Human and avian influenza viruses target different cell types in cultures of human airway epithelium. *Proc Natl Acad Sci U S A* 2004;101:4620-4.
2. Imai M, Watanabe T, Hatta M, et al. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmis-

sion to a reassortant H5 HA/H1N1 virus in ferrets. *Nature* 2012;486:420-8.

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DOI: 10.1056/NEJMp1304661

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Risk, Consent, and SUPPORT

David Magnus, Ph.D., and Arthur L. Caplan, Ph.D.

Comparative effectiveness research has the potential to dramatically improve patient care while reducing costs. In the absence of good evidence about which treatment is best for particular patients, decision making too often hinges on exogenous factors such as advertising and detailing by pharmaceutical companies, what a physician first learned to do, insurance coverage, and local custom. Without good evidence about what is best among competing but generally accepted clinical options, it is often a challenge for physicians to identify the best course of care.

A great deal of effort is under way to make it easier and less expensive to conduct prospective, randomized comparative effectiveness research.¹ Some of the options for conducting such research take advantage of the fact that there is no additional risk to being randomly assigned to one or another equally well-supported treatment option that falls within the stan-

dard range of care in clinical practice. This all seems for the good, but there is cause for concern in a recent decision by the Office for Human Research Protections (OHRP) to issue a letter of determination to investigators at the University of Alabama at Birmingham (UAB) about a large multicenter clinical trial to determine appropriate oxygen-saturation levels in severely premature neonates.² 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 UAB case concerns a trial undertaken to determine the appropriate oxygen-saturation levels to use in very premature infants. 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.³ By the mid-2000s, neonatologists were calling for research that would help clarify the best oxygen-saturation levels for these patients.⁴ Many believed that lower levels would reduce the incidence of retinopathy of prematurity without increasing mortality. The trial, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), randomly assigned patients to higher and lower oxygen-saturation levels within the standard of care.⁵

The OHRP has now found fault with the consent language used when patients were enrolled in SUPPORT. We think it is important to be very clear about the issues at stake here. One is about risk, and the other is about informed consent.

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.

Before the study began, there was insufficient evidence to know what oxygen level within the guideline-specified range was best. 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. The first problem with the OHRP letter and a good deal of the public outrage that followed is the confusion of the risks of the clinical treatment with the risks of the randomization. There were and continue to be well-understood risks in following accepted treatment options involving oxygen administration to extremely underweight babies — but there was no evidence that randomization to one option or another increased that risk.

The OHRP suggested that even though any individual physician could approve settings at either the higher or lower oxygen target while still operating within the standard of care, there might be additional risk because patients were typically allowed to range across the entire spectrum rather than being limited to a narrower band of oxygen-saturation levels. Not only is there no evidence to support the idea that this increases risk, but the study also included a nonrandomized case-control group that showed that patients enrolled in the study did better

than patients who were not enrolled. Although that finding is not definitive, there is absolutely no evidence to support the claim that the infants enrolled in the study were exposed to greater risk than infants outside the study.

The second issue involves informed consent. The OHRP finding that the researchers failed to adequately inform the infants' parents is grounded in the mistaken assumption that there was an increase in risk to being enrolled in the trial. In terms of substantive informed consent, the parents were given the information they needed to make an informed decision and were in fact offered more information than parents are typically given regarding the care of premature newborns. The consent documents state clearly that there is randomization, that the randomization is to specific oxygen levels, and that there is some evidence of a risk of blindness with higher oxygen levels. And this is, of course, all taking place in a clinical context in which parents understand that the standard treatments may be unsuccessful and that there is a grave risk of death. In other words, parents were provided with the relevant information they needed to make informed decisions about study participation. The OHRP's objection lacks merit, since it refers to the true claim that the randomization itself introduced no further risk than the standard of care.

Those in charge of oversight of human-subjects research, such as institutional review boards and the OHRP, have solemn responsibilities. On the one hand, they are charged with protecting participants in human-subjects research. This means ensuring that risks are minimized as much as possible and are reasonable rela-

tive to the benefits of the research and — for most studies — that patients or their surrogates provide informed consent before enrollment. On the other hand, those responsible for oversight must be mindful of the value of important research. Those charged with oversight must discharge that obligation by ensuring that measures that may impede the conduct of valuable research genuinely offer substantive protection to participants.

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. Not only is that not true, but it also poses substantial risk to the conduct of valuable comparative effectiveness research both for premature infants and for the general public who continue to face too many treatments where uncertainty prevails about what is best.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Center for Biomedical Ethics, Stanford University, Stanford, CA (D.M.); and the Division of Medical Ethics, New York University Langone Medical Center, New York (A.L.C.).

This article was published on April 18, 2013, at NEJM.org.

1. Fiore LD, Brophy M, Ferguson RE, et al. A point-of-care clinical trial comparing insulin administered using a sliding scale versus a weight-based regimen. *Clin Trials* 2011;8:183-95.
2. Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. *N Engl J Med* 2013;368:1929-31.
3. Silverman WA. *Retrolenal fibroplasia: a modern parable*. New York: Gune & Stratton, 1980.
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5. Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely preterm infants. *N Engl J Med* 2013;368:1949-50.

DOI: 10.1056/NEJMp1305086

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SHELBY:

Thank you. First of all, I want to associate myself with the remarks of Senator Mikulski. I -- she said it so well. I believe that this committee in this Congress that the top investment we can make in America to save life, to improve lives, to (inaudible) the American people is to invest about here in NIH I believe this. I would -- I'd like to see us double. I know that's hard to do but, you know, at least get on the upward trend not the downward trend of biomedical research in this country.

And I'm saying that because I've seen the results of which Senator Mikulski has pointed out, Senator Harkin as and others, Senator Moran.

Having said that, Dr. Collins, I want to get a little parochial if I can and then I'll get back, researchers at the University of Alabama in Birmingham, as you well know, conducted an important study on very premature babies, a support study from 2004 to 2009 that was funded by the National Institute of Health. Researchers at more than 20 sites were trying to understand, as I understand it, the proper oxygen levels for these vulnerable premature babies by comparing two ranges of oxygen saturation within the standard of care at that time.

It's my understanding that the support study has had an important effect to clinical care. Dr. Collins I am (inaudible) this research like this that study and ultimately improve the standard of care.

COLLINS:

Well, Senator Shelby, thank you for the question, very important indeed. Standard of care reflects what we know at that time, and oftentimes, we don't know enough...

SHELBY:

Yes.

COLLINS:

... and so it may be a rather broad range of options and physicians and other caregivers who are trying to do the best job of taking care of patients and patients who are seeking the best care may not be well served by all the entire range of opportunities that are called standard of care. That was certainly the case for the study of the optimum oxygen levels to give to premature babies.

SHELBY:

But you learned by investigating and by studying, that's the bottom-line...

(CROSSTALK)

COLLINS:

Exactly right. So, for us at NIH, we invest heavily in these kinds of studies. Let me give you another couple of examples. Individuals who are going through hemodialysis and there are a lot, sad to say, many of them because of diabetes. There has never really been a clear understanding of what the right schedule is for hemodialysis. How many times a week? How many hours? And that's a huge impact on somebody's quality of life in terms of how much time they are spending there, but also quality of life is dependent on how effective the dialysis is.

So, a study called Time that we have been funding, aimed to try to get an answer to that. All of the standard of care, everybody in that study is getting the kind of treatment that you would consider standard but we're trying to find the sweet spot to do a refinement of that.

SHELBY:

Sure.

COLLINS:

I could site you two or three others. This is very important and yet we depend upon patient...

(CROSSTALK)

SHELBY:

It goes to the basis of your research, does it not?

COLLINS:

Yes, it does. That's what our goal is, is to try to be sure that people get the best possible information in order to guide their medical care.

SHELBY:

As you -- as you well know, the UAB received a letter from the Office of Human Research Protections about the support clinical trial that we're carrying out under the auspices of NIH. And the OHRP determined that AUB should have informed parents of an increased risk death of their infant by participating in the study. But it was my understanding that the risk were unknown at the time of the study's commencement in 2004, and in there was no scientific -- specific scientific data that existed at the start of the study that shown in the increased risk.

Were babies in that study at any greater risk than babies not in the study? Do you know?

COLLINS:

No, senator. I don't believe they were.

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, May 16, 2013 11:31 AM
To: Jones, Wanda K. (DHHS/OS/OASH)
Subject: Suggested correction to OHRP-UAB draft letter

(b) (5)

Any word from Caya or Andrea about the status of the letter?

-----Original Message-----

From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Thursday, May 16, 2013 9:47 AM
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: Suggested correction to OHRP-UAB draft letter

Kathy, thanks again for your continued work with us on this letter; it's been positive and productive, and I think as hard as it's been, we're all in a better place on this.

(b) (5)

Anyway, looked like yesterday's NIH hearing went well, and we appreciated Francis' deft handling of Sen. Shelby's questions about SUPPORT. Wanda

-----Original Message-----

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Tuesday, May 14, 2013 10:03 PM
To: Menikoff, Jerry (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH)
Subject: RE: Suggested correction to OHRP-UAB draft letter

Thanks for letting us know Jerry.

(b) (5)

(b) (5)

Happy to discuss.

Best,
Kathy

-----Original Message-----

From: Menikoff, Jerry (HHS/OASH)

Sent: Tuesday, May 14, 2013 9:20 PM

To: Hudson, Kathy (NIH/OD) [E]

Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH)

Subject: RE: Suggested correction to OHRP-UAB draft letter

Kathy,

(b) (5)

Thus, after these changes, footnote 2 would read as indicated below.

Best,
Jerry

Here is what the revised footnote 2 would say:

(b) (5)

Blansfield, Earl (NIH/NICHD) [E]

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, May 13, 2013 3:47 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Suggested correction to OHRP-UAB draft letter

That seems very appropriate, and shouldn't be a problem at all.

Jerry

-----Original Message-----

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Monday, May 13, 2013 3:36 PM
To: Menikoff, Jerry (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: Suggested correction to OHRP-UAB draft letter

Thanks. (b) (5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov

On May 13, 2013, at 3:30 PM, "Menikoff, Jerry (HHS/OASH)" <Jerry.Menikoff@hhs.gov> wrote:

> Kathy,
>
> Yes, that is still the plan. Normally, we would wait about 2 weeks to post such letters, but in the current circumstance, I would expect that we could arrange to have it posted right after UAB receives it.

>
> Best,
> Jerry

> -----Original Message-----

> **From:** Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
> **Sent:** Monday, May 13, 2013 3:18 PM
> **To:** Menikoff, Jerry (HHS/OASH)
> **Cc:** Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
> **Subject:** Re: Suggested correction to OHRP-UAB draft letter

> Thanks.

> Also, Jerry, (b) (5)

>
> Best
> Kathy

> Kathy Hudson, Ph.D.
> Deputy Director for Science, Outreach, and Policy NIH
> 301 496 1455
> kathy.hudson@nih.gov<mailto:kathy.hudson@nih.gov>
>
> On May 13, 2013, at 3:07 PM, "Menikoff, Jerry (HHS/OASH)"
<Jerry.Menikoff@hhs.gov<mailto:Jerry.Menikoff@hhs.gov>> wrote:

> Kathy,

> Following up on your point, I just want to let you know that we are

(b) (5)

(b) (5)

>
> Best,
> Jerry
>
> From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
> Sent: Monday, May 13, 2013 10:10 AM
> To: Menikoff, Jerry (HHS/OASH)
> Cc: Koh, Howard (HHS/OASH); Guttmacher, Alan (NIH/NICHD) [E]; Higgins,
> Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey,
> Barbara (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
> Subject: RE: Suggested correction to OHRP-UAB draft letter

> Sure. Here it is.

(b) (5)

(b) (5)

>
> Kathy
>
> From: Menikoff, Jerry (HHS/OASH)
> Sent: Monday, May 13, 2013 10:01 AM
> To: Hudson, Kathy (NIH/OD) [E]
> Cc: Koh, Howard (HHS/OASH); Guttmacher, Alan (NIH/NICHD) [E]; Higgins,
> Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins,
> Francis (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
> Subject: RE: Suggested correction to OHRP-UAB draft letter

> Kathy,

> Would you be willing to share a copy of that New Zealand form with us?

> Thanks,

> Jerry

> From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]

> Sent: Sunday, May 12, 2013 2:11 PM

> To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
> Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD)
> [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E];
> McGarey, Barbara (NIH/OD) [E]
> Subject: Suggested correction to OHRP-UAB draft letter

>
> Hi Howard and Jerry,
>
> Hope you are enjoying this spectacularly beautiful week end.

(b) (5)

>
> Best,
> Kathy
>
> Kathy L. Hudson, Ph.D.
> Deputy Director for Science, Outreach, and Policy National Institutes
> of Health
>
> 301 496 1455
> Kathy.hudson@nih.gov<mailto:Kathy.hudson@nih.gov>
>
> <image001.png>
>
> Celebration of Science at
> NIH<<http://www.youtube.com/watch?v=gYkP9ED5naA>>: watch how medical
> research saves lives and improves health
>

Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, May 13, 2013 10:16 AM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Koh, Howard (HHS/OASH); Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Suggested correction to OHRP-UAB draft letter

Kathy,

At the moment, we aren't contemplating quoting anything that hasn't already been made public. We certainly appreciate your pointing all of this out to us, and we would hope to make appropriate clarifications to our letter.

Thanks,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Monday, May 13, 2013 10:10 AM
To: Menikoff, Jerry (HHS/OASH)
Cc: Koh, Howard (HHS/OASH); Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Suggested correction to OHRP-UAB draft letter

Sure. Here it is.

(b) (5)

(b) (5)

Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, May 13, 2013 10:01 AM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Koh, Howard (HHS/OASH); Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Subject: RE: Suggested correction to OHRP-UAB draft letter

Kathy,

Would you be willing to share a copy of that New Zealand form with us?

Thanks,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Sunday, May 12, 2013 2:11 PM
To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins,

Francis (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Subject: Suggested correction to OHRP-UAB draft letter

Hi Howard and Jerry,

Hope you are enjoying this spectacularly beautiful week end.

(b) (5)

Best,
Kathy

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov



Celebration of Science at NIH: *watch how medical research saves lives and improves health*

Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Sunday, May 12, 2013 6:14 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Subject: Re: Suggested correction to OHRP-UAB draft letter

Kathy,

Thank you for these comments. We will be getting back to you.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Sunday, May 12, 2013 02:10 PM
To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Subject: Suggested correction to OHRP-UAB draft letter

Hi Howard and Jerry,

Hope you are enjoying this spectacularly beautiful week end.

(b) (5)

Best,
Kathy

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov



Celebration of Science at NIH: watch how medical research saves lives and improves health

(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Sunday, May 12, 2013 3:53 PM
To: Koh, Howard (HHS/OASH)
Subject: RE: Touching base

I'll call you at one of those numbers. I might be a few minutes late –

(b) (6)

FC

From: Koh, Howard (HHS/OASH)
Sent: Sunday, May 12, 2013 10:50 AM
To: Collins, Francis (NIH/OD) [E]
Subject: RE: Touching base

Thanks for this message Francis. Chatting about 4:30 today Sunday would be good.
My number is 978-474-(b) (6) or 978-807-(b) (6). Or send me your number and I can call you. Howard

From: Collins, Francis (NIH/OD) [E] [collinsf@od.nih.gov]
Sent: Saturday, May 11, 2013 1:49 PM
To: Koh, Howard (HHS/OASH)
Subject: Touching base

Hi Howard,

(b) (5)

(b) (5)

(b) (5)

Are you around for a phone call tomorrow (Sunday) afternoon?

I could call almost anytime from 1 to 5 PM.

Best, Francis

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 10, 2013 9:12 PM
To: Hawkins, Jamar (HHS/OS)
Cc: Brewer, Ann (NIH/OD) [E]; Koeneman, Sandy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: Correspondence related to the SUPPORT study

Hi Jamar,

I know you are handling a ton of correspondence but I was wondering if you could please send FYI copies to NIH of all correspondence about the SUPPORT study. (b) (5)

(b) (5)

Thanks so much,

Kathy

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455

Kathy.hudson@nih.gov



National Institutes of Health
Turning Discovery Into Health

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

From: Palm, Andrea (HHS/IOS)
To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Wolters, Bradley (OS/OPHS)
Subject: RE: SUPPORT study
Date: Wednesday, May 08, 2013 8:20:15 PM

Thanks Howard. (b)(5) - deliberative process, (b)(5) - Attorney Client privilege

From: Koh, Howard (HHS/OASH)
Sent: Wednesday, May 08, 2013 4:57 PM
To: Collins, Francis (NIH/OD) [E]; Palm, Andrea (HHS/IOS)
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Wolters, Bradley (OS/OPHS)
Subject: RE: SUPPORT study

Andrea and colleagues

Thank you for your feedback and these suggestions.

(b) (5)

The specific responses to your suggestions are:

(b) (5)

(b) (5)

We would welcome discussion on next steps. Howard

From: Collins, Francis (NIH/OD) [E] [mailto:collinsf@od.nih.gov]

Sent: Wednesday, May 08, 2013 5:34 AM

To: Palm, Andrea (HHS/IOS); Koh, Howard (HHS/OASH)

Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

Subject: RE: SUPPORT study

Dear Andrea,

(b) (5)

How do you like your new job so far? We at the NIH are thrilled to have you as the new Chief of Staff.

Best regards, Francis

From: Palm, Andrea (HHS/IOS)

Sent: Tuesday, May 07, 2013 1:06 PM

To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)
Subject: SUPPORT study

Howard and Francis,

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

Thanks again,
Andrea



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-6900
FAX: 240-453-6909

DRAFT

(b) (5)

(b) (5)



(b) (5)



(b) (5)





DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-6900
FAX: 240-453-6909

| DRAFT

(b) (5)

(b) (5)



(b) (5)



(b) (5)



From: Higgins, Rosemary (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Subject: Re: SUPPORT study
Date: Wednesday, May 08, 2013 8:34:10 AM

Agree
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, May 08, 2013 08:29 AM
To: Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT study

(b) (5)

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

31 Center Drive, Room 2A03
Bethesda, MD 20892-2425
Phone:301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, May 08, 2013 08:24 AM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT study

FYI.

(b) (5)

From: Koh, Howard (HHS/OASH)
Sent: Wednesday, May 08, 2013 7:32 AM
To: Collins, Francis (NIH/OD) [E]
Subject: RE: SUPPORT study

Francis

OHRP/OASH will be sending out a reply back today too.
If you want to chat ahead of time before we do so, let me know.
Otherwise, I will just send it to you, Andrea and cc everyone.

We had quite a week last week - the dialogue was very productive.
Many thanks to Kathy for her leadership and outreach . Howard

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, May 08, 2013 5:34 AM
To: Palm, Andrea (HHS/IOS); Koh, Howard (HHS/OASH)
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT study
Attachments: 05 07 13 SUPPORT clarificationAG rdh sd KLH fsc.docx; Cole Pedaitrics editorial 2003.pdf

Dear Andrea,

(b) (5)



How do you like your new job so far? We at the NIH are thrilled to have you as the new Chief of Staff.

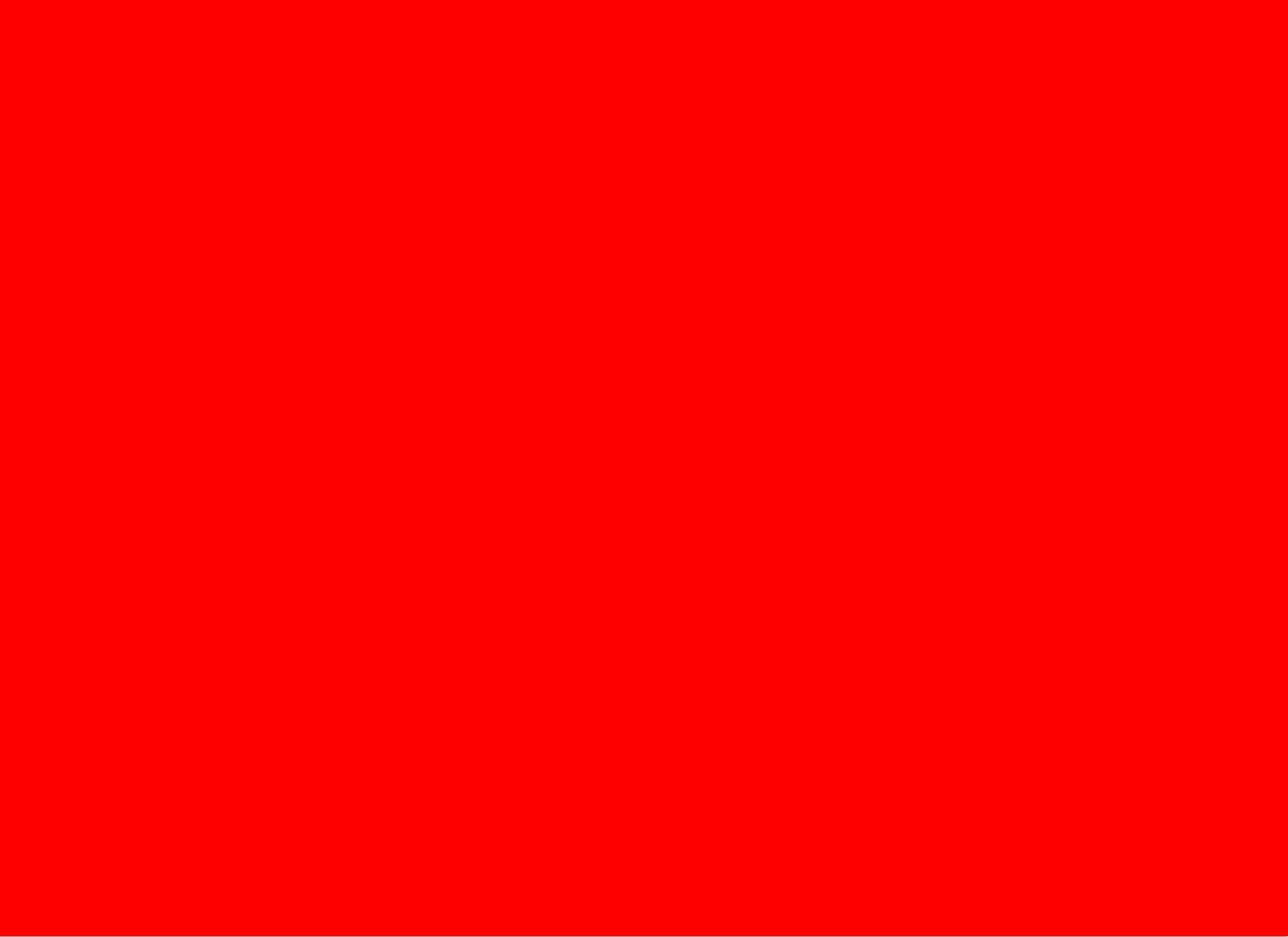
Best regards, Francis

From: Palm, Andrea (HHS/IOS)
Sent: Tuesday, May 07, 2013 1:06 PM
To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)
Subject: SUPPORT study

Howard and Francis,

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



Thanks again,
Andrea



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of the Assistant Secretary for Health

Office for Human Research Protections
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1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
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(b) (5)

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(b) (5)



(b) (5)



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Resolving Our Uncertainty About Oxygen Therapy

Cynthia H. Cole, Kenneth W. Wright, William Tarnow-Mordi and Dale L. Phelps
Pediatrics 2003;112;1415

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/112/6/1415.full.html>

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American Academy of Pediatrics

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were symptom-free for at least 72 hours before the onset of chronic respiratory symptoms. They referenced Wilson and Mikity's report but did not attribute these cases to WMS, although the description is typical. In the report of the National Institute of Child Health and Development Workshop on BPD held in June 2000, Jobe and Bancalari⁷ referred to the change in the pathology of the lungs seen in BPD as smaller, and more immature infants have come to constitute the majority of infants who die of BPD. The most recent references in the January 2003 issue of the *Journal of Perinatology*^{8,9} are case reports involving infants with WMS. The new BPD, described by Jobe¹⁰ in 1999 as occurring in immature infants who do not have much lung disease soon after birth, fits the clinical picture of WMS. Jobe attributes the new BPD to an aberration of lung development, an inhibition of alveolar and vascular development. I believe that the new BPD and WMS are one and the same. As improvements have taken place in the care of women in preterm labor, in surfactant administration and assisted ventilation, classical BPD, a result of injury to the immature lung, has become less common. Chronic lung disease in the premature infant is increasingly likely to be attributable to the response of the immature lung to early air breathing rather than damage from barotrauma or oxygen toxicity. Separating the classification of BPD by cause is important in improving our understanding of the mechanisms involved and the development of potential remedies. The "new" BPD is not so new, having been reported in the 1960s as WMS. The intriguing question that remains is why WMS appears in some infants but not others of presumably the same maturity at birth.

JOAN E. HODGMAN, MD
Department of Pediatrics
Keck School of Medicine
University of Southern California
Los Angeles, CA 90033

REFERENCES

1. Wilson MC, Mikity VG. A new form of respiratory disease in premature infants. *J Dis Child.* 1969;99:489-499
2. Hodgman JE, Mikity VG, Tatter D, Cleland RS. Chronic respiratory distress in the premature infant: Wilson-Mikity syndrome. *Pediatrics.* 1969;44:179-195
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6. Charafeddine L, D'Angio CT, Phelps DL. Atypical chronic lung disease pattern in neonates. *Pediatrics.* 1999;103:759-765
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10. Jobe AH. The new BPD: an arrest of lung development. *Pediatr Res.* 1999;66:641-643

Resolving Our Uncertainty About Oxygen Therapy

ABBREVIATIONS. ROP, retinopathy of prematurity; Pao₂, blood oxygen; tco₂, transcutaneous oxygen; Spo₂, oxygen saturation; RLF, retrolental fibroplasia.

Win Tin¹ eloquently articulated in his editorial "Oxygen Therapy: 50 Years of Uncertainty" that neonatal care providers do not understand how best to use oxygen in the most vulnerable premature infants despite >50 years of oxygen therapy in neonatal medicine.¹ We do not understand optimal oxygenation management in extremely low gestational age neonates (<28 weeks' gestation), because we do not know what are safe and effective upper and lower limits of oxygen levels or saturation ranges in both the early and later neonatal courses.¹⁻⁷ There has been no implementation of the most powerful tool in clinical research, the randomized, controlled trial, to resolve the uncertainty since the early clinical trials in the 1950s.⁸⁻¹⁵ No randomized control trial has clarified the relation between retinopathy of prematurity (ROP) and blood oxygen (Pao₂), transcutaneous oxygen (tco₂), or oxygen saturation (Spo₂) levels. Furthermore, the effects of "higher" versus "lower" oxygen levels or saturation ranges on ROP, growth, brain, lung, and other organ systems have not been studied with respect to gestational age, time of onset or duration of specified oxygen level or saturation range, or method of oxygen termination. Because of the lack of definitive evidence on which to base policy, neonatal care providers differ widely, with no consensus in their policies, practices, and strong beliefs regarding oxygen management in both the early and later neonatal courses of premature infants.^{2,16-20} Thus, the study of oxygen therapy in the neonatal population at highest risk for oxygen-related morbidities is an extremely important and urgent issue. We strongly agree with Tin^{1,2,16} and others¹⁸⁻²² that an adequately powered, large, randomized, controlled trial must be conducted to resolve the uncertainty and determine the impact of different ranges of oxygen levels or saturations, initiated early in the neonatal course, on ROP and other important outcomes such as mortality, long-term neurodevelopmental outcome, bronchopulmonary dysplasia, and growth. One of the most compelling arguments for a randomized trial is that continued treatment of millions of premature infants in ignorance of what is safe and effective oxygenation is not an option. The objectives of this commentary are to advocate for a definitive

Received for publication Jan 13, 2003; accepted May 28, 2003.

This editorial is dedicated to the memory of Dr. Douglas K. Richardson, whose life was a testament to the ideal of mutually supportive collaboration.

Address correspondence to Cynthia H. Cole, MD, MPH, Division of Newborn Medicine, Floating Hospital for Children, Tufts-New England Medical Center, 750 Washington St, Boston, MA 02111. E-mail: ccole@tufts-nemc.org PEDIATRICS (ISSN 0031 4005). Copyright © 2003 by the American Academy of Pediatrics.

clinical trial, summarize the background and rationale for the trial, and emphasize important methodological issues that must be considered in such a trial.

BACKGROUND

The unrestricted use of oxygen proceeded largely without question until clinical trials published in the 1950s established an association between the use of unrestricted, prolonged oxygen exposure and retrolental fibroplasia (or RLF, as ROP was known initially).⁸⁻¹⁵ Meta-analysis of 3 early, randomized trials compared the effect of restricted versus unrestricted oxygen administration on RLF. This analysis revealed a significant reduction, but not complete elimination, in the occurrence of any RLF (event rate ratio: 0.34; 95% confidence interval: 0.25, 0.46) and of severe RLF (event rate ratio: 0.38; 95% confidence interval: 0.17, 0.85) in the restricted oxygen group.²³ Two trials found a statistically insignificant increased risk of mortality.^{10,11,23} In a separate meta-analysis of the effects of lower versus higher oxygen concentrations on multiple outcomes in preterm infants during 5 early trials (1951-1969), Askie and Henderson-Smart²⁴ found that the restriction of oxygen reduced the incidence and severity of RLF without increasing mortality. They calculated that one would only need to treat 3 infants with restricted oxygen to prevent one infant from having an adverse outcome of death or RLF. The drastic curtailment of oxygen administration in the 1950s, subsequent to the clinical trials, was associated with a dramatic reduction in retinopathy. The oxygen curtailment was also associated with a concomitant increase in death and cerebral palsy.²⁴⁻²⁷

These events in the 1950s provide important lessons in medical history regarding ROP. In these early clinical trials, some premature infants developed retinopathy in the restricted oxygen group, and the majority of premature infants in the unrestricted, prolonged oxygen group never developed RLF. One lesson, even from 50 years ago, is that oxygen is an important, but not a sufficient, single cause of ROP. Events of the 1950s also illustrate in hindsight the importance of conducting adequately powered, large, masked, randomized studies with long-term outcomes.

Over the course of the 1970s and 1980s, technical development of means to assess an infant's oxygenation status, either intermittently or continuously, evolved. This included measuring oxygen tension in arterial blood gases or by tCO_2 monitoring and estimation of hemoglobin oxygenation saturation by pulse oximetry.²³ One trial demonstrated no benefit of using intermittent arterial blood gases by umbilical arterial catheters in reducing ROP.¹³ Another study that evaluated continuous versus intermittent tCO_2 monitoring showed that continuous tCO_2 monitoring did not reduce ROP.²⁸ A later analysis of the data from that study suggested that ROP occurred more often when tCO_2 monitoring was >80 mm Hg (10.7 pK_a) in the first 4 weeks of life.²⁹

Among 5 recent observational studies (2 published articles and 3 abstracts), 4 provide evidence of less

severe ROP, and 3 provide evidence of less chronic lung disease in nurseries that had policies of lower SpO_2 ranges compared with higher SpO_2 ranges.^{16,18,19,30,31} The SpO_2 ranges evaluated differed among the 5 studies. Two of the 5 cohort studies suggest that a lower versus higher SpO_2 range ($\text{SpO}_2 \sim 80 < 90\%$ vs $> 90\%$) early in the neonatal course can reduce the induction of severe ROP without increasing mortality or cerebral palsy.^{16,30} Sun¹⁸ analyzed data from the Vermont-Oxford Network of infants with birth weights 500 to 1000 g to explore possible association between choice of target SpO_2 levels and rate of chronic lung disease, severe ROP, and ROP surgery. Sun found significantly less chronic lung disease, less stage 3 ROP, less need for ROP surgery, and slightly less mortality (although not statistically significantly different) among nurseries that maintained maximum $\text{SpO}_2 \leq 95\%$ vs $> 95\%$.¹⁸ A recent national survey of pulse oximetry before and after 2 weeks of life found significantly less retinal ablative surgery in neonatal intensive care units with policies of maximum $\text{SpO}_2 \leq 98\%$ vs $> 98\%$ in the first 2 weeks of life. There was also less stage 3 ROP and less need for retinal ablative surgery in nurseries that had maximum $\text{SpO}_2 \leq 92\%$ vs $> 92\%$ after the first 2 weeks of life.¹⁹ Only one observational study suggests that a lower SpO_2 range is associated with increased ROP greater than stage 2, but no increase in surgically treated ROP.³¹ These cohort studies illustrate the ongoing uncertainty about oxygen therapy in premature infants and underscore the importance of conducting a randomized, control trial regarding different SpO_2 ranges. The findings of these cohort studies justify testing the hypothesis that a strategy of maintaining a functional SpO_2 level in a "lower" versus "higher" range early in the course of extremely low gestational age neonates reduces the incidence of severe ROP without increasing important adverse neonatal outcomes. We plan to test this hypothesis through an international, multicenter, masked, clinical trial in which extremely low gestational age neonates (< 28 weeks' gestation) will be randomly assigned to 1 of 2 scientifically and clinically acceptable pulse oximetry saturation ranges such as 85% to 89% vs 91% to 95% (functional saturation). Acceptability of these ranges would be confirmed additionally through surveys. Randomly assigned intervention would occur shortly after birth and continue through the first several weeks. Tin and Wariyar² expanded the background and clearly articulated the justification for such a trial in a separate recent publication.

METHODOLOGICAL IMPLICATIONS FOR A TRIAL OF OXYGEN THERAPY

Sufficiently Powered, Randomized Trial

This important research hypothesis can be tested only by using a sufficiently powered, randomized trial that ensures long-term follow-up. The randomized trial is widely accepted as the best way to minimize systematic bias. Too often, however, unreliable or incorrect answers are generated by randomized trials that have insufficient power to detect clinically

important, small to moderate effects.³² Sufficient power to detect clinically important, small to moderate effects, in relatively uncommon outcomes such as severe ROP and death, beyond a reasonable doubt may require surprisingly large numbers. Two examples illustrate this. Oral aspirin therapy in myocardial infarction was not widely accepted until after the Second International Study of Infarct Survival in 1988, which enrolled >17 000 patients³³ and confirmed a highly significant 23% reduction in mortality. This finding occurred 14 years after the first trial and after 6 trials showed statistically insignificant reductions (between 10% and 30%) in mortality.³⁴ It took 20 years, 15 trials, and >3500 infants before it became accepted that antenatal steroids reduced respiratory distress syndrome and intraventricular hemorrhage by 50% and neonatal mortality by 40%.^{35,36} Medical research, and specifically neonatal research, needs to find ways of greatly increasing the size of randomized studies. Otherwise moderate but worthwhile benefits may be missed.³⁷

Several hundred patients (15–25 centers) may be sufficient to demonstrate important differences in severe ROP. However, a much larger sample (and many more collaborators) will be needed to exclude smaller, important differences in outcomes such as mortality and disability to adequately address real concerns about the safety of lower oxygen tensions. For example, a 5% difference in an outcome of death or cerebral palsy is “small” but would have major implications for public health. Preliminary calculations suggest that the trial may require a sample size between 2000 and 4000 extremely low gestational age infants (born at <28 weeks’ gestation) to answer these important questions. Participation of centers that undertake long-term follow-up in >90% of their survivors will be necessary.

Thus, the most expedient, ethical, scientifically rigorous way to resolve the uncertainty of oxygen therapy in extremely low gestational age neonates is to conduct a large, multicenter, randomized, masked trial. International collaboration will certainly be needed to ensure timely recruitment of sufficient numbers of extremely premature infants. Furthermore, international collaboration will permit more robust generalizability of the results. Any outcome is more likely to gain broader clinical acceptance, maximizing the benefit to be derived from what is inevitably going to be a major investment of research money. It is unlikely that funding agencies would repeatedly fund trials of the necessary magnitude. Therefore, if it is to be definitive, it must be rigorous and as complete as possible the first time.

Intervention

The intervention will be different pulse oximetry targets such as 85% to 89% vs 91% to 95%. Masking of oximeters, as was done for the Australian Benefits of Oxygen Saturation Targeting trial,⁷ is essential to minimize co-intervention and contamination by bias of neonatal care providers. Masking of the pulse oximeters can be accomplished by offsetting the SpO₂ readings by ±3% such that each study group (85–89% vs 91–95%) displays the same SpO₂ range of 88%

to 92%. Actual SpO₂ values would appear for SpO₂ <85% and >95%. Establishment and maintenance of equipoise throughout the intervention and assessments are imperative, because we do not yet know if potential clinically important reductions in retinopathy may offset increases in other potentially competing outcomes such as mortality or neurodevelopmental/neurosensory disability.

The trial will face at least 1 challenge in this regard. Some neonatal units regard SpO₂ >90% as mandatory. Accepting uncertainty about this may be difficult. However, there are cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy.^{16,30} Creating an international climate of equipoise could be enhanced by surveys^{17–19} of potential study centers to identify local target ranges and establish current limits of collective uncertainty. The trial should compare target ranges for SpO₂ within those limits of acceptable uncertainty.

Outcomes

It is essential, both ethically and scientifically, that the trial carefully select and define meaningful outcomes of neonatal intensive care related to oxygen deficit or toxicity. These outcomes include severe ROP, blindness, bronchopulmonary dysplasia, growth, death, and different types of major neurodevelopmental or neurosensory impairment beyond infancy.

Data Safety Monitoring Committee and Plan

It is also essential, both ethically and scientifically, to have an external monitoring committee to ensure that if major differences between the groups with respect to outcomes such as death or severe ROP are detected, they will be detected during the recruitment phase. Appropriate decisions regarding study termination or continuation can be achieved if stringent stopping rules for the Data Monitoring and Safety Committee are based on evidence beyond reasonable doubt of net clinical benefit or harm or futility of finding a difference before recommending trial termination.³⁷ Evidence of net benefit or harm from one outcome should be considered in the context of other major outcomes. For example, it would be inappropriate to terminate recruitment because of a 3% reduction in severe ROP in the lower oxygen group before the trial had accumulated sufficient power to exclude a 6% increase in mortality or severe neurodevelopmental impairment in the same group. In this case, if the trial were terminated prematurely and lower oxygen became the clinical standard, for every infant whose sight was saved, 2 would die or survive with major disability.

Pragmatic Design and Data Collection

Successful conduct of a much larger-scale trial requires that the design of the trial be as simple and pragmatic as possible to optimize recruitment and maximize the quality of data. Collection of information only on variables related to the major outcomes

of the trial should enable centers to participate enthusiastically without undue burden. Information on ROP, duration of oxygen therapy, survival, neurodevelopmental, neurosensory, and growth status should be recorded prospectively for this trial. Several recent studies have demonstrated that large-scale recruitment^{38–42} and follow-up^{39,43} in prospective perinatal studies is feasible. The wisdom of collecting only the relevant, necessary data are reflected in the following comment by Peto and Baigent:³²

Collecting less information may mean bigger numbers and hence better science: many trials still collect ten or a hundred times too much information per patient, often at the behest of study sponsors or their committees. Requirements for large amounts of defensive documentation imposed on trials by well intentioned guidelines . . . may, paradoxically, substantially reduce the reliability with which therapeutic questions are answered, if their indirect effect is to make randomized trials smaller or even to prevent them starting.

Educational Program

A trial acknowledging that we don't understand how to provide optimum oxygenation requires extensive education and dialogue with all staff caring for eligible infants. Their insight and support will be crucial. Therefore, one critical element in preparing for this trial is to develop a comprehensive education package that explains the background and rationale of the study that can be used in many national settings.

Trial Planning

The planning for such a trial is in progress. The proposed trial, Pulse Oximetry Saturation Trial for Prevention of ROP (POST ROP), will be adequately powered to reliably detect small to moderate, clinically important differences in severe ROP, chronic lung disease, and differences in mortality, adverse neurodevelopmental and neurosensory (visual/auditory) outcome, and growth. The POST ROP Planning Study Group evolved from collective individual and group endeavors, meetings, and discussions of ophthalmologists and neonatologists over the past year. The POST ROP Planning Group welcomes contact from centers that may be interested in participating in a large trial of oxygen therapy. Without whole-hearted international collaboration, we face many more years of uncertainty about one of the most basic priorities of neonatal care—providing an appropriate concentration of oxygen for our patients.

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Zinc, Low Birth Weight, and Breastfeeding

ABBREVIATION. SGA, small for gestational age.

The article by Sur et al¹ in this issue further emphasizes the value of both breastfeeding and an adequate zinc intake for infants. The notable contribution of zinc deficiency in infancy and early childhood to stunting² and infectious disease morbidity³ and mortality,⁴ especially from diarrhea and pneumonia, is now well-documented in developing countries.

In the study by Sur et al, zinc supplementation of low birth weight infants for the first year of life was associated with improved growth and reduced diarrheal morbidity. In another study from India, zinc supplementation of small for gestational age (SGA) infants from ~1 to 10 months postnatal age was associated with a two-thirds reduction in mortality.⁵ Most low birth weight infants in developing countries are SGA. Neonatal reserves of zinc in SGA infants are lower than those of appropriate for gestational age infants, even on a body weight basis,⁶ and these supplementation studies support a particular vulnerability to zinc deficiency in this group. Thus special attention to an adequate postnatal zinc intake is indicated for the SGA infant.

The independent protective effect of exclusive breastfeeding noted in this study raises the question of whether the diarrhea associated with introduction of potentially contaminated complementary foods at 4 months caused increased zinc losses and whether, had exclusive breastfeeding been continued longer, the onset of zinc deficiency would have been delayed. Alternatively, zinc deficiency may have been developing by 4 months, resulting in increased susceptibility to diarrhea. This study does not answer these questions but illustrates well the challenge of defining optimal timing of introduction of complementary foods, especially in vulnerable infants in vulnerable conditions. There is little doubt that even the term, appropriate for gestational age, older breastfed infant is susceptible to zinc deficiency after ~6 months when milk zinc concentrations are very low relative to requirements.^{7,8} The availability of complementary foods of favorable bioavailability, especially animal products, is critical to attaining adequate zinc intake. In our experience, poor appetite and slow growth attributable to zinc deficiency occur in North America in older breastfed infants if complementary foods with bioavailable zinc, such as meats, are not consumed. The studies by Sur et al and others are reminders of both the importance and complexity of meeting the needs of this micronutri-

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Resolving Our Uncertainty About Oxygen Therapy

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Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 6:57 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]
Subject: SUPPORT - the saga continues
Attachments: 130508_Public Citizen's SUPPORT Study Report With Cover Letter_FINAL_EMBARGOED.pdf

Importance: High

Hi,

Here is the latest from Public Citizen though not yet sent apparently.

(b) (5)

(b) (5)

Kathy



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PUBLICCITIZEN

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.

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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.*

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- (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.*

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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 FiO₂ 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

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May 8, 2013, Letter to Secretary Sebelius

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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Board of Directors and Past President, International Association of Bioethics

Enclosure

Public Citizen

May 8, 2013, Letter to Secretary Sebelius

cc: The Honorable Howard K. Koh, Assistant Secretary for Health, HHS
Dr. Francis Collins, Director, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health
and Development
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borrer, Director, Division of Compliance Oversight, OHRP

EMBARGOED UNTIL 9:00 AM ON WEDNESDAY, MAY 8

**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

Michael Carome, M.D.
Sidney Wolfe, M.D.
Ruth Macklin, Ph.D.



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Public Citizen Analysis of the Complete Protocol and Consent Form for the SUPPORT Study

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.

About Ruth Macklin

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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% (Alarm)	85%	86%	87%	88%	89%	90%	91%	92%	93%	94%	95%	96% (Alarm)
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 FiO_2 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 FiO_2 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 FiO_2 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

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 1:15 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT study
Attachments: 05 07 13 SUPPORT clarification.docx

FYI, I've only scanned...

From: Palm, Andrea (HHS/IOS)
Sent: Tuesday, May 07, 2013 1:06 PM
To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)
Subject: SUPPORT study

Howard and Francis,

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



(b)(5) - deliberative process, (b)(5) - Attorney Client privilege

Thanks again,
Andrea



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-6900
FAX: 240-453-6909

DRAFT

(b) (5)

(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 05, 2013 3:06 PM
To: Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: Preemie studies - heads up
Attachments: Partial Release Letter.pdf

Andrea,

(b) (5)

And, on behalf of the entire NIH, congratulations on your new position!

Kathy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 05, 2013 2:37 PM
To: Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: Preemie studies - heads up

(b) (5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 5, 2013, at 1:48 PM, "Palm, Andrea (HHS/IOS)" <Andrea.Palm@hhs.gov> wrote:

Thanks Kathy

(b)(5) - deliberative process

(b)(5) - deliberative process Thanks.

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Sunday, May 05, 2013 12:54 PM
To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Palm, Andrea

(HHS/IOS)

Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]

Subject: Preemie studies - heads up

<http://jama.jamanetwork.com/article.aspx?articleid=1684963>

Wanted to make sure you were aware that Canadian study analogous to SUPPORT was published online in JAMA this morning. [REDACTED] (b) (5)

[REDACTED] (b) (5)

[REDACTED] (b) (5)

Let me know if you have questions.

Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov



April 30, 2013

Michael A. Carome, M.D.
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009

FOIA Case No. 41203

Dear Dr. Carome:

This is a partial response to your two April 8, 2013 Freedom of Information Act (FOIA) requests addressed to Earl Blansfield. You requested a copy of all institutional review board-approved versions of the consent/parental permission forms for the study site's enrolled subjects in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized (SUPPORT) Study (ClinicalTrials.gov #NCT00233324), conducted by the NICHD Neonatal Research Network. In addition, you requested a copy of all versions of the protocol and all versions of the sample template for the consent/parental permission form for the Surfactant, Positive Pressure, and Pulse Oximetry Randomized (SUPPORT) Study (ClinicalTrials.gov #NCT00233324).

We searched the files of the NICHD Pregnancy and Perinatology Branch. So far, that search produced 259 pages responsive to your request. This partial release includes seven versions of the SUPPORT study protocol. The most recent version of the protocol is included in this response and is also available online at <http://www.nih.gov/icd/od/foia/index.htm#foialibrary>. We are still in the process collecting and clearing documents related to IRB approved consent/parental permission forms and the sample template for the consent/parental permission form.

In certain circumstances provisions of the FOIA and Department of Health and Human Services FOIA Regulations allow us to recover part of the cost of responding to your request. Because the cost is below the \$25 minimum, there is no charge for the enclosed materials.

Sincerely,

Earl H. Blansfield
Freedom of Information Coordinator
National Institute of Child Health and
Human Development
31 Center Drive, Rm. 2A32, MSC 2425
Bethesda, MD 20892

Enclosures: 7 Protocols – 259 pages

Bartok, Lauren (NIH/OD) [C]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Saturday, May 04, 2013 3:49 PM
To: Menikoff, Jerry (HHS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

And it really is wonderful using this as a teachable moment, as the expanded letter does.

Best, Alan

From: Menikoff, Jerry (HHS/OASH)
Sent: Saturday, May 04, 2013 3:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Thanks again, Kathy, to you and Alan and your colleagues for the collegial manner in which we reached this point. And we will welcome the similar discussions that you mentioned that will be needed as we move forward.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Saturday, May 04, 2013 03:27 PM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Thanks for taking time to chat on a spring Saturday afternoon. Here are the edits we discussed.

Have a great week end everyone.

Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 4:54 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E];

Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]

Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,

Jerry

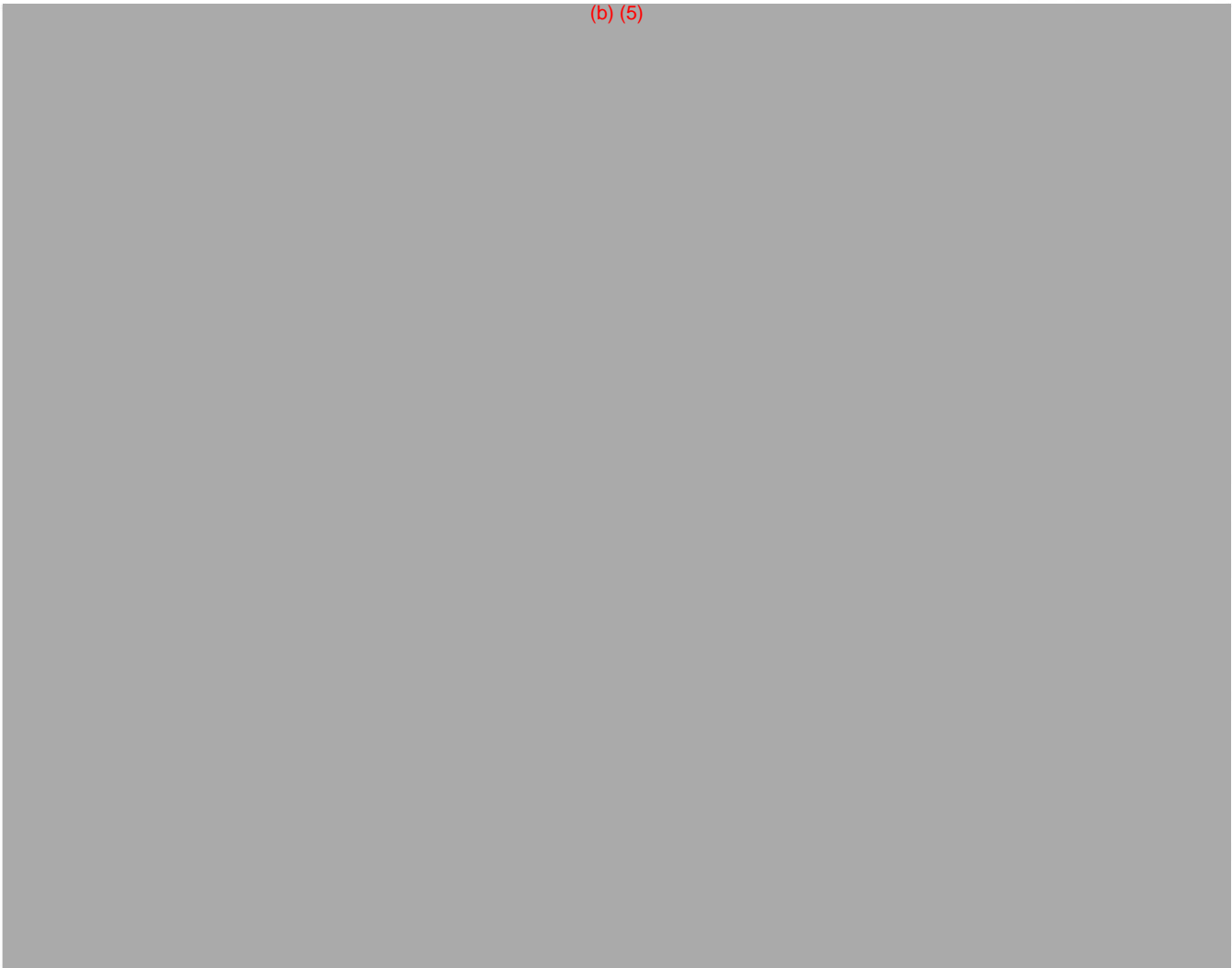


DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-6900
FAX: 240-453-6909

(b) (5)



(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Saturday, May 04, 2013 6:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

And if you are referring to the status of a final version of this letter, after it has been sent to UAB: I would expect that, consistent with usual policies, this would get posted on an OHRP web site, a couple weeks after the letter was sent out.

Jerry

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, May 03, 2013 06:17 PM
To: Menikoff, Jerry (HHS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Is this in the public domain?

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 04:53 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

(b) (5)



(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 6:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

(b) (5)

Jerry

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, May 03, 2013 06:17 PM
To: Menikoff, Jerry (HHS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Is this in the public domain?

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 04:53 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 01, 2013 10:18 PM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Support study -
Attachments: Follow-up SUPPORT letter 5-1-2013 1009pm.docx

Thanks so much Jerry. This marks a real turning point.

(b) (5)

(b) (5)

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 6:46 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

Kathy,

Attached are our edits to your version. To stick with your suggestion regarding making things simpler, we first accepted all of your changes, and so the markings only show our changes to what you were most recently proposing.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Wednesday, May 01, 2013 12:11 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

Hi Jerry,

Thanks so much for your response

(b) (5)

(b) (5)

(b) (5)

However, at the end of the day (and my

clock reads 11:59 pm so it truly is the end of the day),

(b) (5)

(b) (5)

(b) (5)

Thanks Howard and team for a productive series of discussions today. We really appreciated being able to work through the issues with you.

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Koh, Howard (HHS/OASH)
Sent: Wednesday, May 01, 2013 6:19 AM
To: Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

Thank you Kathy and colleagues.

I am seeing Bill at 9:30 this morning for my regular meeting.
I have already shared by email to him that we made substantial progress yesterday- let's see what he advises.

I am willing to host more calls today to get this process over the finish line, if at all possible.
Thank you Kathy and colleagues for working so hard on this. We appreciated the good dialogue yesterday and still hope this can be resolved. Howard

From: Hudson, Kathy (NIH/OD) [E] [Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 12:10 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

Hi Jerry,

Thanks so much (b) (5)
(b) (5)
(b) (5) However, at the end of the day (and my clock reads 11:59 pm so it truly is the end of the day), (b) (5)
(b) (5)

Thanks Howard and team for a productive series of discussions today. We really appreciated being able to work through the issues with you.

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)

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Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]

Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, May 01, 2013 2:15 AM
To: Corr, Bill (HHS/IOS)
Subject: NIH support summary - nih response
Attachments: Follow-up SUPPORT letter 2NICHD edits klh.docx

Hi Bill,

Though I am in Los Angeles for the Milken Global conference, I have been closely tracking efforts of my staff (Kathy Hudson, Alan Guttmacher, and others) who have been working productively with Howard Koh and others in ASH and OHRP, to develop a consensus set of statements that OHRP could put forward to clarify the situation with the SUPPORT study. Attached is the most recent version (clocked in at 11:59 PM). I understand that you are meeting with Howard in the AM, so I thought you might want to see this.

(b) (5)

Francis

(b) (5)



(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Corr, Bill (HHS/IOS)
Sent: Wednesday, May 01, 2013 5:45 AM
To: Collins, Francis (NIH/OD) [E]
Subject: Re: NIH support summary - nih response

(b)(5) - deliberative process

Bill

From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Wednesday, May 01, 2013 02:14 AM
To: Corr, Bill (HHS/IOS)
Subject: FW: NIH support summary - nih response

Hi Bill,

Though I am in Los Angeles for the Milken Global conference, I have been closely tracking efforts of my staff (Kathy Hudson, Alan Guttmacher, and others) who have been working productively with Howard Koh and others in ASH and OHRP, to develop a consensus set of statements that OHRP could put forward to clarify the situation with the SUPPORT study. Attached is the most recent version (clocked in at 11:59 PM). I understand that you are meeting with Howard in the AM, so I thought you might want to see this.

(b) (5)

Francis

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, April 30, 2013 5:21 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E].
Subject: Latest SUPPORT call with Howard and Jerry

Hi Francis –

Alan, Rose, Steph, and I talked with Howard, Jerry, and a few others from OHRP at 3:15.

(b) (5)

(b) (5)

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Will keep you posted.

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, April 30, 2013 12:32 PM
To: Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Menikoff, Jerry (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: NIH support summary
Attachments: NIH two pager SUPPORT - Revised 042513 1115 rh.docx; OHRP response options - bullets 4-30-13.docx

Four things.

(b) (5)

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(b) (5)

A very large rectangular area of the document is redacted with a solid grey fill. The text "(b) (5)" is centered at the top of this redacted area.

Talk to you at 3:15

(b) (5)



(b) (5)

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(b) (5)

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(b) (5)

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(b) (5)

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Saturday, April 27, 2013 2:06 PM
To: Collins, Francis (NIH/OD) [E]
Subject: Re: SUPPORT trial and OHRP

Nope. (b) (5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On Apr 27, 2013, at 1:53 PM, "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov> wrote:

Any update I should know about before I talk with Bill?

From: Corr, Bill (HHS/IOS)
Sent: Saturday, April 27, 2013 1:17 PM
To: Collins, Francis (NIH/OD) [E]
Subject: Re: SUPPORT trial and OHRP

Will try to catch you between 5 and 6. Thx

From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Saturday, April 27, 2013 11:28 AM
To: Corr, Bill (HHS/IOS)
Subject: RE: SUPPORT trial and OHRP

I'm in Chicago at the clinical meetings, but glad to talk anytime except 3 – 5 PM EDT when I'm on a panel for trainees. Just name a good time.

Francis

From: Corr, Bill (HHS/IOS)
Sent: Saturday, April 27, 2013 11:01 AM
To: Collins, Francis (NIH/OD) [E]
Subject: Re: SUPPORT trial and OHRP

Sorry for delay in responding; will speak with Andrea this afternoon when I return to DC.

(b)(5) - deliberative process

Bill

From: Collins, Francis (NIH/OD) [E] [mailto:collinsf@od.nih.gov]
Sent: Friday, April 26, 2013 01:57 PM
To: Corr, Bill (HHS/IOS)
Subject: SUPPORT trial and OHRP

Hi Bill,

I'm sorry to land in your inbox again.

(b) (5)

(b) (5)

What can I do to help?

Francis

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health
301-496-2433
www.nih.gov/about/director

Collections

How the feds got it wrong in their critique of a children's health study

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July 4, 2011

POSTED: April 25, 2013

Featured speaker Dr. Arthur Caplan discusses the ethics of personalized medicine at the First Annual Berkowitz Lecture at the Cooper Medical School of Rowan University on March 5, 2013. (Hillary Petrozziello / Staff Photographer)

By Arthur Caplan

and David Magnus



GALLERY: Featured speaker Dr. Arthur Caplan discusses the ethics...

The headlines were frightening. Parents had not been properly informed that doctors were putting their extremely premature infants at risk in a study of oxygen treatment. The lead government agency providing oversight to biomedical research said the informed-consent forms did not tell the parents about "reasonably foreseeable risks," which included blindness and death.

This would be a horrific violation of research ethics if it were true. But the truth about this study is far more complicated than the headlines and the government reprimand they were based upon.

When you or your child goes to the doctor and she recommends a treatment, we all like to believe that it will be the best treatment available. The reality is that there are often several treatment options. Different hospitals and doctors favor different drugs, different dosing schedules, different equipment, and even different procedures. Which specific treatment you or your child gets may depend upon who your doctor is or where you happen to live.

In light of this uncertainty, it is imperative to research whether one standardly used treatment is better than the others. Comparative effectiveness research tries to do just that. Yet this is exactly the kind of research that was slammed by government watchdogs and mauled in the press.

The Office for Human Research Protections of the federal Department of Health and Human Services sent a letter to investigators at the University of Alabama at Birmingham blasting the consent form used in a clinical trial to determine appropriate oxygen saturation levels in severely premature neonates. The history of practice in this area is complicated, and the standard of care has varied over the decades. Clinical management of these vulnerable infants is tricky - too much oxygen produces blindness and lung damage, while too little can lead to brain damage and death. It is not clear what levels of oxygen saturation should be the goal, and centers follow different practices.

Neonatologists, to their credit, tried to set up a study that would let them better understand the risks and benefits in the range of oxygen levels being used. University of Alabama investigators took the lead in a large trial to try to get the answers. At all participating institutions, infants were receiving anywhere from low (85 to 89 percent) to high (91 to 95 percent) oxygen levels. Researchers proposed that instead of allowing random or non-evidence-based factors to determine where in that range oxygen

levels were set, infants would be randomized to groups where they got oxygen at the lower and higher ends of what doctors were giving. Since both of these ranges are within the standard of care (85 to 95 percent), many researchers argued that the study they wanted to do carried minimal new risk. Everything they proposed to do with the preemies was already being done, but no one could say what was best.

Federal officials disagree. They claim that limiting the range of oxygen levels, instead of allowing them to randomly range across the spectrum of what is already being tried, alters the risks and benefits to the infants. There is no evidence to support this claim. Any preemie prior to the study could have received oxygen at one of the levels in the study.

Studying treatments to determine which is best is just as important as studying new drugs, vaccines, or devices. In many ways, it is more important, since many more people are exposed to a range of treatments, some of which may be worse or more costly than others. The irony is that the risks in studying treatment are far, far less, since nothing new is being introduced.

The reality is that those regulating research need to update their thinking so as not to scare all of us about this long-overdue and much-needed form of research.

Arthur Caplan is head of the division of medical ethics at New York University's Langone Medical Center. David Magnus is director of the Center for Biomedical Ethics at Stanford University. E-mail them at arthur.caplan@nyumc.org and dmagnus@stanford.edu.

FEATURED ARTICLES



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'Rock of Ages' song list

Sobering realities of Parkinson's

Young cancer patient's good news: 'Total remission!'

How area hospitals rate

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, April 26, 2013 1:30 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: responses to

Caya,

(b) (5) OHRP has said in its letter to UAB that the consent should have explained that the level of oxygen provided could increase the risk of death. 45CFR46 requires that a consent form provide "A description of any reasonably foreseeable risks or discomforts to the subject." "Risks" are generally understood to mean risks associated with the research activities and not risks that individual research participants face independent of the research study. (b) (5)

(b) (5)

The materials provided below support what we have been saying all along; (b) (5)

(b) (5)

As far as the first bullet point from below- this is taken from the introduction of the SUPPORT paper. If one reads on, the W Tin study is quoted "rates of death and CP did not differ...."

Second bullet point is taken from Dr. Colin Morley's editorial published with the NEJM SUPPORT paper- Dr. Tin did his study and showed no difference in mortality or neurodevelopmental problems, thus the need for further study.

Finally, the Askie cochrane review (published in 2009) main results are "in the meta analysis of the five trials included in this review, the restriction of oxygen significantly reduced the incidence and severity of ROP without unduly increasing death rates. The one prospective, multi center, double-blind, randomized trial investigating lower vs. Higher oxygen levels.....showed no significant differences in the rates of ROP, mortality or growth and development...."

(b) (5)

From: Lewis, Caya (HHS/IOS)
Sent: Thursday, April 25, 2013 12:48 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Palm, Andrea (HHS/IOS); Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]
Subject: RE: NIH two pager SUPPORT 042413 11PM
Importance: High

Kathy,

(b)(5) - deliberative process

(b)(5) - deliberative process

Thanks,

Caya

(b)(5) - deliberative process

prospective meta-analysis to help resolve this remaining question." The "five ongoing" trials that the authors refer to include the SUPPORT study and its counterparts in other countries.

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Thursday, April 25, 2013 12:19 AM
To: Lewis, Caya (HHS/IOS)
Cc: Palm, Andrea (HHS/IOS); Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
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It would be great if you could send us the specific studies ohrp is citing. Our folks are familiar with every study in this area. They live and breath this work and will be able to tell you how the ohrp cited studies fit into the overall portrait of studies on preemies.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On Apr 25, 2013, at 12:04 AM, "Lewis, Caya (HHS/IOS)" <Caya.Lewis@hhs.gov> wrote:

Thanks so much for the quick turn around.

(b)(5) - deliberative process

I hanks again,

Caya

From: Hudson, Kathy (NIH/OD) [E] [Kathy.Hudson@nih.gov]
Sent: Wednesday, April 24, 2013 11:40 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
Subject: NIH two pager SUPPORT 042413 11PM

Caya,

You asked for a two pager on the support study by 1 pm tomorrow. Please accept our slightly longer (3.15 pages) that has not undergone extensive review here but please know that the nih team is all standing firmly together about our views on this. (b) (5)

kathy

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 1:01 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC); Corr, Bill (HHS/IOS)
Subject: revised NIH two pager on Support Study
Attachments: NIH two pager SUPPORT - Revised 042513 1133.docx

Hi,

We have made some modest changes to the document on the SUPPORT study. We look forward to continuing the conversation and reaching a good resolution.

Thanks

Kathy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 11:41 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
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kathy

(b) (5)





(b) (5)



NIH's Concerns about OHRP's Complaint

(b) (5)



(b) (5)



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Subject: NIH two pager SUPPORT 042413 11PM
Attachments: NEJM--Editorial.pdf; Cochrane Review of use of oxygen 2009.pdf; NEJM--Support study results.pdf
Importance: High

Kathy,

(b)(5) - deliberative process

Thanks,

Caya

Referencing the researchers' own write-up of the study results in the New England Journal (NEJM Support study results, attached):

(b)(5) - deliberative process

(b)(5) - deliberative process

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kathy

EDITORIALS



CPAP and Low Oxygen Saturation for Very Preterm Babies?

Colin J. Morley, M.D.

The survival rate among extremely preterm babies — those born at 24 to 27 weeks of gestation — is about 75%, and there is a high prevalence of neurodevelopmental problems. Reducing the rates of complications and death among these infants is a key research area. Traditionally, extremely preterm babies have been treated with intubation and ventilation soon after birth. However, these interventions may contribute to lung injury. Many infants breathe adequately but not normally at birth, and some can be assisted with the less invasive strategy of nasal continuous positive airway pressure (CPAP) and receive ventilation and surfactant only if this strategy fails.^{1,2} Oxygen therapy is very toxic for preterm babies, and maintaining even slightly high arterial levels contributes to retinopathy of prematurity and increases the duration of oxygen treatment.³ Unfortunately, an oxygen saturation (SpO₂) range that reduces retinopathy of prematurity optimally but does not increase the rates of death or neurodevelopmental problems has not been accurately defined.

The results of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a randomized, 2-by-2 factorial trial in which 1316 babies who were born between 24 weeks 0 days and 27 weeks 6 days of gestation were enrolled, are reported in this issue of the *Journal*.^{4,5} In this trial, early treatment with CPAP was compared with immediate intubation followed by surfactant, and a target oxygen saturation range of 85 to 89% was compared with a target range of 91 to 95%.

In one part of the trial,⁵ babies were randomly assigned, before birth, to either intubation in the delivery room and surfactant administration within an hour or nasal CPAP started in the delivery room. Babies who were randomly assigned to CPAP could be intubated in the delivery room,

for the purpose of resuscitation, or later, if predefined criteria were met. Extubation criteria were also predefined; the criteria for threshold levels of the partial pressure of arterial carbon dioxide (PaCO₂), pH, the fraction of inspired oxygen (FiO₂), and SpO₂ were more stringent for the intubation group than for the CPAP group. The rates of the primary outcome of death or bronchopulmonary dysplasia⁶ did not differ significantly between the CPAP group and the surfactant group (47.8% and 51.0%, respectively; $P=0.30$). The CPAP group, as compared with the surfactant group, less frequently required intubation in the delivery room (34.4% vs. 93.4%) or postnatal corticosteroids for the treatment of bronchopulmonary dysplasia (7.2% vs. 13.2%) ($P<0.001$ for both comparisons), and required ventilation for an average of 3 days less ($P=0.03$). There were no significant differences between the two groups in the incidences of death or other major outcomes before discharge from the hospital. These results are similar to those of the Continuous Positive Airway Pressure or Intubation at Birth trial (COIN; Australian New Zealand Clinical Trials Registry number, 12606000258550),² in which 610 babies who were born at 25 to 28 weeks of gestation were randomly assigned to CPAP or intubation and ventilation at 5 minutes after birth.

Some limitations of the present trial should be noted. Randomization was performed before delivery (i.e., before it was known whether babies would breathe or have respiratory distress); as a result, some of the infants in the CPAP group were intubated immediately after birth and did not receive CPAP. The median duration of ventilation for both groups was 3 to 4 weeks, which was much longer than the 3 to 4 days in the COIN trial,² and suggests that the extubation criteria in this trial were more stringent than were those in

the COIN trial. In the COIN trial,² pneumothorax occurred in 9.1% of the infants in the CPAP group and in 3.0% of the infants in the ventilation group. In the SUPPORT trial, they occurred in 6.8% of the infants in the CPAP group and in 7.4% of the infants in the ventilation group, a finding that suggests that early CPAP is not associated with pneumothorax.

In the other part of SUPPORT,⁴ the babies were randomly assigned to a target range for peripheral oxygen saturation of 85 to 89% or 91 to 95%. Staff members were unaware of the true levels because the oximeters had been altered to read 3% above or 3% below the true reading, so that they displayed a range of 88 to 92% for both ranges. The unmasked trial data showed that the distribution of oxygen saturation levels was within or above the target range in the higher-oxygen-saturation group, but in the lower-oxygen-saturation group, it was about 90 to 95% (i.e., above the target range). The difference in oxygen saturation levels between the groups was about 3 percentage points instead of the 6 percentage points that had been planned. Therefore, this study actually compared saturation levels of about 89 to 97% with saturation levels of 91 to 97%; the results should be ascribed to these higher ranges. There is evidence that nurses tend to keep a baby's oxygen saturation level toward the higher end of the range,⁷ which may account for the shift of both groups toward higher saturation levels than those targeted.

There was no significant difference between the oxygen-saturation groups in the primary outcome of severe retinopathy of prematurity or death before discharge. However, even with the relatively modest difference in oxygen saturation levels between the groups, the rate of severe retinopathy of prematurity was lower in the lower-oxygen-saturation group than in the higher-oxygen-saturation group (8.6% vs. 17.9%, $P < 0.001$).

Moderate-to-severe bronchopulmonary dysplasia is defined as the need for supplemental oxygen in a very preterm infant at 36 weeks of postmenstrual age.⁸ This trial also used a physiological definition of bronchopulmonary dysplasia, which calls for the FiO_2 to be reduced at 36 weeks in order to determine whether supplemental oxygen is really required.⁶ As in previous studies,⁹ the rate of needed treatment with supplemental oxygen at 36 weeks among survivors was lower in the lower-oxygen-saturation group than in the higher-oxygen-saturation group ($P = 0.002$). When the

physiological definition of bronchopulmonary dysplasia was used, the rate of oxygen use at 36 weeks was not altered in the lower-oxygen-saturation group but it was reduced in the higher-oxygen-saturation group, with the result that the difference between the groups was no longer significant. The rate of the composite of death or bronchopulmonary dysplasia (according to either definition) by 36 weeks did not differ significantly between the groups.

There was weak evidence¹⁰ of an increased rate of death before discharge in the lower-oxygen-saturation group ($P = 0.04$). An association between lower oxygen-saturation targets and increased mortality has been reported previously in some¹¹ but not other^{3,12} nonrandomized studies and was not observed in a previous randomized trial.⁹ This is a most important outcome, but caution is warranted in interpreting this result. Additional research is needed to clarify this finding. There were no significant differences between the groups in short-term outcomes that have been associated with relative ischemia.

How do the results of this trial help neonatologists? They show that starting CPAP at birth in very preterm babies, even if it fails in some, has important benefits and no serious side effects. Predicting which babies will not have an adequate response to treatment with CPAP and should therefore receive early ventilation and surfactant should be a future goal. Targeting oxygen saturation levels is difficult, and a recommended oxygen saturation range that is effective yet safe remains elusive. A lower oxygen saturation level significantly reduces the incidence of severe retinopathy of prematurity but may increase the rate of death. Long-term follow-up is vital to determine whether either intervention was associated with neurodevelopmental problems.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Royal Women's Hospital and the Department of Obstetrics, University of Melbourne — both in Melbourne, Australia.

This article (10.1056/NEJMe1004342) was published on May 16, 2010, and updated on July 21, 2010, at NEJM.org.

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Hypoplastic Left Heart Syndrome

Carolyn A. Bondy, M.D.

Just 30 years ago, the newborn with hypoplastic left heart syndrome faced certain death. This congenital defect involves a rudimentary mitral valve and left ventricle, coupled with a hypoplastic aortic valve and ascending aorta.¹ Multistage surgical remediation of hypoplastic left heart syndrome, introduced in the 1980s, has led to survival rates that exceed 60%, and in this issue of the *Journal*, Ohye et al. report a further survival benefit with the use of a newly developed shunt.²

The fetus with hypoplastic left heart is able to survive until birth because of the unique fetal circulatory pattern. In the fetus with hypoplastic left heart syndrome, since fetal blood is oxygenated by the placenta, the right-heart and pulmonary circulation is usually sidetracked before birth, so the right heart may pinch hit for the left to serve the systemic circulation. Oxygenated blood entering the left atrium crosses the foramen ovale to the right heart and is pumped into the pulmonary artery. This blood then bypasses the defective ascending aorta and reaches the systemic circulation via a dilated ductus arteriosus (see Fig. 1 of the article by Ohye et al.²). Birth is a catastrophic event in hypoplastic left heart syndrome. Under normal circumstances, the foramen ovale and ductus close at birth to allow the newborn's blood to be oxygenated by means of the pulmonary circulation. In newborns with hypoplastic left heart syndrome, however, these changes effectively shut down the systemic circulation, causing right heart failure and death within a few days.

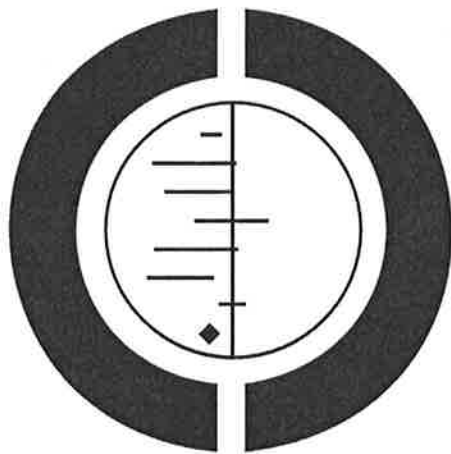
Hypoplastic left heart syndrome is a genetically heterogeneous disorder that affects 1 in 5000 live

births.³ About one third of cases occur in the context of a recognized genetic disorder such as Turner's syndrome (in which all or major parts of one sex chromosome are deleted) or Jacobsen's syndrome (in which the terminal part of 11q is deleted) or in the context of a monogenic disorder such as Noonan's or Holt–Oram's syndrome. Screening studies involving family members of nonsyndromic probands with hypoplastic left heart syndrome suggest that heritability is complex, encompassing various left ventricular outflow tract defects, and no single disease-causing gene or pathway has as yet been identified.⁴

In the early 1980s, Norwood and colleagues at the Children's Hospital of Philadelphia pioneered a three-stage surgical intervention for hypoplastic left heart syndrome.⁵ Their goal was to establish a right-heart–based systemic circulation, using the Fontan procedure to create a separate pulmonary circulation, in which venous blood returns passively to the lungs. The first stage, known as the Norwood procedure, is the most difficult to perform and is associated with a high risk of death; it must be undertaken soon after birth to save the infant's life and prevent damage to the right heart and pulmonary vasculature. The procedure involves excising the atrial septum, so that oxygenated blood entering the left atrium crosses to the right heart; remodeling the ascending aorta, which is then patched into the proximal pulmonary artery, allowing the right ventricle to drive the systemic circulation; and establishing a separate conduit to deliver blood from the right ventricle to the pulmonary circulation.

Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review)

Askie LM, Henderson-Smart DJ, Ko H



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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3

<http://www.thecochranelibrary.com>



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[Intervention Review]

Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

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ABSTRACT

Background

While the use of supplemental oxygen has a long history in neonatal care, resulting in both significant health care benefits and harms, uncertainty remains as to the most appropriate range to target blood oxygen levels in preterm and low birth weight infants. Potential benefits of higher oxygen targeting may include more stable sleep patterns and improved long-term growth and development. However, there may be significant deleterious pulmonary effects and health service use implications resulting from such a policy.

Objectives

To determine whether targeting ambient oxygen concentration to achieve a lower vs. higher blood oxygen range, or administering restricted vs. liberal supplemental oxygen, effects mortality, retinopathy of prematurity, lung function, growth or development in preterm or low birth weight infants.

Search strategy

The standard search strategy of the Neonatal Review Group was used. An additional literature search was conducted of the MEDLINE and CINAHL databases in order to locate any trials in addition to those provided by the Cochrane Controlled Trials Register (CENTRAL/CCTR). Search updated to week two July 2008.

Selection criteria

All trials in preterm or low birth weight infants utilising random or quasi-random patient allocation in which ambient oxygen concentrations were targeted to achieve a lower vs. higher blood oxygen range, or restricted vs. liberal oxygen was administered were eligible for inclusion.

Data collection and analysis

The methodological quality of the eligible trials was assessed independently by each review author for the degree of selection, performance, attrition and detection bias. Data were extracted and reviewed independently by the each author. Data analysis was conducted according to the standards of the Cochrane Neonatal Review Group.

Main results

In the meta-analysis of the five trials included in this review, the restriction of oxygen significantly reduced the incidence and severity of retinopathy of prematurity without unduly increasing death rates. The one prospective, multicenter, double-blind, randomized trial investigating lower vs. higher blood oxygen levels from 32 weeks postmenstrual age showed no significant differences in the rates of ROP, mortality or growth and development between the two groups. However, this study did show increased rates of chronic lung disease and home oxygen use.

Authors' conclusions

The results of this systematic review confirm that (the now historical) policy of unrestricted, unmonitored oxygen therapy has potential harms without clear benefits. However, the question of what is the optimal target range for maintaining blood oxygen levels in preterm/LBW infants was not answered by the data available for inclusion in this review.

PLAIN LANGUAGE SUMMARY

Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Restricting oxygen supplementation significantly reduces the rate and severity of vision problems (retinopathy) in premature and low birth weight babies. Babies born either prematurely (before 37 weeks) or with a low birth weight often have breathing problems and need extra oxygen. Oxygen supplementation has provided many benefits for these babies but can cause damage to the eyes (retinopathy) and lungs. The review of trials found that unrestricted oxygen supplementation has these potential adverse effects without any clear benefits. Restricted oxygen significantly reduces these risks. More research is needed to find the best level of oxygen supplementation.

BACKGROUND

The administration of supplemental oxygen has a long history in neonatal care (Wilson 1942). The use of oxygen in preterm and low birth weight infants suffering respiratory insufficiency has resulted in significant health care benefits, such as reduced mortality and spastic diplegia (Avery 1960; McDonald 1963), but has also been associated with significant deleterious effects such as retinopathy of prematurity and lung toxicity (Duc 1992).

Improvements in technology in the past few decades have led to both the increased survival of preterm and low birth weight infants and an ability to measure their oxygen levels more accurately. Despite the exceedingly common use of supplemental oxygen in this population of infants, there is little consensus as to the optimal mode of administration and appropriate levels of oxygen for maximising short or long-term growth and development, while minimising harmful effects (Poets 1998; McIntosh 2001).

Uncertainty remains as to the most appropriate range to target blood oxygen levels in preterm and low birth weight infants. Usher (Usher 1973) examined the effect of targeting a lower vs. higher range of PaO₂ on death, the need for mechanical ventilation and

other clinical outcomes and concluded there was no benefit in targeting a higher range, and there may in fact be deleterious respiratory effects (Coares 1982). A cohort study by Tin et al (Tin 2001) also suggested an increase in adverse respiratory outcomes and a significant increase in the incidence of ROP occurred when higher oxygen ranges were targeted in preterm infants. However, Phelps and Rosenbaum (Phelps 1984) demonstrated significantly more severe retinopathy in kittens recovering from hyperoxic-induced disease when allowed to recover in lower levels of ambient oxygen, suggesting that targeting higher blood oxygen levels may be beneficial to visual outcomes. The STOP-ROP trial (STOP-ROP 2000) found that higher oxygen targeting did not significantly decrease the incidence of pre-threshold ROP progression, but did cause an exacerbation of adverse pulmonary events. The results of this trial are included in a separate Cochrane review entitled: "Supplemental oxygen for the treatment of pre-threshold retinopathy of prematurity" (Lloyd 2003). The effects of either policy of oxygen administration on long-term growth and development in preterm or low birth weight infants remains uncertain.

Two related Cochrane reviews have summarised the findings on

gradual vs. abrupt (Askie 2001a) and early vs. late discontinuation of oxygen therapy (Askie 2001b) in preterm or low birth weight infants.

OBJECTIVES

To determine whether targeting ambient oxygen concentration to achieve a lower vs. higher blood oxygen range, or administering restricted vs. liberal supplemental oxygen effects mortality, retinopathy of prematurity, lung function, growth or development in preterm or low birth weight infants.

A priori sub-group analyses:

- Method of oxygen monitoring. Infants born at different gestational age and birth weight subgroups: as there are differing baseline risks of the outcome measures in these subgroups. Time of discontinuation: early vs. late discontinuation as this is hypothesized to influence outcome measures (Gunn 1980). Method of discontinuation: gradual vs. abrupt discontinuation as this is hypothesized to influence outcome measures (Chan-Ling 1995)

METHODS

Criteria for considering studies for this review

Types of studies

Trials utilising random or quasi-random patient allocation were eligible for inclusion.

Types of participants

Preterm (< 37 weeks gestation) or low birth weight (< 2500 g) infants receiving supplemental oxygen.

Types of interventions

Restricted vs. liberal administration of supplemental oxygen; or targeting a lower vs. higher range of blood oxygen levels.

Types of outcome measures

- Retinopathy of prematurity (ROP) - any, severe (stage 3 or greater)
- Mortality - any, early neonatal period (< 1 week postnatal age), later neonatal period (\geq 3 weeks postnatal age)

- ROP (severe) or death (any)
- Apnea of prematurity
- Chronic lung disease/bronchopulmonary dysplasia
- Growth - neonatal period and long-term
- Neurodevelopment - long-term
- Visual function - long-term

Outcome data with attrition rates greater than 20% were not included in analyses.

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used. This includes searches of the Cochrane Controlled Trials Register (CENTRAL/CCTR, The Cochrane Library, Issue 2, 2008), the Oxford Database of Perinatal trials, MEDLINE, previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal hand searching mainly in the English language.

An additional literature search, using OVID software, was conducted of the MEDLINE (1996 - June, Week 2, 2008), Maternity and Infant Care (1971 - June 2008), and CINAHL (1982 - June 2008) databases in order to locate any trials in addition to those provided by the Cochrane Controlled Trials Register (CENTRAL/CCTR, The Cochrane Library, Issue 2, 2008). The search strategy involved various combinations of the following keywords, using the search fields of abstract, MeSH subject heading, exploded subject heading, floating subject heading, publication type, registry number word, subject heading word, text word, and title: oxygen, preterm, premature, neonate, newborn, infant, oxygen saturation, hypoxia, retinopathy of prematurity, retrolental fibroplasia, low birth weight, very low birth weight, extremely low birth weight, randomized controlled trial, controlled clinical trial, clinical trial, random allocation, placebo.

Data collection and analysis

The standard methods of the Cochrane Collaboration and its Neonatal Review Group were used to select trials, assess quality and extract and synthesise data. For each trial, each author independently assessed the methodological quality and extracted the data from the report. Results were compared and differences resolved as required. Level of agreement between the two authors was greater than 90% in all cases. Eligible trials were assessed for the degree of selection, performance, attrition and detection bias. Additional information was requested from authors to clarify methodology or results as necessary.

Meta-analyses were carried out with use of relative risk (RR) and risk difference (RD). When appropriate, number needed to treat (1/RD) was calculated. The fixed effects "assumption free" model was used. Evaluation of heterogeneity, subgroup and sensitivity analyses were undertaken as appropriate.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The systematic review located six trials that addressed the question of targeting oxygen administration in preterm/LBW infants. Fourteen other studies were excluded from the analysis as they either did not address this particular question or did not involve random allocation of one of the interventions under review.

Participants:

The enrolment period for five included studies was between 1951 - 1969 (referred to as “pre-1990” trials or studies hereon in) and one (Askie 2003) included study was conducted between 1996 - 2000 (referred to as “post-1990” trials or studies hereon in). The five pre-1990 studies were done during an early era of neonatal care, with therapies and practices quite different from modern “intensive” care. These studies included only small numbers of survivors with birth weights under 1000 g, the infants who carry the greatest mortality and morbidity burden today. There was a wide range of birth weights among trial participants, from less than 1000 to 2500 g. The largest pre-1990 era trial (Kinsey 1956) only enrolled infants who survived beyond 48 hours, while the other four trials randomized infants on admission to the neonatal nursery anywhere from two hrs (Usher 1973) to > 48 hours (Kinsey 1956). Infants from these five trials have been categorised as belonging to the early neonatal period (< 1 week postnatal age), which was defined as treatments starting at < 1 week of age. The only post-1990 trial (Askie 2003) enrolled infants < 30 weeks gestation who remained dependent on supplemental oxygen at 32 weeks postmenstrual age; therefore, infants in this trial were at least three weeks postnatal age at randomization. Infants in this trial have been defined in this review as belonging to the later neonatal period (\geq 3 weeks postnatal age). The five pre-1990 trials used birth weight as inclusion criteria, with the most recent trial using gestational and postmenstrual age as inclusion criteria. Three trials also selected infants for inclusion based on a diagnosis of respiratory distress syndrome (Usher 1973) or hypoxia/acidemia (Sinclair 1968) or continued dependence on supplemental oxygen more than three weeks after birth (Askie 2003).

Intervention:

Three trials (Askie 2003; Usher 1973; Sinclair 1968) administered oxygen based on actual arterial, saturation or capillary blood oxygen levels. The other three trials were conducted in an era before accurate blood oxygen monitoring in infants was possible. As such, these trials could only test the effects of cruder measures of oxygenation, such as ambient oxygen concentration, and even these in only general terms, labelled “liberal” and “restricted” oxygen administration in this review. For the included studies, due to the variation in measurement methods, restricted oxygen ranged from values of Fn SpO₂ 91-94% (Askie 2003), either 0.4

or 0.5 maximum FiO₂ (Kinsey 1956; Lanman 1954; Patz 1954), or PaO₂<45mmHg (PcapO₂<35mmHg) (Usher 1973) or maximum O₂ of 35% (in a headbox, PaO₂ 50-120mmHg) (Sinclair 1968). Liberal O₂ ranged from values of Fn SpO₂ 95-98% (Askie 2003), O₂ levels at 50% (Kinsey 1956), 60-70% (Patz 1954), or 100% (in a headbox; PaO₂ 50-120mmHg) (Sinclair 1968), FiO₂ 69% (Lanman 1954), or minimum O₂ 40% (PaO₂ 80-120mmHg or PcapO₂ 50-60mmHg) (Usher 1973).

Five of the included trials started the intervention in the early neonatal period (< 1 week postnatal age), but continued it for a wide range of time; from one day to seven weeks. Of these, four studies randomized infants from birth (defined as < 48 hours after birth) (Lanman 1954; Patz 1954; Sinclair 1968; Usher 1973), while one study did not randomize infants until > 48 hours after birth (Kinsey 1956). One trial started the intervention in the later neonatal period (from 32 weeks postmenstrual age) (Askie 2003), and continued for a median of 17.5 days (IQR 7.0 to 41.0 days) for lower oxygen targeting and a median of 40.0 days (IQR 20.5 to 73.0 days) for the higher oxygen targeting group. When oxygen weaning was indicated, it was done so gradually in two trials, abruptly in one trial, and the method not specified in the remaining three trials.

Outcomes:

Outcome measures were assessed at time periods ranging from two days to 12 months. Only Askie 2003 reported the longer term (12 months corrected age) effects of the interventions on growth, neurodevelopment, lung function, or chronic lung disease. Coates 1982 reported some long-term outcomes on infants from Usher's 1973 study (Usher 1973). Unfortunately, he was only able to obtain outcome data for 23% of survivors, and in keeping with our *a priori* specification of only including outcome measures with 80% or greater ascertainment, these data are not included in the review. Only one study (Askie 2003) reporting eye outcome data used the International Classification of Retinopathy of Prematurity grading system (ROP Committee 1984). This was assessed by routine ophthalmic examinations at two-week intervals from enrolment until the resolution of retinopathy.

The only other study to report eye outcome data used the retrolental fibroplasia (RLF) classifications (Reese 1953). Vascular RLF grade 1, vascular RLF grade 2, and cicatricial RLF / RLF grade 3 correspond approximately with retinopathy of prematurity (ROP) stage 3, ROP stage 4, and ROP stage 5 / blindness respectively. These inferred classifications were gathered from references to RLF/ROP cross-classification from the International Classification of Retinopathy of Prematurity system (ROP Committee 1984; ROP Committee 1987; Garner 1985; Hindle 1986; Hindle 1990; Sira 1988; Szewczyk 1953). Ascertainment of RLF in the five trials from 1951 - 1969 was by direct ophthalmoscopy, visualising the posterior pole only. The only findings that could be identified using this method were dilation and tortuosity of the retinal vessels (“plus disease”, using the 1984 and 1987 classifications, as above). The more common findings in the anterior pole that can today be

identified with indirect ophthalmoscopy were unable to be identified. Hence, even the least severe eye outcomes reported in this review equate with what today would be described as "threshold" ROP.

The largest trial (Askie 2003, n = 358) only enrolled infants who survived and were oxygen dependent beyond three weeks postnatal age. The second largest trial (Kinsey 1956, n = 212) only enrolled infants who survived beyond 48 hours. Unfortunately, the third largest trial (Patz 1954, n = unknown, but greater than 120) did not report any mortality data and these data are not retrievable (Duc 1992).

Risk of bias in included studies

All included trials used either quasi-random or random patient allocation, had at least one clinically meaningful outcome, and were thus included in the analyses. The overall methodological quality of the included trials was fair. Askie 2003 stratified the randomization with the use of a dynamic balancing method to ensure a balance of treatment group assignment within each stratum defined according to hospital, singleton or multiple birth, and gestational age.

Three of the trials had adequate allocation concealment: Askie 2003 and Kinsey 1956 used central telephone randomization, and Sinclair 1968 used a method of sealed envelopes. Allocation concealment is unclear in the other three trials. Patz 1954 used quasi-random patient allocation, while the remaining five trials were truly randomized. Askie 2003 was the only trial to employ masking with families, clinicians and outcome assessors in this trial unaware of treatment allocation. Askie 2003 and Kinsey 1956 were the only two trials to report power calculations *a priori*. Five of the included studies had adequate short-term outcome measure ascertainment. The Patz 1954 trial did not report deaths or losses to follow-up, but it is assumed that outcome data were reported only on survivors and assessed by six months age.

Effects of interventions

RESTRICTED VS. LIBERAL OXYGEN THERAPY (ALL PRETERM/LBW INFANTS) IN EARLY NEONATAL PERIOD (Comparison 1):

In this meta-analysis, restricted compared with liberal oxygen administration when started during the early neonatal period did not have any statistically significant effect on the incidence of death. It should be noted that there were a range of times for enrolment in this early period from two hrs (Usher 1973) to > 48 hrs (Kinsey 1956). However, restricted oxygen administration did significantly reduce the incidence of all forms of retrolental fibroplasia (RLF) in survivors. Cicatricial RLF (any grade) was significantly reduced in

surviving infants who were exposed to a restricted oxygen regime (summary RR 0.26, 95% CI 0.11-0.58). There was also a significant reduction in the precursor, vascular RLF (any stage), in surviving infants exposed to restricted oxygen (summary RR 0.34, 95% CI 0.25-0.46).

During the early neonatal period, neither restricted compared with liberal oxygen administration nor lower vs. higher blood oxygen levels (where blood oxygen was directly measured) had significant independent effects on death rates, either in all preterm/LBW infants or in a sub-group of infants with birth weights < 1250 g. However, restricted compared with liberal oxygen administration did significantly reduce a combined measure of adverse outcome, death or RLF (vascular, any stage) (summary RR 0.59, 95% CI 0.48-0.72). Thus, one would need to treat only three infants with restricted oxygen to prevent one infant from having the adverse outcome of death or RLF (NNT = 1/RD = 1/0.310 = 3.2). Restricted compared with liberal oxygen administration also reduced the more severe measure of adverse outcome, death or RLF (cicatricial, any grade) (summary RR 0.77, 95% CI 0.56-1.07) for the trial where the intervention was used in the early neonatal period, although this result was not statistically significant.

No other outcome measures specified *a priori* as clinically meaningful were reported in enough detail or with satisfactory follow-up rates to be included in the analysis (chronic lung disease; long-term growth, development, lung or visual function).

SUBGROUP ANALYSIS FOR THE EARLY NEONATAL PERIOD (Comparisons 2-4):

Only one of the *a priori* stated subgroup analyses was possible with the available data for the early neonatal period.

Subgroup analysis of lower vs. higher blood oxygen levels in the early neonatal period showed that for infants with BW < 1250 g weeks gestational age, there was no significant difference in the incidence of death. However, it should be noted that this trial (Usher 1973) only enrolled 45 infants. The only reported effect of restricted vs. liberal oxygen saturation targeting on infants with birth weight less than 1000g was a non-significant decrease in RLF (cicatricial, severe) in the Patz 1954 trial. The analysis was based on very small numbers, with uneven denominators in each group. This may reflect a difference in the number of survivors in the two groups resulting from deaths which were not accounted for by Patz 1954. This result should thus be interpreted with caution as the small numbers in this subgroup (as reflected in the wide confidence intervals) and non-reported deaths make any meaningful interpretation of these data difficult.

It was not possible to undertake any of the other *a priori* specified subgroup analyses such as time or method of oxygen weaning, or a comprehensive analysis of the method of oxygen monitoring due to insufficient data.

LOWER VS. HIGHER BLOOD OXYGEN LEVELS (ALL PRETERM/LBW INFANTS) IN THE LATER NEONATAL

PERIOD (Comparison 5):

Only one study (Askie 2003), with 358 infants, contributed to the results in the later neonatal period. There was no significant difference in the incidence of death between lower or higher oxygen saturation targeting when started in the later neonatal period. There were no statistically significant differences in the incidence of ROP (any stage) in survivors, the incidence of ROP > Stage 2 nor ROP Stage 4 or 5 or blindness between the infants receiving lower or higher oxygen saturation targeting. There were no statistically significant differences between intervention strategies for the combined outcomes of death or ROP > Stage 2, nor with death or ROP Stage 4 or 5 or blindness.

Some outcome measures specified *a priori* as clinically meaningful were reported. There was no statistically significant difference in the incidence of major developmental abnormality at 12 months corrected age between lower or higher oxygen saturation targeting. In relation to lung function, there was a significant reduction on the dependence of supplemental oxygen at 36 weeks of postmenstrual age with using a lower oxygen saturation target (RR 0.71, 95% CI 0.59-0.87). There was no statistically significant difference between interventions for the incidence of use of postnatal corticosteroids and diuretics for chronic lung disease with the use of either a lower or higher oxygen saturation targeting. Some outcomes were either not reported at all or not reported in enough detail or with satisfactory follow-up rates to be included in the analysis (long-term lung or visual function).

SUBGROUP ANALYSIS FOR THE LATER NEONATAL PERIOD (Comparison 6):

Only one of the *a priori* stated subgroup analysis could be undertaken with the available data for the later neonatal period.

Comparison of lower vs. higher oxygen saturation targeting when started in the later neonatal period in infants < 28 weeks gestational age revealed no statistically significant difference in the incidence of death, ROP Stage 3 or 4, nor in the incidence of blindness.

Evaluation of heterogeneity:

No statistical heterogeneity was demonstrated in any of the outcome measures analysed that included more than one trial.

There was considerable clinical heterogeneity amongst the six trials included in this review. All included trials contained a wide range of birth weights, followed infants for a relatively wide ranging period (and all but one in the short-term only), used different definitions of outcome measures (five trials used RLF and one trial used ROP eye outcome definitions), and implemented the interventions in either an early or later neonatal period. There was a very wide range of exposure to the interventions under review (1 day to >10 weeks). Moreover, there were three distinct intervention comparisons included in the review (hence the division of comparisons into restricted vs. liberal oxygen administration in the early neonatal period, lower vs. higher blood oxygen levels in the early neonatal period, and lower vs. higher blood oxygen

levels in the later neonatal period). The Kinsey 1956, Lanman 1954 and Patz 1954 trials were conducted in an early (pre-1990) era of neonatal care where methods of oxygen monitoring and administration were crude in comparison to today's techniques and thus only restricted vs. liberal oxygen administration could be compared in these trials. The Usher 1973 and Sinclair 1968 trials used more modern techniques (including umbilical artery catheterization, arteriased capillary sampling, micromethods for blood gases and acid-base), so comparison of lower vs. higher blood oxygen levels were possible with these data. The Askie 2003 trial used pulse oximeters whose algorithm assessed functional oxygen saturation, and thus comparisons of lower vs. higher blood oxygen level via oxygen saturation targets were possible with data from these trials.

Sensitivity analyses:

The results of the meta-analyses were tested for robustness with regard to study quality. We had stated *a priori* that trials containing outcome measures with greater than 20% attrition would not be included in the analysis. In one trial, Patz 1954, it was unclear whether outcome ascertainment was complete as attrition due to losses to follow-up and deaths were not reported. This, plus the fact that it was the only trial using a quasi-random method of patient allocation, led us to test the results without the inclusion of this trial.

There were two outcome measures for the early neonatal period analysis that included data from the Patz 1954 trial. The outcomes to which the Patz trial contributed were RLF (vascular, any stage) and RLF (cicatrical, severe grades). The results for neither of these outcome measures were significantly affected by the exclusion of the Patz trial. Hence, the results of these meta-analyses were not sensitive to the effect of study quality.

DISCUSSION

The answer to the question of what is the optimal therapeutic range of blood oxygen level for preterm/LBW infants to maximise benefits, while minimising harms, remains uncertain.

To date only two randomized trials (Askie 2003; Usher 1973) have attempted to address this question directly. Sinclair 1968 assessed the effects of lower vs. higher blood oxygen levels and other co-interventions in a group of hypoxic, acidaemic low birth weight infants. The related, but now historic, question of restricted vs. liberal oxygen administration was addressed by three randomized trials (Kinsey 1956; Lanman 1954; Patz 1954) in an era before accurate and/or continuous monitoring of infant blood oxygen levels was possible. Both interventions were included in this review, which addresses the general question of the effect of oxygen dose on outcomes for preterm/LBW infants.

In this analysis, restricting oxygen exposure in the early neonatal period significantly reduced the incidence and severity of RLF

without unduly increasing death rates. The results of the largest trial contributing to these outcomes (Kinsey 1956) have often been misinterpreted, with the resulting extrapolation of aggressive restriction of oxygen from birth leading to a substantial increase in mortality rates among preterm/LBW infants in the years following its publication (Cross 1973). This trial did not enrol infants until at least 48 hours of age. It should also be noted that the second largest trial, Patz 1954, did not report any mortality data and this information is not retrievable (Duc 1992). Unfortunately, the confidence intervals around the point estimate for this outcome are quite wide (RR 1.20, 95% CI 0.80-1.80), and the addition of the Patz 1954 mortality data would have been helpful in resolving this issue. It is possible that the difference in RLF rates seen in survivors may be influenced by the trend toward excess deaths caused by the restricted oxygen policy.

Since the publication of these earlier era trials, other authors have attempted to further investigate the association between RLF/ROP and blood oxygen levels. A large, prospective, non-randomized study (Kinsey 1977) involving a detailed survey across five collaborating centres in the USA was undertaken between 1969 and 1972. No definitive relationship between blood oxygen levels and the occurrence of RLF could be established. It should be noted that this analysis was undertaken using the limited information available from intermittent blood gas sampling. The study did find an association between susceptibility to RLF and decreasing birth weight and increasing time in oxygen. However, no guidelines for the optimal range of blood oxygen level were suggested by this study.

Two trials (Sinclair 1968; Usher 1973) that addressed the question of low vs. higher blood oxygen levels in the early neonatal period (< 1 week postnatal age) found no significant effect on death in the early neonatal period, but did not report (in sufficient detail to warrant inclusion) the effect of this intervention on eye or other outcomes. The effects of either of these oxygen administration policies on other clinically meaningful outcomes, including chronic lung disease, long-term growth, neurodevelopment, lung or visual function were not reported.

No further trials were undertaken until a prospective, multicenter, double-blind, randomized, controlled trial (Askie 2003) involving eight collaborating centres in Australia was conducted between 1996 and 2000. There were no significant differences in the rates of ROP at any stage between the lower and higher oxygen saturation target groups in the later neonatal period (≥ 3 weeks postnatal age). There were no significant differences between the groups in mortality rates either. However, this study noted that there was a disadvantage to using higher oxygen saturation targeting because of the increase in the proportion of infants needing oxygen therapy for longer, as well as supplemental oxygen after discharge. Again, this study made no recommendations for an optimal blood oxygen level, but suggested that targeting higher blood oxygen levels may increase the burden of health services for

these infants. This trial enrolled oxygen-dependent infants at 32 weeks postmenstrual age who were at least 3 weeks of age. There is therefore a need to evaluate this therapy when commenced soon after birth as this may alter the rates of ROP or death. A number of trials currently underway are examining this (BOOST NZ (NZ); BOOSTII (Australia); BOOSTII (UK); COT (Canada); SUPPORT (USA)).

All studies included in this review measured eye outcomes. Unlike the pre-1990 studies, the Askie 2003 trial also reported the effect of interventions on growth and development. However, these outcomes were not measured beyond 12 months corrected age and thus studies with longer term outcomes will need to be conducted. Since 2001, several observational studies (Tin 2001; Anderson 2004; Sun 2002; Chow 2003) have been published that have suggested short-term ophthalmic and respiratory outcomes might be significantly improved by a policy of lower oxygen range targeting without causing increases in mortality or long-term morbidity. However, 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. Currently, there are five ongoing randomized trials being conducted to assess the effects of lower vs. higher oxygen saturation levels in extremely preterm infants from birth. The individual patient data from these trials will be combined in a prospective meta-analysis to help resolve this remaining question.

The role of careful, continuous monitoring of oxygen levels on the incidence of retinopathy of prematurity has also been investigated by several authors since the publication of the earlier studies included in this review. Bancalari and co-workers (Bancalari 1987a; Bancalari 1987b; Flynn 1987) conducted the only large randomized trial of continuous transcutaneous PO₂ monitoring to date. This study showed no significant difference in the incidence or severity of ROP, mortality or chronic lung disease in the continuously monitored infants compared with those who received standard (intermittent) monitoring of PO₂ levels. The utility of pulse oximetry monitoring in preventing adverse neonatal outcomes remains largely untested. The value of pulse oximetry in reducing major hypoxic events during anaesthesia among 152 children undergoing surgery has been assessed in one study (Core 1988). Another trial (Watkin 1999) compared near infrared spectroscopy and pulse oximetry in the detection of hypoxaemia in neonates with pauses in nasal airflow. Roemer and colleagues (Roemer 2005) examined the diagnostic power of pulse oximetry, other blood oxygen measures and acid-base measurements for hypoxia in term fetuses. However, randomized controlled trial evidence for the effectiveness of pulse oximetry monitoring in the early neonatal period is still unavailable.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review confirm that (the now historical) policy of unrestricted, unmonitored oxygen therapy has potential harms without clear benefits. However, the question of what is the optimal target range for maintaining blood oxygen levels in preterm/LBW infants in the modern clinical setting from birth or soon thereafter was not answered by the data available for inclusion in this review.

Implications for research

As the question of what is the optimal target range for maintaining blood oxygen levels remains unclear, further research should be undertaken to resolve this important clinical question. An ongoing international collaboration is attempting to address this issue. The BOOSTII trials (BOOST NZ (NZ); BOOSTII (Australia); BOOSTII (UK); COT (Canada); SUPPORT (USA)) are all assessing the effects of higher oxygen levels on infants 27 weeks or less gestational age in terms of both short and long-term outcomes. Results from these trials will be combined in a prospective meta-analysis (known as the NeOProm Collaboration) and will be incorporated into this systematic review as they become available. The STOP-ROP trial (STOP-ROP 2000) assessed the effect of higher oxygen levels on the progression of pre-threshold ROP. The results of this trial are included in a separate Cochrane review entitled: "Supplemental oxygen for the treatment of pre-threshold retinopathy of prematurity" (Lloyd J, Askie LM, Smith J, Tarnow-Mordi WO). It should be noted that this trial did not address the effect of oxygen levels administered in the early neonatal period either as infants were 35.6 weeks postmenstrual age at enrolment into this trial.

ACKNOWLEDGEMENTS

None.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Askie 2003

Methods	<p>Randomization was stratified with the use of a dynamic balancing method to ensure a balance of treatment-group assignment within each stratum defined according to hospital, singleton or multiple birth, and gestational age. Central telephone randomization ensured adequate allocation concealment.</p> <p>The intervention group (standard oxygen) received oxygen to achieve Fn SpO₂ 91-94%, while the control group (high oxygen) received oxygen to achieve Fn SpO₂ 95-98%. Masking of all interventions was achieved by using oximeters designed to display levels either 2% higher or lower than what it really was, thereby giving readings between 93-96%. Caregivers were not aware of the offset level (double-blinding).</p> <p>There were no losses in follow-up. There were detailed power calculations.</p>
Participants	<p>358 infants < 30wks gestation who remained dependent on supplemental oxygen at 32 wks of postmenstrual age. The mean birth weight for standard saturation group was 918g and for high saturation group 916g. Infants were followed and measured at 12 months corrected age.</p>
Interventions	<p>Experimental group (standard oxygen): received oxygen to achieve Fn SpO₂ 91-94%. Intervention treatment applied at 32wks postmenstrual age and maintained for the duration of the supplemental oxygen therapy.</p> <p>Control group (high oxygen): received oxygen to achieve Fn SpO₂ 95-98%. Intervention treatment applied at 32 wks postmenstrual age and maintained for the duration of the supplemental-oxygen therapy.</p>
Outcomes	<p>Worst retinopathy of prematurity (< stage 3)</p> <p>Worst retinopathy of prematurity (stage 3 or 4)</p> <p>Ablative retinal surgery for severe retinopathy of prematurity</p> <p>Death (after randomization)</p> <p>Growth measures:</p> <ul style="list-style-type: none"> - weight - length - head circumference <p>Major developmental abnormality</p> <p>Dependence on supplemental oxygen at 36 wks of postmenstrual age</p> <p>Home-based oxygen therapy & duration of oxygen therapy after randomization</p> <p>Postmenstrual age at cessation of oxygen therapy</p> <p>Duration of assisted ventilation after randomization</p> <p>Postnatal corticosteroids</p> <p>Diuretics for chronic lung disease</p> <p>Length of stay after randomization</p> <p>Postmenstrual age at discharge from hospital</p> <p>Postmenstrual age at time of fully oral feeding</p> <p>Infant rehospitalized</p> <p>Number of health service visits per infant</p>

Askie 2003 (Continued)

Scores on psychological measures
 -Edinburgh postnatal depression scale (mother)
 -infant temperature scale
 -toddler temperament scale
 -parenting stress index, short form
 -impact-on-family scale

Notes

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was stratified with the use of a dynamic balancing method.
Allocation concealment?	Yes	Central telephone randomization.
Blinding? All outcomes	Yes	Oxygen saturation levels were adjusted to display a value 2% higher than the actual saturation in infants in the standard O2 group or 2% lower than the actual saturation in infants in the high-saturation group.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up for outcome data.
Free of selective reporting?	Yes	All outcomes were reported.

Kinsey 1956

Methods	Central telephone randomization ensured adequate allocation concealment. The ratio of experimental group : control group was 2:1 in first 3 months of enrolment. Following that, 574 infants were consecutively allocated to the experimental group and had no concurrent controls. These infants are not included in this review. The number of infants excluded before randomization is not known. Randomization was stratified by birth weight categories and institution. The intervention was not blinded and the blinding of outcome assessments is unclear. The follow-up rate for outcome measures was 97%. There were detailed power calculations.
Participants	212 infants with BW <1500g who survived to 48 hours. Enrolment commenced in July 1953. The mean BW in the two groups was 1242g (restricted) and 1234g (liberal) respectively. Infants were followed until 2.5 months of age.
Interventions	Experimental group (restricted oxygen): received oxygen only if clinical condition indicated and maximum FiO ₂ permitted was 0.5. Control group (liberal oxygen): received supplemental oxygen in excess of 50% for a minimum of 28 days and were then weaned over 3 days.

Kinsey 1956 (Continued)

Outcomes	Vascular RLF (any stage) in survivors Vascular RLF (severe stages) in survivors Cicatrical RLF (any grade) in survivors Cicatrical RLF (severe grades) in survivors Mortality (48 hours-40 days) Of the 144 infants assigned to the restricted oxygen group, 36 died before 40 days and 4 were lost to follow-up. There were 15 deaths and no losses to follow-up among the 68 infants allocated to the liberal oxygen group.
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Notes

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Block and stratified randomization.
Allocation concealment?	Yes	Central telephone randomization.
Blinding? All outcomes	No	Blinding not stated.
Incomplete outcome data addressed? All outcomes	Yes	Follow-up was 97%. Reasons were given for loss to follow-up (e.g. death)
Free of selective reporting?	Yes	There were 21 tables and 8 appendices tables of results and measured data reporting various analyses of the outcome data and breakdown of the characteristics of the populations from all the participating centres.

Lanman 1954

Methods	Infants were randomized by random numbers, method unspecified, and thus allocation concealment is unclear. There was no blinding of the intervention and it is unknown if outcome assessments were done blinded to treatment allocation. There was only one loss to follow-up of the 86 infants enrolled. Power calculations were inadequate with the completion of the study being determine by a date specified one year in advance.
Participants	86 infants with BW 1000-1850g admitted within 12 hours of birth. Infants were followed until 3 months age.
Interventions	Experimental group (restricted oxygen): only received oxygen when cyanosed, at a maximum FiO ₂ of 0.5. The mean FiO ₂ received by this group was 0.38. Control group (liberal oxygen): received supplemental oxygen for a minimum of 2 weeks or until reaching 1500g, and were then weaned abruptly. The mean FiO ₂ received by this group was 0.69.

Lanman 1954 (Continued)

Outcomes	Vascular RLF (any stage) in survivors Cicatricial RLF (any grade) in survivors Mortality (12 hours-3 months)
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Notes

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers, but method was not specified.
Allocation concealment?	Unclear	Allocation was in order of admission by random numbers but method was not specified. Allocated to one of 4 groups: high oxygen, high oxygen + estrogen given orally, low oxygen, & low oxygen + estrogen given orally.
Blinding? All outcomes	No	For restricted oxygen intervention, oxygen was given only when infants were cyanosed, so blinding would not have been easily done.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up, and infants who were lost to follow-up were accounted for.
Free of selective reporting?	Yes	All participants and outcomes were reported, even those that were lost to follow-up were reported.

Patz 1954

Methods	Quasi-random treatment allocation, based on alternate admission basis. Allocation concealment was thus inadequate. There was no blinding of the intervention and it is unclear whether outcome assessments were blinded to treatment allocation. Attrition due to deaths or losses to follow-up are not reported, so it is unclear whether there was complete outcome measure ascertainment. No power calculations were reported.
Participants	An unknown number of very low birthweight infants (≤ 1500 g) were enrolled from Jan 1951 to May 1953. 120 infants survived and had eye outcome assessments completed by 6 months age and were included in the analysis.
Interventions	Experimental group (restricted oxygen): infants received oxygen only for clinical indications, and to a maximum FiO_2 of 0.4. The range of duration of oxygen in this group was 1 day - 2 weeks. Once weaning was indicated, it proceeded over 1-3 days.

Patz 1954 (Continued)

Control group (liberal oxygen): infants were placed in supplemental oxygen of 60-70% for 4-7 weeks, then weaned over one week.

Outcomes
 Vascular RLF (any stage) in survivors
 Cicatricial RLF (severe grades) in survivors
 Cicatricial RLF (severe grades), BW <1000g, in survivors
 There are no data available, either published or unpublished, on mortality rates. The number of infants allocated to each group was not reported, hence outcome data can only be expressed in relation to the surviving infants presenting for follow-up assessment.

Notes

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Quasi-random allocation based on alternate admission basis.
Allocation concealment?	No	Quasi-random allocation based on alternate admission basis.
Blinding? All outcomes	No	Blinding not stated. Also, the experimental and control interventions were applied for different lengths of time, so treatment differences would have been obvious.
Incomplete outcome data addressed? All outcomes	Unclear	The focus of results seemed to be on qualitative histological data. The quantitative results seemed to report on all outcomes.

Sinclair 1968

Methods
 Randomized to one of 4 treatment groups, using sealed envelopes and thus allocation concealment was adequate. There was no blinding of treatment intervention, and it is unclear whether there was blinding of outcome assessments. No power calculations were reported. Short-term follow up was complete.

Participants
 20 infants with BW 1000-2500g less than 24 hours age who were hypoxic and acidemic were included.

Interventions
 Infants were randomized to one of four treatment groups including combinations of the following treatments: restricted vs. liberal ambient oxygen, rapid vs. slow alkali infusion, assisted vs. spontaneous ventilation. There was random allocation of the other two treatments within the two oxygen therapy groups, hence the data from this trial were included in the review.
 Experimental group (restricted oxygen): supplemental oxygen, to a maximum of 35%, to keep PaO₂ 50-120 mmHg. If PaO₂ fell below 40 mmHg or infant became bradycardic, could give unlimited oxygen and would be considered as a treatment failure.

Sinclair 1968 (Continued)

Control group (liberal oxygen): received 100% headbox oxygen for first 2 hours, then aimed to maintain PaO₂ at 50-120 mmHg using any FiO₂ needed.

Outcomes	<p>Mortality (any)</p> <p>Physiological measures including:</p> <ul style="list-style-type: none"> - acid-base balance - PaO₂ levels - percentage right-left shunt - serum electrolytes, blood urea nitrogen, serum lactate - urinary net acid excretion - plasma bicarbonate - "apparent" bicarbonate space <p>Long-term neurological assessments reported as "in progress" in the paper were never completed (personal communication J. Sinclair, July 1998).</p>
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Notes

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Sealed envelopes & stratified
Allocation concealment?	Yes	Random allocation to 1 of 4 treatment groups, using sealed envelopes; stratified by severity of A (severe vs. moderate).
Blinding? All outcomes	No	Blinding not stated.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up (but not specified). Short-term follow-up was complete.
Free of selective reporting?	Yes	There were 14 tables and 15 figures of results and analysed data reporting various analyses of the outcome data. It seemed all outcomes were reported.

Usher 1973

Methods	Infants were randomized by a stratified random sampling technique. Allocation concealment is unclear. There was no blinding of the intervention. One author was unblinded to the treatment allocation, but is unclear whether this author was involved in outcome assessments. No power calculations were reported. Early outcome data were reported completely. However, long-term outcome data included only 15% of the enrolled infants and thus have not been included in this review.
Participants	150 infants with a diagnosis of respiratory distress syndrome or BW <1000g were eligible for inclusion. The numbers excluded prior to randomization are not reported.
Interventions	Experimental group (low PaO ₂): infants received oxygen only if their PaO ₂ fell below 40 mmHg or PcapO ₂ fell below 35 mmHg. Sufficient oxygen was used to maintain these tensions. Control group (high PaO ₂): infants were kept in a minimum of 40% oxygen for 72 hours. Aim was to maintain PaO ₂ 80-120 mmHg or PcapO ₂ 50-60 mmHg. Mechanical ventilation was not available to either group.
Outcomes	Mortality (any) Mortality (respiratory) Descriptive results of respiratory failure measures were reported (such as retractions, grunting, respiratory pattern and rate, chest Xray changes).

Notes

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Stratified random sampling technique.
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Blinding not stated.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up for early outcomes, but not for late outcomes. Only 15% follow-up at 10yrs (Coates).
Free of selective reporting?	Yes	There were 10 tables and 16 figures of results and analysed data reporting various analyses of the outcome data. It seemed that all outcomes were reported.

Characteristics of excluded studies *[ordered by study ID]*

Bard 1996	Infants were not randomly assigned to target two different arterial blood oxygen saturations (90% and 95%). Infants acted as their own controls. This was not a random or quasi-random trial and was thus excluded from the review.
Cunningham 1995	This non-randomized, retrospective study assessed the effects of variability of oxygen levels, as measured by transcutaneous oxygen monitoring, on the incidence of retinopathy of prematurity. Patient allocation was not randomized, and thus the study was excluded from the review.
Deulofeut 2007	This was a non-randomized study of infants from January 2000 to December 2004, where there was a change from SpO ₂ 92-100% to SpO ₂ 85-93% from January 2003. Since allocation of treatment was non-randomized, this study was excluded from the review.
Engleson 1958	This non-randomized trial addressed a different question from that under review. It examined the effects of keeping preterm infants at oxygen concentrations below that of room air, and was thus not included in the review.
Fitzgerald 1998	Infants in this study were randomized to receive either air/usual supplementary oxygen (to maintain SpO ₂ >93%) or increased supplementary oxygen (to maintain SpO ₂ >97%) only for one night whilst the sleep study was done. Included trials randomized infants to an ongoing policy of higher / lower SpO ₂ . Infants also already had CLD at the start of the study (which was one of this study's population inclusion criteria).
Gaynon 1997	The study was a retrospective analysis of different target ranges of oxygen saturation on the incidence of ROP. There was no random allocation of patients to different treatment groups, thus the trial was excluded from the review.
Kitchen 1978	This study was a randomized trial of a "package" of intensive care, including intravenous glucose, umbilical arterial catheterisation, bicarbonate infusion, and high PaO ₂ levels, vs. the standard neonatal care regimen of the late 1960s. The trial was excluded from the review because the entire "package" of interventions, rather than the separate elements within it, was the randomized intervention. Thus, other interventions that could affect clinical outcomes were unbalanced between oxygen exposure groups.
Lundstrom 1995	This randomized trial addressed a different question from that under review. It compared the use of atmospheric air vs. 80% oxygen for preterm infants during initial stabilization in the delivery room, and was thus excluded from the review.
Mendicini 1971	This study was a randomized trial of a "package" of intensive care, including intravenous glucose, bicarbonate infusion, and high PaO ₂ levels, vs. the standard neonatal care regimen of the late 1960s. The trial was excluded from the review because the entire "package" of interventions, rather than the separate elements within it, was the randomized intervention. Thus, other interventions that could affect clinical outcomes were unbalanced between oxygen exposure groups.
Schulze 1995	This was a non-randomized, crossover trial comparing the effects of two different oxygen saturation target ranges on cardiac output, oxygen extraction, and oxygen consumption in mechanically ventilated, low birth weight infants. As treatment allocation was not random or quasi-random, the trial was excluded from the review.

(Continued)

STOP-ROP 2000	This trial included preterm/LBW infants with pre-threshold ROP. The intervention tested was supplemental oxygen for the treatment of pre-threshold ROP, not a preventative strategy. The results of this trial will be included in a separate Cochrane review entitled: "Supplemental oxygen in the treatment of pre-threshold retinopathy of prematurity" (Lloyd J, Askie LM, Smith J, Tarnow-Mordi WO).
Wallace 2007	This was a non-randomized retrospective cohort study of infants. Eligible infants born between October 1, 2002, and July 31, 2003, were given SpO ₂ 98-100%. Eligible infants born between January 1, 2004, and April 30, 2005, were given SpO ₂ 90-96%. Since allocation of treatment was non-randomized, this study was excluded from the review.
Weintraub 1956	The planned scheme of quasi-random, alternate allocation was not adhered to, resulting in the possibility of substantial selection bias, and the study was thus excluded from the review.
Wright 2006	This was a non-randomized prospective observational study of infants from 3 centres where there was a change in SpO ₂ from >90%, 89-94% or 90-95% to 83-93% for all centres. Eligible infants born after the transition year were given the lower SpO ₂ treatment. Since allocation of treatment was non-randomized, this study was excluded from the review.

Characteristics of ongoing studies [ordered by study ID]

BOOST NZ (NZ)

Trial name or title	Benefits of oxygen saturation targeting trial (NZ)
Methods	<p>Infants are randomized centrally by telephone, using a computerized interactive voice response system. Randomization is stratified by site, sex, gestation and inborn and outborn. Computer-generated randomization lists are prepared by an independent statistician and not accessible to staff involved in the daily care of infants. The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO₂ by +/-3% points. Staff will (a) target SpO₂ 88-92% and (b) aim to maximize time spent with SpO₂ between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO₂. Outside 85-95%, study oximeters read actual SpO₂.</p> <p>320 infants will be enrolled. This data will be analysed with the data from the Australian BOOST-II trial. A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.</p>
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO ₂ 85-89%) vs higher (Fn SpO ₂ 91-95%) O ₂ targeting
Outcomes	Survival and major disability at 2 years corrected age, other secondary outcomes
Starting date	2006
Contact information	Professor Brian Darlow; Email: brian.darlow@chmeds.ac.nz

BOOST NZ (NZ) (Continued)

Notes

BOOSTII (Australia)

Trial name or title	Benefits of oxygen saturation targeting trial 2 (Australia)
Methods	<p>Infants are randomized centrally by telephone, using a computerized interactive voice response system. Randomization is stratified by site, sex, gestation and inborn and outborn. Computer-generated randomization lists are prepared by an independent statistician and not accessible to staff involved in the daily care of infants. The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO₂ by +/-3% points. Staff will (a) target SpO₂ 88-92% and (b) aim to maximize time spent with SpO₂ between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO₂. Outside 85-95%, study oximeters read actual SpO₂.</p> <p>A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.</p>
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO ₂ 85-89%) vs higher (Fn SpO ₂ 91-95%) O ₂ targeting
Outcomes	Death or major disability at 2 years corrected age, other secondary outcomes
Starting date	2006
Contact information	Alpana Ghadge; Tel: +61 2 9562 5000; Fax: +61 2 9562 5094

Notes

BOOSTII (UK)

Trial name or title	Benefits of oxygen saturation targeting trial 2 (UK)
Methods	<p>Infants are randomized centrally by a secure website at the National Perinatal Epidemiology Unit (NPEU) in Oxford. A computer-generated program that used minimization will be used to ensure balanced allocation to the two arms of the trials in each recruiting unit from a knowledge of weight, gestation and sex at birth. The NPEU is write the randomization program and hold the code.</p> <p>The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO₂ by +/-3% points. Staff will (a) target SpO₂ 88-92% and (b) aim to maximize time spent with SpO₂ between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO₂. Outside 85-95%, study oximeters read actual SpO₂.</p> <p>A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.</p> <p>Data analysis will be intention to treat.</p>

BOOSTII (UK) (Continued)

Participants	Infants <28 weeks' gestation at birth and <12 hours old (24 hours old if the baby is outborn)
Interventions	Lower (Fn SpO ₂ 85-89%) vs higher (Fn SpO ₂ 91-95%) O ₂ targeting
Outcomes	Death or serious neurosensory disability at 2 years corrected age, other secondary outcomes
Starting date	2007
Contact information	Professor Peter Brocklehurst; Email: peter.brocklehurst@npeu.ox.ac.uk
Notes	

COT (Canada)

Trial name or title	Canadian oxygen trial
Methods	<p>Infants are randomized centrally by telephone. Randomization is stratified by gestational age (23-25 and 26-27 weeks) and by study centre. Allocation will incorporate variable block sizes. The concealed study allocation will be determined, in advance, using a computer-based random number generator.</p> <p>The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO₂ by +/-3% points. Staff will (a) target SpO₂ 88-92% and (b) aim to maximize time spent with SpO₂ between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO₂. Outside 85-95%, study oximeters read actual SpO₂.</p> <p>A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.</p>
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO ₂ 85-89%) vs higher (Fn SpO ₂ 91-95%) O ₂ targeting
Outcomes	Death or major disability (cognition, neuromotor function, vision, hearing) at 2 years corrected age, other secondary outcomes
Starting date	October 2006
Contact information	Dr Barbara Schmidt; Email: schmidt@mcmaster.ca
Notes	

SUPPORT (USA)

Trial name or title	The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants
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SUPPORT (USA) (Continued)

Methods	<p>This is a prospective, randomized, factorial 2x2 design multi-centre trial. Randomization will be stratified by gestational age, and will be done utilizing double-sealed envelopes.</p> <p>The individual factors to be tested will be: 1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (<1 hour) surfactant and mechanical ventilation; 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.</p> <p>The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO₂ by +/-3% points. Staff will (a) target SpO₂ 88-92% and (b) aim to maximize time spent with SpO₂ between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO₂. Outside 85-95%, study oximeters read actual SpO₂.</p> <p>Power has been calculated to be 80% for detecting an absolute difference of 10% in the primary and secondary outcomes, with a sample size of 1310.</p>
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO ₂ 85-89%) vs higher (Fn SpO ₂ 91-95%) O ₂ targeting
Outcomes	Death or major disability at 2 years corrected age, survival without BPD at 36 weeks, survival without ROP, other secondary outcomes
Starting date	February 2005
Contact information	Dr Neil Finer; Email: nfiner@ucsd.edu
Notes	

DATA AND ANALYSES

Comparison 1. Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any)	2	298	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.80, 1.90]
2 Cicatricial RLF (any grade) in survivors	2	221	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.11, 0.58]
3 Vascular RLF (any stage) in survivors	3	341	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.25, 0.46]
4 Vascular RLF (severe stages) in survivors	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.85]
5 Cicatricial RLF (severe grades) in survivors	2	277	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.07, 0.50]
6 Death or vascular (RLF (any stage)	2	298	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.48, 0.72]
7 Death or cicatricial RLF (any grade)	2	298	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.07]
8 Cicatricial RLF (severe grades) in survivors (excluding Patz 1954)	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.11, 0.93]
9 Vascular RLF (any stage) in survivors (excluding Patz 1954)	2	221	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.26, 0.51]

Comparison 2. Restricted versus liberal oxygen therapy (BW<1000g) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cicatricial RLF (severe grades) in survivors	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.02, 3.79]

Comparison 3. Lower versus higher blood oxygen levels (all preterm/LBW infants) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any)	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.57, 1.44]

Comparison 4. Lower versus higher blood oxygen levels (BW<1250g) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.75, 1.58]

Comparison 5. Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.19, 1.64]
2 ROP (any stage) in survivors	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.19]
3 ROP >Stage 2 in survivors	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.77, 2.16]
4 ROP Stage 4 or 5 or blindness in survivors	1	358	Risk Ratio (M-H, Fixed, 95% CI)	5.06 [0.60, 42.85]
5 Death or ROP >Stage 2	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.69, 1.68]
6 Death or ROP Stage 4 or 5 or blindness	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.43, 2.37]
7 Dependence on supplemental oxygen at 36 weeks of postmenstrual age	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.59, 0.87]
8 Postnatal corticosteroids	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.05]
9 Diuretics for chronic lung disease	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.68, 1.05]
10 Major developmental abnormality at 12 months corrected age	1	334	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.71, 1.53]

Comparison 6. Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period

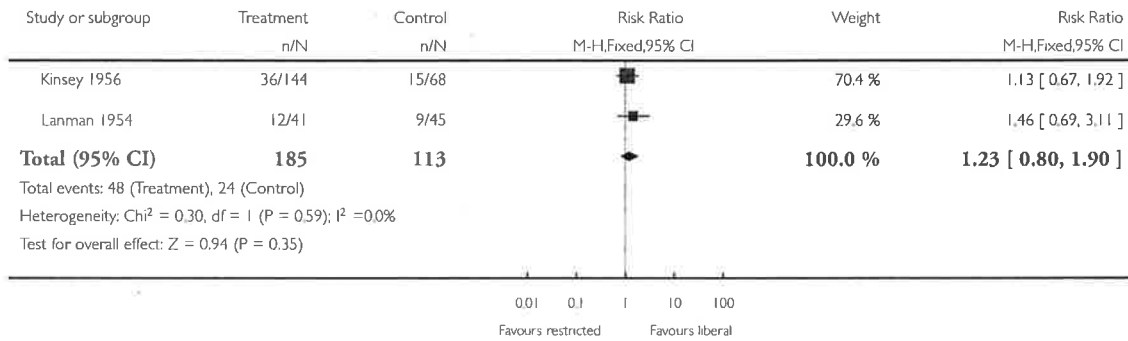
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ROP Stage 3 or 4	1	256	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.85, 2.36]
2 Blindness	1	240	Risk Ratio (M-H, Fixed, 95% CI)	4.14 [0.47, 36.46]

Analysis 1.1. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 1 Death (any).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 1 Death (any)

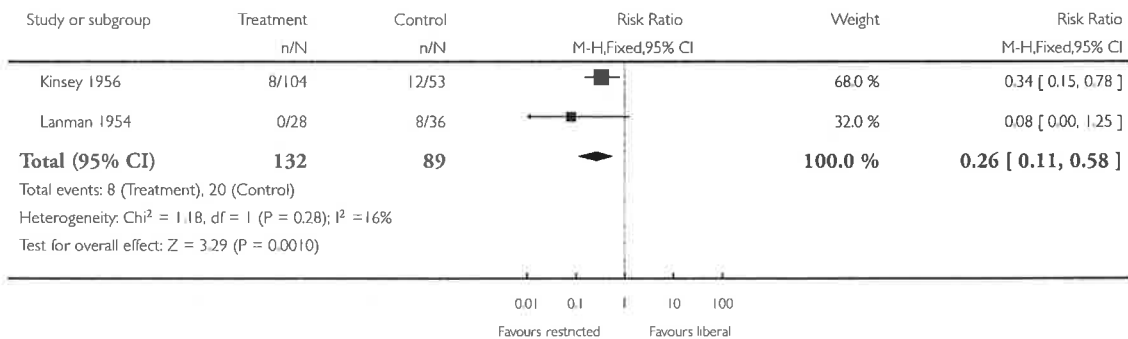


Analysis 1.2. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 2 Cicatricial RLF (any grade) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 2 Cicatricial RLF (any grade) in survivors

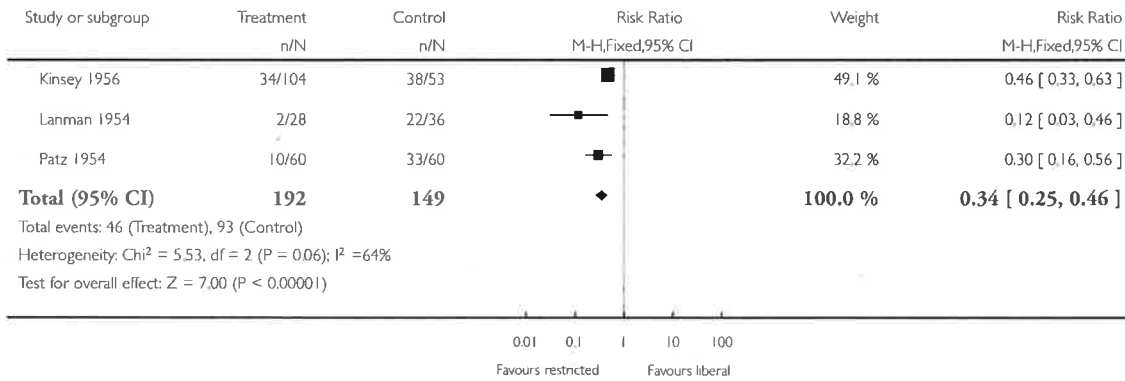


Analysis 1.3. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 3 Vascular RLF (any stage) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 3 Vascular RLF (any stage) in survivors

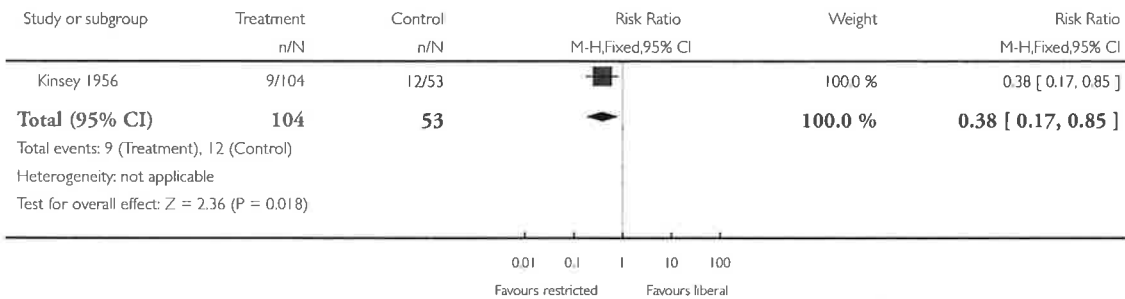


Analysis 1.4. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 4 Vascular RLF (severe stages) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 4 Vascular RLF (severe stages) in survivors

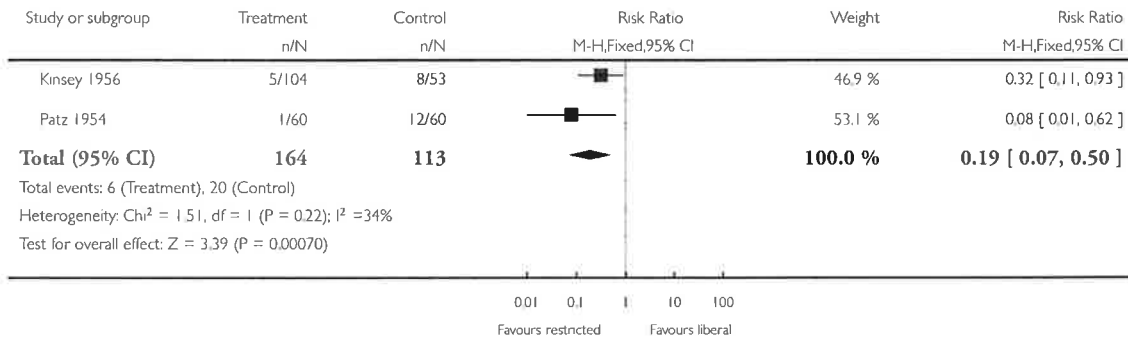


Analysis 1.5. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 5 Cicatricial RLF (severe grades) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 5 Cicatricial RLF (severe grades) in survivors

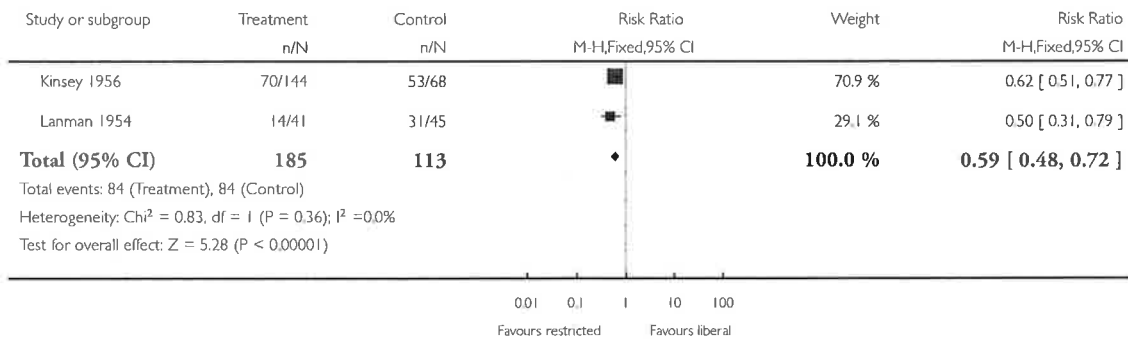


Analysis 1.6. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 6 Death or vascular (RLF (any stage)).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 6 Death or vascular (RLF (any stage))

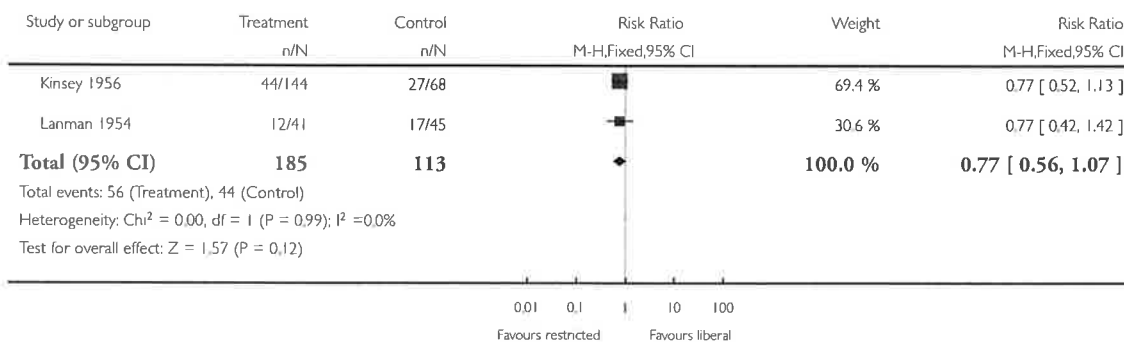


Analysis 1.7. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 7 Death or cicatricial RLF (any grade).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 7 Death or cicatricial RLF (any grade)

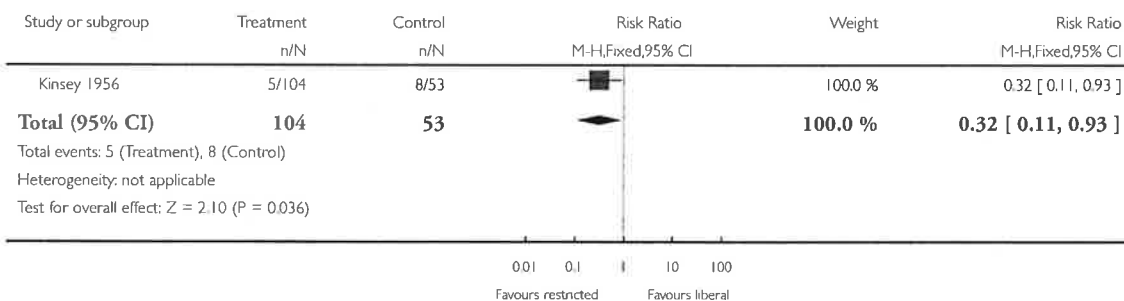


Analysis 1.8. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 8 Cicatricial RLF (severe grades) in survivors (excluding Patz 1954).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 8 Cicatricial RLF (severe grades) in survivors (excluding Patz 1954)

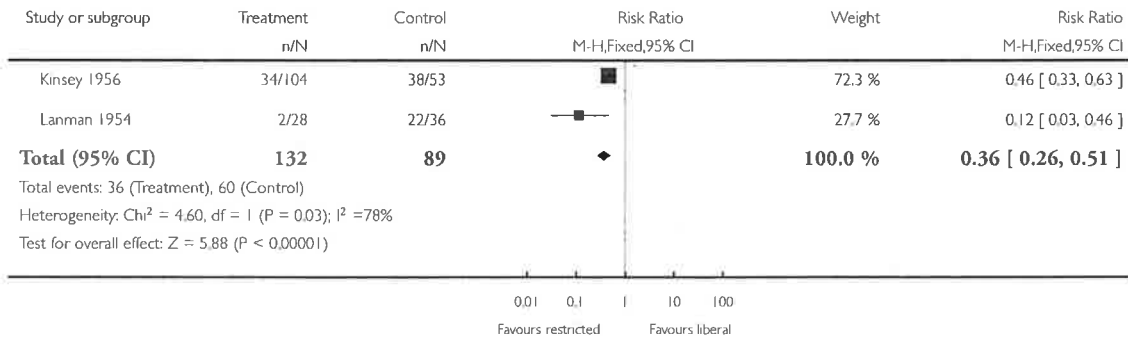


Analysis 1.9. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 9 Vascular RLF (any stage) in survivors (excluding Patz 1954).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 9 Vascular RLF (any stage) in survivors (excluding Patz 1954)

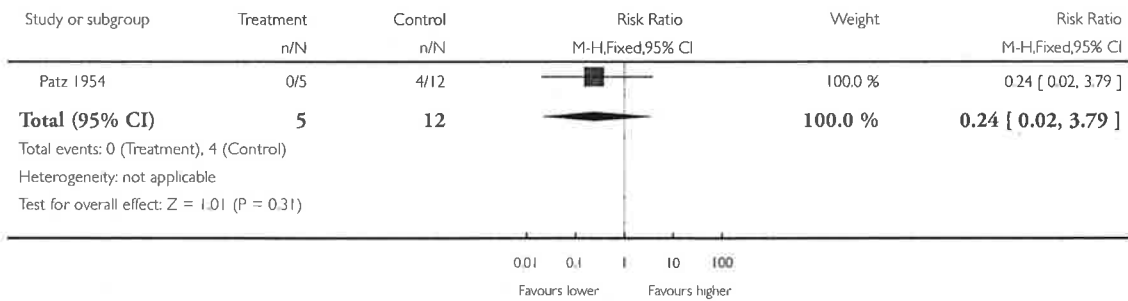


Analysis 2.1. Comparison 2 Restricted versus liberal oxygen therapy (BW<1000g) in early neonatal period, Outcome 1 Cicatricial RLF (severe grades) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 2 Restricted versus liberal oxygen therapy (BW<1000g) in early neonatal period

Outcome: 1 Cicatricial RLF (severe grades) in survivors

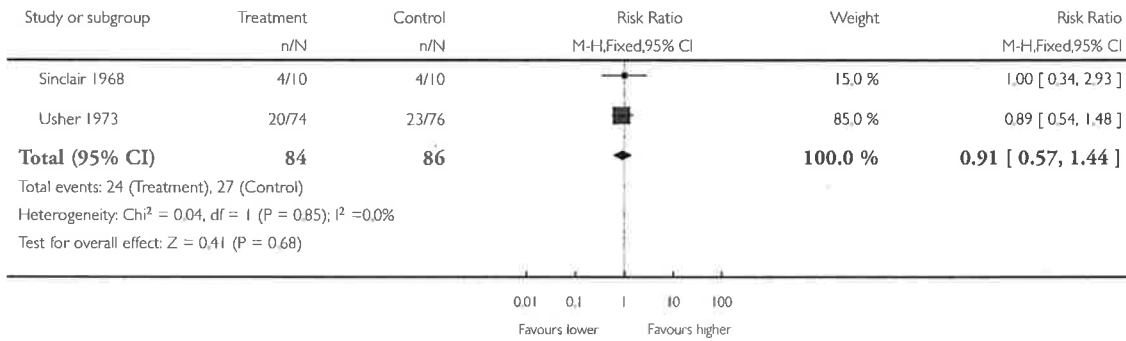


Analysis 3.1. Comparison 3 Lower versus higher blood oxygen levels (all preterm/LBW infants) in early neonatal period, Outcome 1 Death (any).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 3 Lower versus higher blood oxygen levels (all preterm/LBW infants) in early neonatal period

Outcome: 1 Death (any)

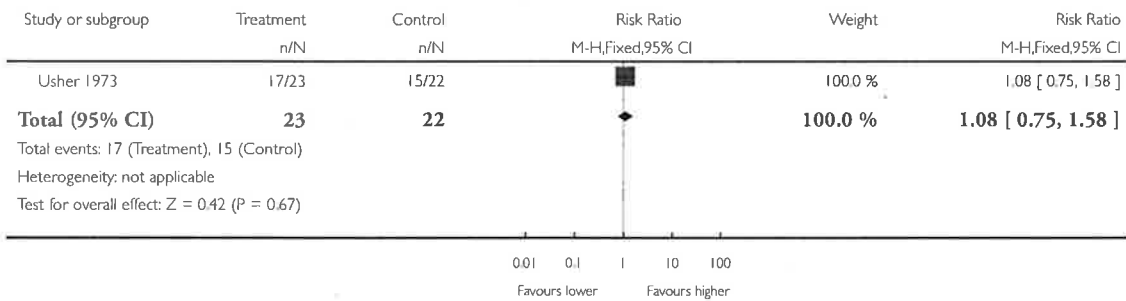


Analysis 4.1. Comparison 4 Lower versus higher blood oxygen levels (BW<1250g) in early neonatal period, Outcome 1 Death (any).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 4 Lower versus higher blood oxygen levels (BW<1250g) in early neonatal period

Outcome: 1 Death (any)

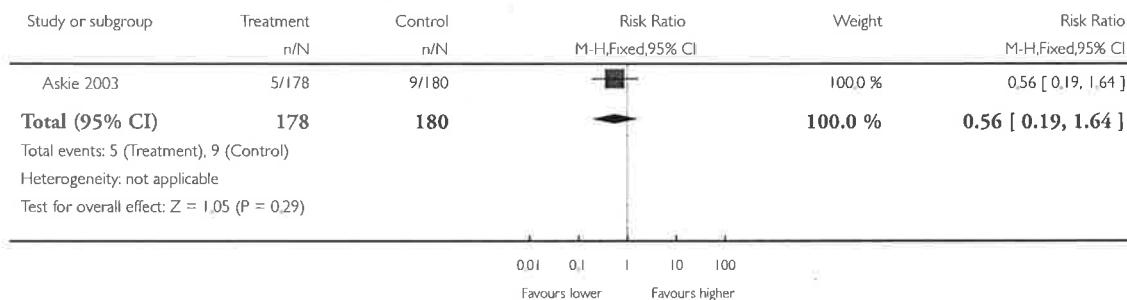


Analysis 5.1. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 1 Death.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 1 Death

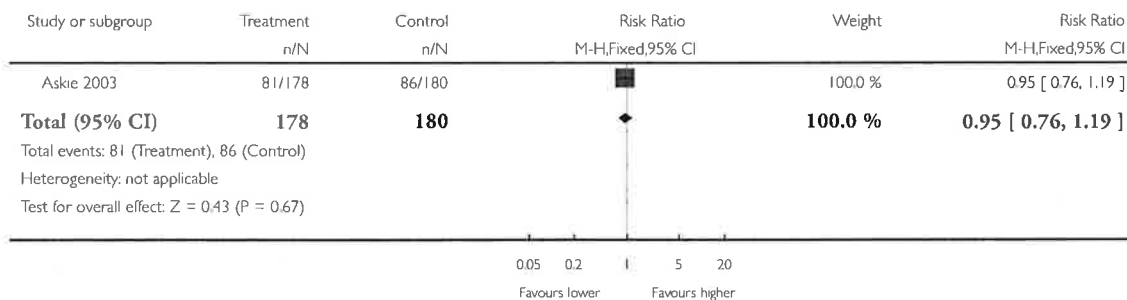


Analysis 5.2. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 2 ROP (any stage) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 2 ROP (any stage) in survivors

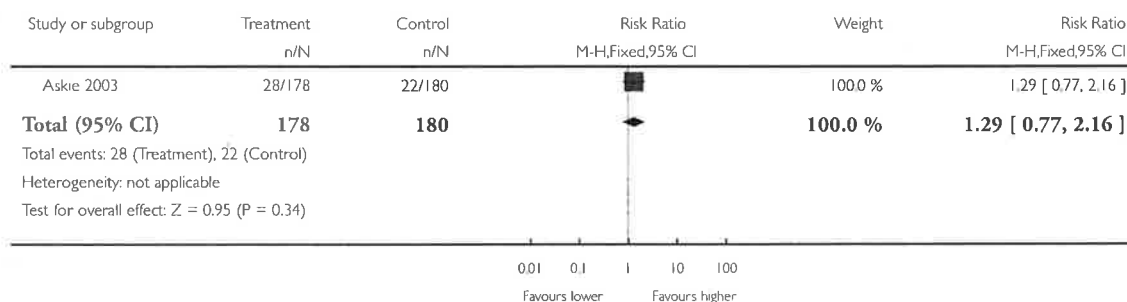


Analysis 5.3. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 3 ROP >Stage 2 in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 3 ROP >Stage 2 in survivors

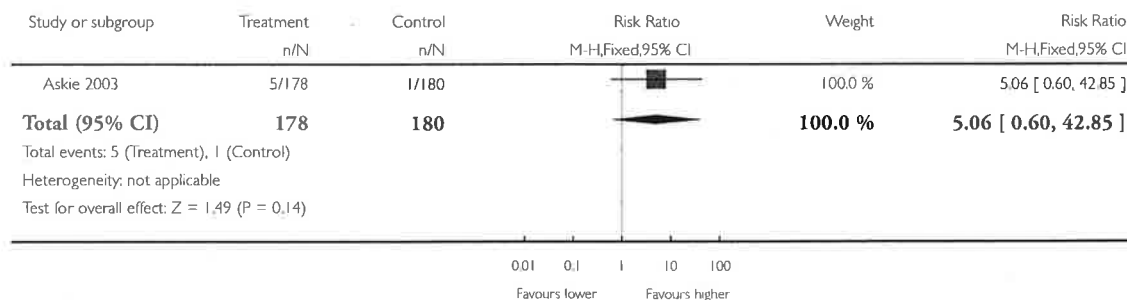


Analysis 5.4. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 4 ROP Stage 4 or 5 or blindness in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 4 ROP Stage 4 or 5 or blindness in survivors

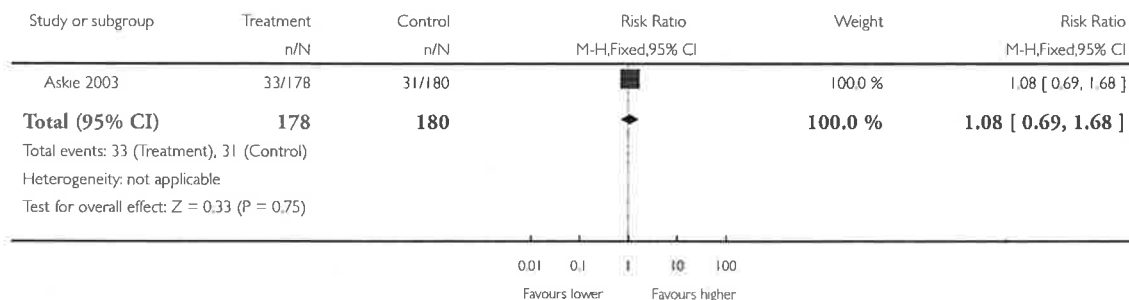


Analysis 5.5. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 5 Death or ROP >Stage 2.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 5 Death or ROP >Stage 2

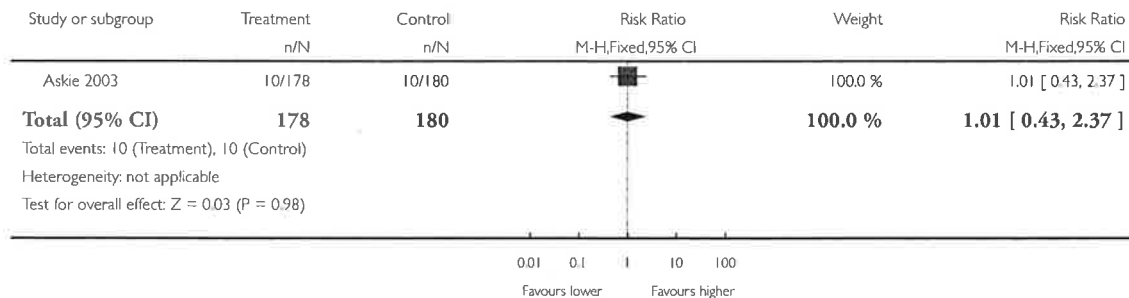


Analysis 5.6. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 6 Death or ROP Stage 4 or 5 or blindness.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 6 Death or ROP Stage 4 or 5 or blindness

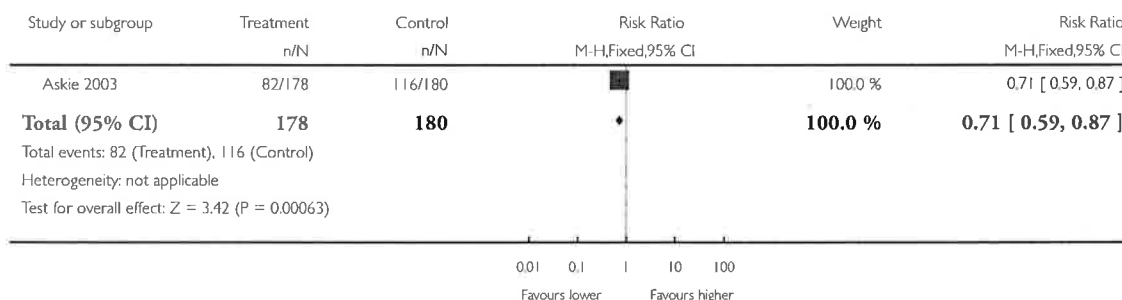


Analysis 5.7. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 7 Dependence on supplemental oxygen at 36 weeks of postmenstrual age.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 7 Dependence on supplemental oxygen at 36 weeks of postmenstrual age

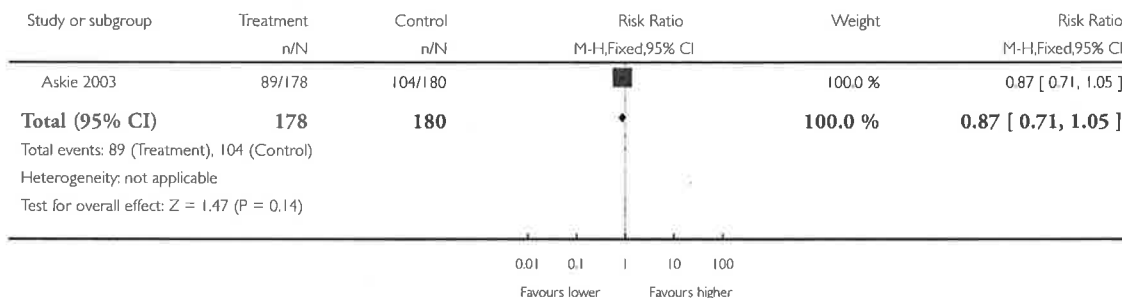


Analysis 5.8. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 8 Postnatal corticosteroids.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 8 Postnatal corticosteroids

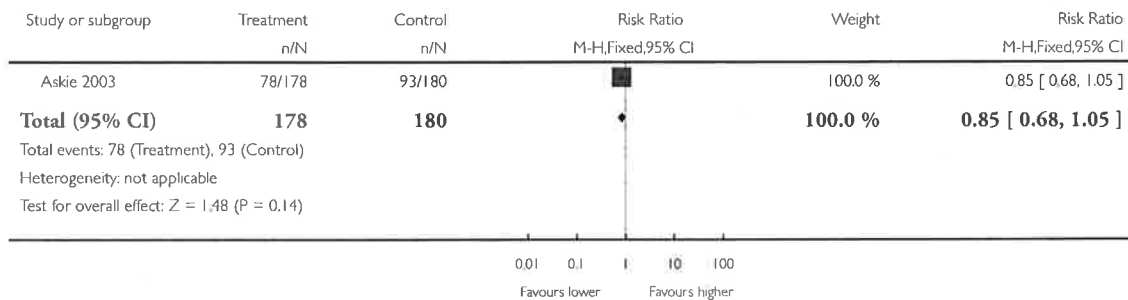


Analysis 5.9. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 9 Diuretics for chronic lung disease.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 9 Diuretics for chronic lung disease

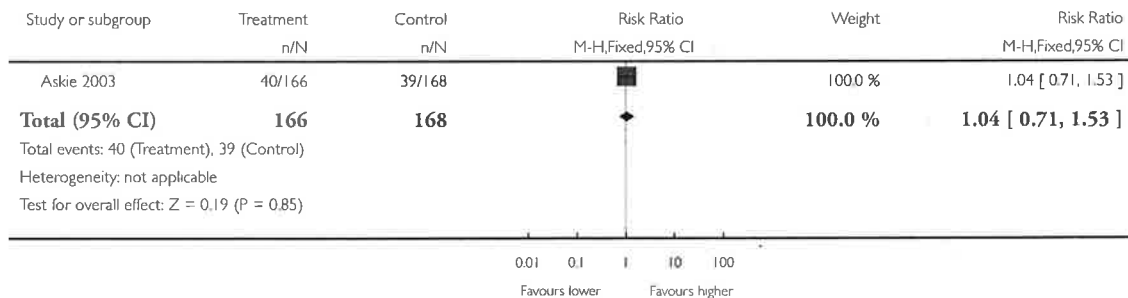


Analysis 5.10. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 10 Major developmental abnormality at 12 months corrected age.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 10 Major developmental abnormality at 12 months corrected age

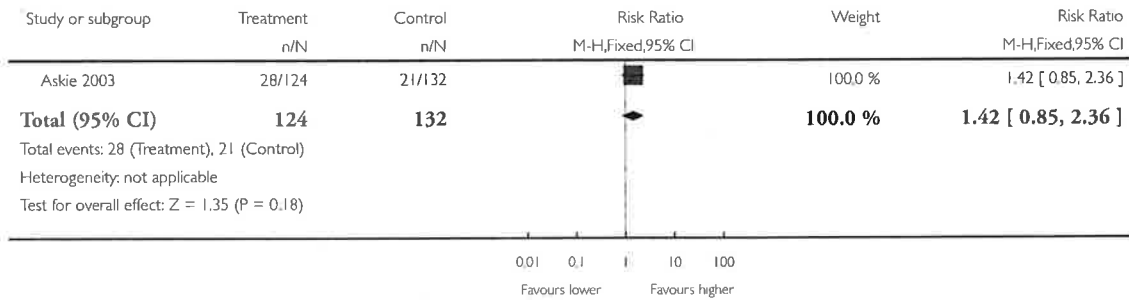


Analysis 6.1. Comparison 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period, Outcome 1 ROP Stage 3 or 4.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period

Outcome: 1 ROP Stage 3 or 4

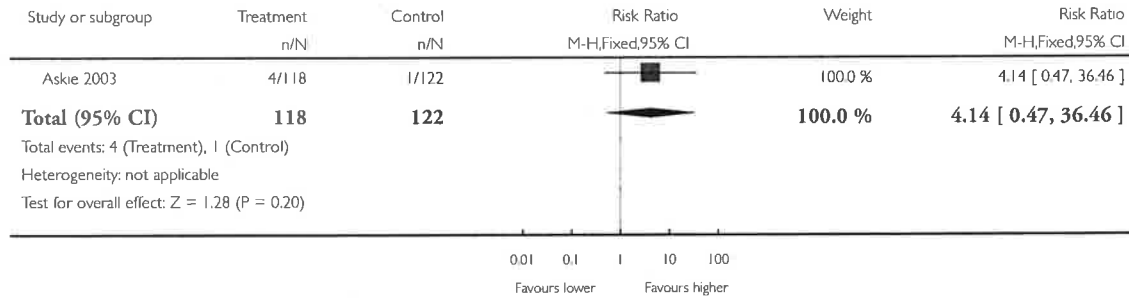


Analysis 6.2. Comparison 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period, Outcome 2 Blindness.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period

Outcome: 2 Blindness



WHAT'S NEW

Last assessed as up-to-date: 14 August 2008.

13 May 2009 Amended Minor amendment - References Watkin and Roemer added

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 2, 1999

14 August 2008	New search has been performed	This review updates the existing review "Restricted versus liberal oxygen for preventing morbidity and mortality in preterm or low birth weight infants" published in the Cochrane Database of Systematic Reviews. This update includes an updated literature search, revised Background section including RLF/ROP cross-classification information and references, revised data analysis with a new included study, updated Discussion and conclusion sections, updated information regarding ongoing clinical trials.
14 August 2008	New citation required but conclusions have not changed	Substantive amendment
25 January 2008	Amended	Converted to new review format.
1 October 2003	New search has been performed	This review updates the existing review "Restricted versus liberal oxygen for preventing morbidity and mortality in preterm or low birth weight infants" which was published in the Cochrane Library Issue 2, 2001. The background section has additional references; The STOP-ROP 2000, trial previously listed as ongoing, has now been listed as an excluded trial and will be included in another Cochrane systematic review entitled "Supplemental oxygen in the treatment of pre-threshold retinopathy of prematurity" (Lloyd J, Askie LM, Smith J, Tarnow-Mordi WO); a synopsis and a background section to the abstract have also been added. No new trials were identified as a result of the most recent search, and hence no substantive changes have been made to either the results or conclusions of the review.

CONTRIBUTIONS OF AUTHORS

Askie and Henderson-Smart developed the original protocol for this review, as well as doing the original literature searching, background, data analysis, discussion and conclusions. Askie and Henderson-Smart also contributed to the updated version of the review. Ko updated the review with an updated literature search, background with RLF/ROP cross-classification information and references, data analysis with the new included trial, updated the discussion and conclusions, updated the information on the ongoing clinical trials, and created the GRADE summary of findings tables which will be

included at a later date. Askie and Henderson-Smart reviewed this.

DECLARATIONS OF INTEREST

Askie and Henderson-Smart have conducted and published a randomized, controlled trial of the effect of higher vs. standard oxygen saturation targeting on long-term growth and development of preterm infants.

SOURCES OF SUPPORT

Internal sources

- NHMRC Clinical Trials Centre, University of Sydney, Australia.
- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.

External sources

- Department of Public Health and Community Medicine, University of Sydney, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol, visual function was to be recorded only in the first year of life, but in the review it was expanded to measure long-term visual function. The outcomes from long-term visual function observations fit well with the original protocol and subsequent review outcome measures of long-term growth and neurodevelopment.

In the current review, results have been split into observations made in the early neonatal period of life and the later neonatal period of life. This differentiation was not stated in the protocol. The splitting of the observations was due to the large time gap between when infants commenced the different oxygen strategies: either early in the neonatal period (< 1 week) and later in the neonatal period (\geq 3 weeks postnatal age).

As stated in the review, some long-term growth and development measures could not be measured due to no data being available for those outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Oxygen Inhalation Therapy [adverse effects]; Infant, Low Birth Weight [*physiology]; Infant, Newborn; Infant, Premature [*physiology]; Infant Mortality; Oxygen [administration & dosage; adverse effects; *blood]; Partial Pressure; Randomized Controlled Trials as Topic; Retinopathy of Prematurity [etiology]

MeSH check words

Humans

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, April 25, 2013 10:26 AM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Fwd: SUPPORT study issue still unresolved

Spoke with Bill, he's on it. (b) (5)
(b) (5)

Sent from my iPhone

Begin forwarded message:

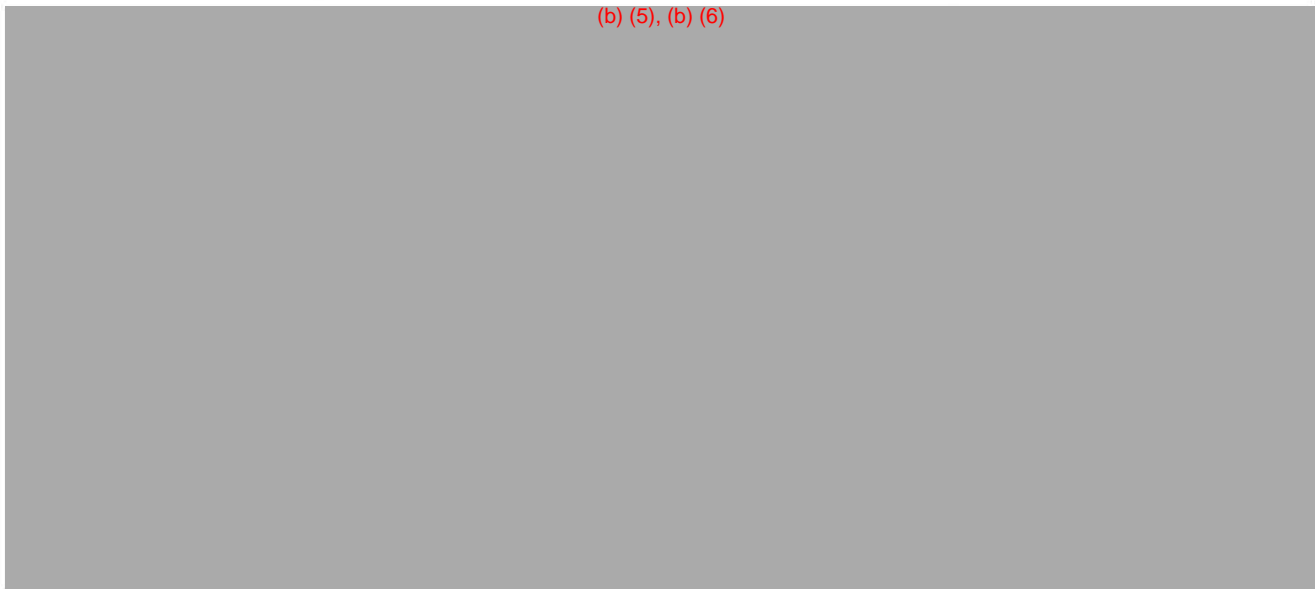
From: "Corr, Bill (HHS/IOS)" <Bill.Corr@hhs.gov>
Date: April 25, 2013 7:51:10 AM EDT
To: "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov>
Subject: RE: SUPPORT study issue still unresolved

Francis,
Heading to SCIF, will try to reach you before 8:30am.

From: Collins, Francis (NIH/OD) [E] [<mailto:collinsf@od.nih.gov>]
Sent: Wednesday, April 24, 2013 9:54 PM
To: Corr, Bill (HHS/IOS)
Subject: SUPPORT study issue still unresolved
Importance: High

Hi Bill,

(b) (5), (b) (6)



Do you have a few minutes early tomorrow to discuss this? I could call anytime before 8:30 AM.

Thanks, and sorry to trouble you,

Francis

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 11:45 PM
To: Corr, Bill (HHS/IOS)
Subject: NIH two pager SUPPORT 042413 11PM
Attachments: NIH two pager SUPPORT 042413 11PM.docx

I note that FC has engaged you tonight on this issue so I wanted to include you on the communications below.

Please let me know how I can be helpful.

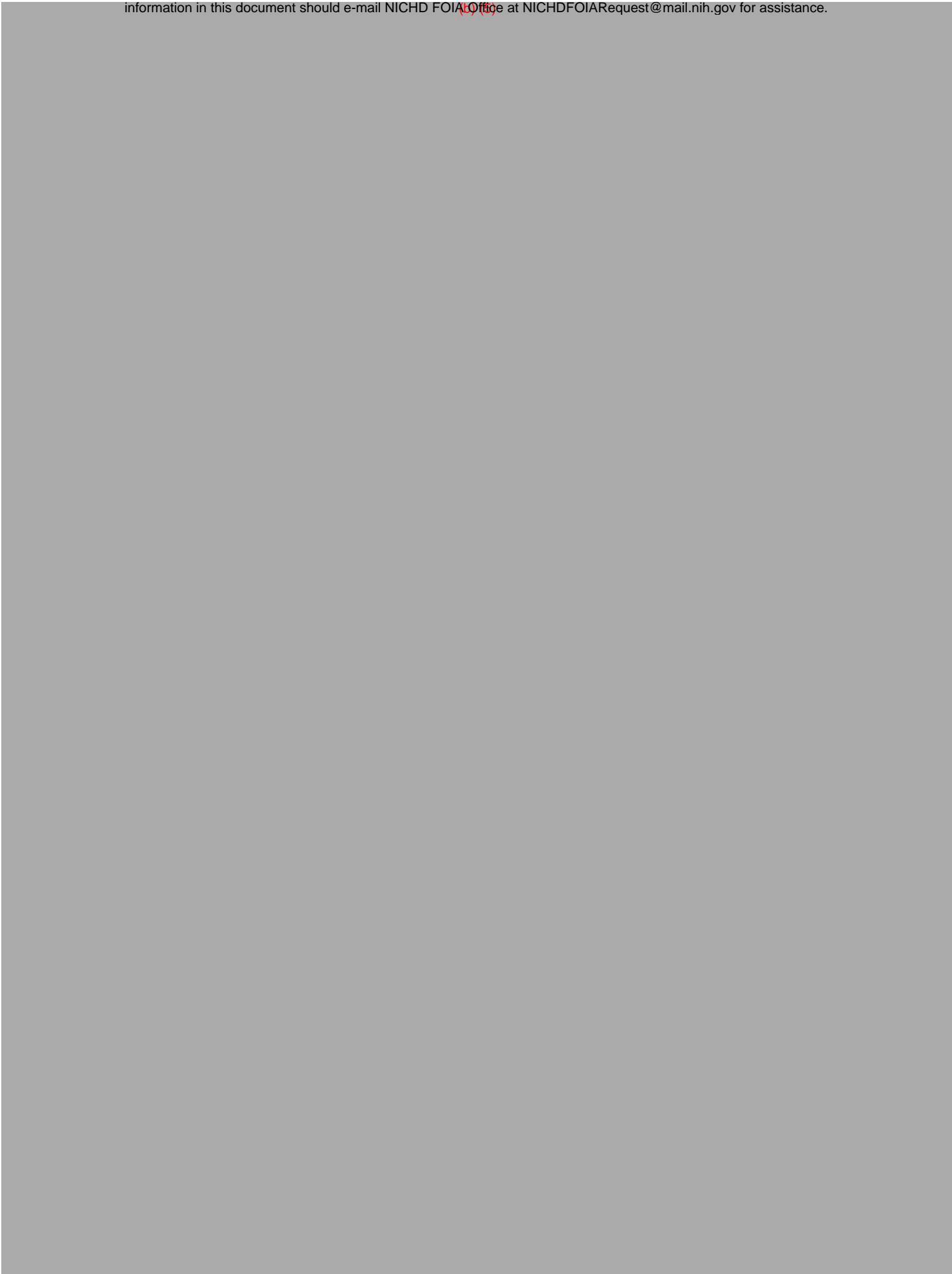
From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 11:41 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHHD) [E]; Higgins, Rosemary (NIH/NICHHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
Subject: NIH two pager SUPPORT 042413 11PM

Caya,

You asked for a two pager on the support study by 1 pm tomorrow. Please accept our slightly longer (3.15 pages) that has not undergone extensive review here but please know that the nih team is all standing firmly together about our views on this. (b) (5)

kathy

(b) (5)



(b) (5)



(b) (5)

(b) (5)

NIH's Concerns about OHRP's Complaint

(b) (5)

(b) (5)



Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 7:00 PM
To: Lewis, Caya (HHS/IOS)
Cc: Howard, Sally (HHS/IOS); McGarey, Barbara (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: support study protocol - release under FOIA

Yes we posted as did the investigators. Our FOIA person says this is consistent with how we operate under HHS transparency rules. If you need more detail than that I will need to bring in experts.

In answer to your questions-

Only public citizen foia.

We post documents in our possession - irrespective of type. Very often the protocols are published with the data - for example nejm requires protocols be submitted with trials and they often post on nejm site. So - trend is release.

Hope this helps.

also in case you missed this -

<http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blogid=140>

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On Apr 24, 2013, at 6:23 PM, "Lewis, Caya (HHS/IOS)" <Caya.Lewis@hhs.gov> wrote:

Did this go up today?

And can you provide answers to my questions below. Thanks.

From: Lewis, Caya (HHS/IOS)
Sent: Tuesday, April 23, 2013 07:30 PM
To: Hudson, Kathy (NIH/OD) [E] <Kathy.Hudson@nih.gov>
Cc: Howard, Sally (HHS/IOS); McGarey, Barbara (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: support study protocol - release under FOIA

(b)(5) - deliberative process

Thanks.

From: Hudson, Kathy (NIH/OD) [E] [<mailto:Kathy.Hudson@nih.gov>]
Sent: Tuesday, April 23, 2013 9:03 AM
To: Lewis, Caya (HHS/IOS)
Cc: Howard, Sally (HHS/IOS); McGarey, Barbara (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: Re: support study protocol - release under FOIA

We have been asked repeatedly by public citizen and, as our FOIA person outlines below, we release when high level of public interest.

"The fact that no one else has requested the SUPPORT protocol yet or that we haven't posted others in the FOIA Library isn't the dispositive factor in deciding whether to post. We are to proactively post any document that we anticipate the public will be interested in. Given the amount of press coverage this study has received, this protocol falls within our obligation to be proactive. We must provide examples of our proactive postings in the Annual Chief FOIA Officers report. "

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On Apr 23, 2013, at 7:57 AM, "Lewis, Caya (HHS/IOS)" <Caya.Lewis@hhs.gov> wrote:

Kathy,

Thanks for the heads up.

(b)(5) - deliberative process

From: Hudson, Kathy (NIH/OD) [E] [Kathy.Hudson@nih.gov]
Sent: Monday, April 22, 2013 8:15 PM
To: Lewis, Caya (HHS/IOS); Howard, Sally (HHS/IOS)
Cc: McGarey, Barbara (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: support study protocol - release under FOIA

The support study protocol has been FOIA'd (repeatedly) and, as per standard procedures, we plan to post it on our foia webpage tomorrow. This is a document you have seen before. The investigators in the trial also have plans to post the protocol but I am not sure of the time frame.

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 4:06 PM
To: Koh, Howard (HHS/OASH)
Subject: OHRP NIH kerfuffle
Attachments: SUPPORT Trial Protocol.pdf; OHRP Letter to UAB.pdf; NEJM letter to the editor 4-17-13 study researchers.pdf; NEJM 4-17-13 Editorial.doc; AAP 2007 Perinatal Guidelines 6th Ed.pdf

Hi Howard,
I hope you are well. I am hoping you might have some time to chat about (b) (5) concerning the SUPPORT study.

As you know, NIH believes that OHRP (b) (5)
(b) (5)

(b) (5) If you have not read the protocol, please do so.

This matter needs a rapid resolution. (b) (5)
(b) (5)
(b) (5) Drazen article attached) and the bioethics community is now also weighing in. <http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blogid=140>
(b) (5)

And please give me a call to discuss how we can move forward effectively.

Thanks

Kathy

Kathy L Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

Bartok, Lauren (NIH/OD) [C]

From: Howard, Sally (HHS/IOS)
Sent: Friday, April 19, 2013 10:11 AM
To: Menikoff, Jerry (HHS/OASH); Collins, Francis (NIH/OD) [E]; Koh, Howard (HHS/OASH); Smolonsky, Marc (HHS/IOS); Lewis, Caya (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Sye, Tait (OS/ASPA)
Cc: Corr, Bill (HHS/IOS); Allen, Vikki (HHS/IOS); Cheema, Subhan (HHS/IOS)
Subject: RE: SUPPORT research

The meeting will need to be at 10:45. We will be sending a conference call number as well

From: Howard, Sally (HHS/IOS)
Sent: Friday, April 19, 2013 10:08 AM
To: Menikoff, Jerry (HHS/OASH); Collins, Francis (NIH/OD) [E]; Koh, Howard (HHS/OASH); Smolonsky, Marc (HHS/IOS); Lewis, Caya (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Sye, Tait (OS/ASPA)
Cc: Corr, Bill (HHS/IOS); Allen, Vikki (HHS/IOS)
Subject: SUPPORT research
Importance: High

Good morning,

(b)(5) - deliberative process, (b)(5) - Attorney Client privilege



An invitation will follow shortly

Sally
Sally Howard
Chief of Staff
U.S. Department of Health and Human Services
200 Independence Ave., S.W.
Washington, DC 20201
(202) 690-8157

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 18, 2013 8:43 PM
To: Corr, Bill (HHS/IOS); Howard, Sally (HHS/IOS); Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS); Smolonsky, Marc (HHS/IOS)
Cc: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Materials for SUPPORT Study
Attachments: SUPPORT Trial Protocol.pdf; Alabama, SUPPORT Consent, 2008-06-04.pdf; NEJM Support Study 2010.pdf; OHRP Letter to UAB.pdf; UAB Response to OHRP 032213.pdf; OHRP Media Quotes_Statement_TP_QA klh.doc

Thanks so much for your time this afternoon.

(b) (5)

Attached are the following materials related to the SUPPORT Study:

- SUPPORT Study Protocol
- SUPPORT Study Consent Form (University of Alabama)
- SUPPORT Study Results Published in NEJM in 2010
- OHRP Compliance Letter to UAB, March 7, 2013
- UAB Response to OHRP, March 22, 2013
- Press statements and materials prepared by OHRP

Please let me know if you have questions.

Protocol for the NICHD Neonatal Research Network

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial

Final

August 28, 2004

Revised September 16, 2004

Updated March 28, 2005

1.1 Statement of Problem

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO₂ which was the threshold for triggering the pathophysiology of this disorder.¹ However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO₂ ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO₂ ranges for managing the ELBW infant from birth.

1.2 Background

Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation². Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours (\pm 12.4hrs) for their infants < 1500 gm at birth, improved oxygenation³ in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP⁴. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation⁵. CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.⁶ A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era suggested that early CPAP may improve survival in infants greater than 1500 gm.⁷

Similarly, there is no definite recommendation or standard teaching regarding the level of oxygenation that should be maintained in ELBW infants. Oxygen supplementation has to be used liberally as ELBW infants frequently have desaturation episodes and thus wide saturation ranges are tolerated clinically. However, oxygen toxicity can result in increased risk for CLD, retinopathy of prematurity (ROP) and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. The pulse oximeter is a newer technology that can be used to improve the control of oxygenation levels. There is great potential benefit to determining the oxygenation levels that prevents ROP and CLD but does not result in neurodevelopmental impairment with a randomized controlled trial of levels of oxygen saturations on the high and low side of the currently utilized levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia because of the marked variability in oxygen in ELBW infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and CLD are deleterious for brain development and result in impaired neurologic outcome.

1.3 Animal Studies

Nilsson et al demonstrated that the use of 5 cm H₂O PEEP in the initial ventilation of premature rabbit pups resulted in increased lung-thorax compliance, and reduced the extent of bronchiolar epithelial lesions seen with mechanical ventilation⁸. The use of early PEEP starting at delivery, improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury.^{9,10}

More recently studies by Jobe et al have demonstrated that premature lambs treated with CPAP alone at birth had significantly decreased neutrophils and hydrogen peroxide in their alveolar wash when compared with animals who were ventilated from birth.¹¹

1.4 Human Experience: Ventilatory Support

CPAP was introduced by Gregory et al in 1970 and was shown to improve gas exchange and outcomes in preterm infants with respiratory distress.¹² A subsequent review of CPAP for respiratory distress concluded that "In preterm infants with RDS the application of CDP either as CPAP or CNP is associated with benefits in terms of reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s when four out of five of these trials were done."¹³

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery¹⁴. From 1991 onward, infants with severe distress or apnea were intubated for a PaCO₂ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality (p=0.038), and shortened the duration of intubation and length of stay¹⁵. In this study the CPAP was applied as soon as signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al¹⁶ in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those ≥1000 g (P <0.02 and <0.01, respectively). The decrease in intubation was not associated with a significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leukomalacia, or BPD. The proportion of infants <1000 g that survived without BPD increased from 38% in 1992 to 48% in 1994; p < .05, and the proportion of infants =1000 g in whom BPD developed decreased from 14% to 9%; p < .05. None of these observations was from a prospective controlled trial, and in none was there a contemporaneous control group who did not receive early CPAP.

The first prospective trial comparing prophylactic CPAP, started at birth, with conventional management was that of Han et al. They compared the use of nasal CPAP given by nasopharyngeal tube with conventional management in 82 infants, 32 weeks gestational age at birth, and in this study it would appear that CPAP was begun in the DR, but may have been delayed for up to 2 hours.¹⁷ No infants in this trial received surfactant, and no mothers were treated with antenatal steroid. There was no advantage observed with the use of early CPAP, and oxygenation was worse in the early CPAP treated infants. The reviewers of the use of prophylactic CPAP in the Cochrane library concluded that "A multicenter randomized controlled trial comparing prophylactic nasal CPAP with "standard" methods of treatment is needed to clarify its clinical role."¹⁸

In the post surfactant era, Verder et al conducted the first prospective evaluation of early CPAP (not necessarily delivery room CPAP) and short-term intubation for surfactant administration in a multicenter collaborative trial conducted from September 1991 to October 1992.¹⁹ The primary hypothesis was that the use of early CPAP and brief intubation for surfactant in infants meeting pre-established criteria would reduce the percentage of infants requiring mechanical ventilation from 80% to 40%. Infants randomized to surfactant [Curosurf®] received 200 mg/kg, (2.5 ml/kg) following intubation, with manual ventilation for 2-5 minutes and were then extubated if stable. This study was stopped after an interim analysis demonstrated a significant benefit for the surfactant treated infants. Thirty-three of the 35 infants randomized to early surfactant were extubated after such treatment, and 13 required reintubation at a median of nine hours after surfactant treatment, compared with 28 of 33 control infants who were intubated a median of three hours after randomization, ($p=0.003$). The overall duration of ventilation in both groups was 2.5 days; there were no other differences between the groups. Verder et al performed a second multicenter prospective trial from April 1995 to January 1997 and enrolled infants <30 weeks with similar criteria to the previous trial, apart from an entry a/A ratio of .35 to .22, which decreased over 30 minutes, which was less stringent, allowing infants to be treated at lesser degrees of oxygen requirement, than their first study. These infants were initially all treated with CPAP and were enrolled up to 72 hours of age (median 4.1 hours, range 0.3 to 40.1 hrs). This trial was also stopped after an interim analysis demonstrated a statistically significant reduction in the need for ventilation or death within seven days from 63% in the late-treated infants to 21% in early-treated infants. The median duration of ventilation in both trials was 2.5 days²⁰. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages, and they did not evaluate infants of less than 25 weeks gestation.

Lindner et al recently reviewed their experience using a continuous prolonged (15 seconds duration) pressure controlled (20 to 25 cm H₂O) inflation of the lungs followed by continuous positive airway pressure (CPAP) of 4 to 6 cm H₂O for all ELBW infants immediately after delivery to establish a functional residual capacity (FRC) and to avoid intubation and ventilation²¹. The criteria for subsequent intubation were a PaCO₂ > 70 mmHg, an FiO₂ >.6 and respiratory distress with severe recurrent apnea. The rate of early intubation and mechanical ventilation in the delivery room decreased from 84% in 1994 to 40% in 1996. In 1996, 25% of the ELBW infants were never intubated (compared with 7% in 1994). There was no difference in mortality and overall there was less IVH > Grade 2 and BPD for the later cohort. No infant had an air leak upon admission to the NICU, suggesting that use of a prolonged inflation was well tolerated. Only 1 of 11 infants of 24 weeks gestation was able to avoid intubation in this study. Once again, there was no contemporaneous control group who did not receive delivery room CPAP. All of the above studies required high levels of PaCO₂ before initiating ventilation for this indication.

There is retrospective evidence suggesting a benefit for early CPAP in experiences from the USA. A survey of eight neonatology units in the USA in 1987 demonstrated that one unit, Columbia, had the lowest rate of CLD²². A more recent comparison of practices and outcomes between two neonatology units in Boston and the Babies and Children's Hospital unit (Columbia) evaluated VLBW infants born in 1991 to 1993.²³ This study revealed that 75% of infants at the Boston centers were initially treated with mechanical ventilation compared with 29% at Columbia, whereas initial CPAP was used in 63% of infants at Columbia vs. 11% at the Boston centers. Columbia also used less surfactant, 10% versus 45%, (all $p < 0.001$). In addition the rates of CLD were significantly lower at Columbia compared to the other two centers (4% vs. 22%).

de Klerk and de Klerk recently published a five-year retrospective review of the outcome of 1 to 1.5 kg infants (n=116) treated with early CPAP vs. usual care (delayed CPAP)²⁴. During 1996-1998 infants were placed on CPAP within 10 minutes of admission (they did not describe the use of delivery room CPAP). Early CPAP beginning following admission to the neonatal unit decreased endotracheal intubation from 65 to 14%, $p < 0.001$ and surfactant use (40 to 12%, $p < 0.001$). Ventilator days were reduced from a median of 6 to 2 days ($p < 0.01$) and oxygen supplementation or death at 28 days from 16 to 3%, $p < 0.05$. Oxygen supplementation or death at 36 weeks did not significantly decrease (11 to 3% $p = 0.25$). Ventilation and surfactant use were very high during the delayed CPAP (control period) so it is unclear whether other improvements in care may have coincided with the change to early CPAP.

Sandri et al²⁵ have recently published preliminary data from a multicenter randomized controlled trial of 155 infants 28 to 31 weeks gestation randomized to CPAP within 30 minutes of birth or to CPAP if the FiO_2 requirement exceeded 40%. Use of surfactant (22 to 21%, NS) and ventilator support (10 to 9%, NS) was not reduced with early CPAP. However, this trial included relatively bigger infants and the control group received CPAP at relatively low FiO_2 , minimizing the difference between the experimental and control groups. This study did not evaluate the use of delivery room CPAP.

More recently Thomson et al presented the results of a multicenter trial of 237 infants from 27 to 29 weeks gestation²⁶, who were randomized to prophylactic surfactant followed by nasal CPAP using the Infant Flow DriverTM, early nasal CPAP followed by rescue surfactant, early IPPV with prophylactic surfactant, and conventional management. They reported that CPAP was initiated by 6 hours of age in 76% and 79% of the first 2 treatment groups, and those infants in the CPAP and rescue surfactant and prophylactic surfactant followed by CPAP groups required the lowest duration of ventilation. There were no differences in the incidence of CLD or other neonatal complications. Neither of these studies instituted the use of CPAP in the delivery room.

In a preliminary feasibility trial we have evaluated the ability of 5 sites of the NICHD Network to initiate CPAP during resuscitation, and continue its use in the NICU. In that study 103 infants were randomized to receive resuscitation with either CPAP/PEEP or no CPAP/PEEP. All infants were treated with CPAP following NICU admission. During delivery room resuscitation, 46 infants were intubated, 27 of 55 CPAP infants and 19 of 48 control infants ($p = 0.33$). All 23 week gestation infants were intubated in the delivery room, irrespective of treatment group, whereas only 3 of 22 (13%) infants of 27 weeks required such intubation. When evaluated by birth weight, all 3 infants of less than 500 gm birth weight and 6 of 11 infants between 500-600 gm birth weights were intubated in the delivery room. All remaining infants were admitted to the NICU and had CPAP initiated. For infants not intubated in the DR, 36 infants were subsequently intubated in the NICU by day 7, 16 CPAP infants and 20 Control infants, ($p = 0.21$). Infants in the CPAP group developed criteria for intubation sooner than the Control infants, with means and medians of 10.5 and 1.8 hours versus 20.7 and 3.3 hours,

$p=0.41$. These infants met criteria established for this trial which included an $FiO_2 > .3$ to maintain an $SpO_2 > 90\%$ or a $PaO_2 > 45$ torr, an arterial $PaCO_2 > 55-60$ with a $pH < 7.25$. or apnea requiring bag and mask ventilation. CPAP infants were intubated at an average $FiO_2 = 0.5$ compared to 0.4 for control infants.

The literature thus suggests that early CPAP may be of substantial benefit, although none of this information has been obtained from prospective randomized trials of CPAP randomly applied in the delivery room to a population of VLBW or ELBW infants, with an appropriate control group. The terms early CPAP in the above studies (apart from that of Lindner et al¹⁵) involved the application of CPAP shortly following birth, not immediately after delivery. It is not surprising, therefore, that the recent revised NRP guidelines do not mention the use of CPAP/PEEP for neonatal resuscitation.²⁷ There is also some evidence that the level of CPAP needed may vary depending on the actual device utilized. Pandit et al and Courtney et al have demonstrated that variable flow CPAP was associated with a lower work of breathing and increased compliance at all levels of CPAP whereas constant flow nasal CPAP increased compliance only at 8 cm H₂O.²⁸ In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.²⁹ A more recent trial compared the use of variable flow CPAP to conventional CPAP at extubation for 162 ELBW infants and reported no significant differences with either form of CPAP.³⁰ This study noted that 40% of ELBW infants failed extubation primarily because of apnea.

There are no studies in the surfactant and antenatal steroid era which have prospectively compared delivery room, CPAP with a more conventional approach, such as the use of prophylactic surfactant and conventional ventilation. The current available evidence demonstrates that prophylactic natural surfactant treatment significantly decreases mortality, air leak, and BPD in preterm infants.³¹ Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.³² These reviewers noted that "early surfactant administration significantly reduces the risk of key clinical outcomes including pneumothorax, PIE, chronic lung disease, and neonatal mortality. Given the efficacy of prophylactic surfactant therapy (Soll 1999), this meta-analysis suggests that early selective surfactant administration to intubated infants with early signs of RDS may be part of a clinical spectrum of improved outcomes with earlier treatment". The most recent experience regarding early surfactant was presented by Horbar et al at the SPR in May, 2003. Their study which involved a cluster randomization in 57 NICUs of a practice to administer surfactant earlier compared with 57 control NICUs. They noted that infants at the intervention sites received their surfactant more often in the DR (54.7 vs 18.2%, $p < 0.001$) and earlier than the control sites (21 vs 78 minutes, $p < 0.001$). There were no differences in mortality and pneumothoraces, the intervention centers had a lower rate of overall and severe IVH (28% vs 33%, $p < 0.04$, 10% vs 14%, $p < 0.001$) which were secondary outcomes of this trial.³³

The most recent published study by Tooley and Dyke evaluated the use of prophylactic surfactant and early extubation to CPAP versus prophylactic surfactant and continuing management.³⁴ In this study 42 infants of 25 to 28(+6) wk of gestation were intubated at birth and given one dose of surfactant. They were then randomized within one hour of birth to either continue with conventional ventilation or to be extubated to nCPAP. They reported that 8 out of 21 (38%) babies randomized to nCPAP did not require subsequent re-ventilation. (Ventilation rates of 62% vs 100%, $p = 0.0034$). The smallest baby successfully extubated weighed 745 g. There were also significantly fewer infants intubated in the nCPAP group at 72 h of age (47% vs 81%, $p = 0.025$). There was no significant difference between the two groups in the number of babies that died, developed chronic lung disease or severe intraventricular hemorrhage. This study demonstrates that a significant number of very preterm babies with RDS can be extubated

to nCPAP after receiving one dose of surfactant. The current SUPPORT study will address this population, extended to 24 weeks, using a similar methodology for the infants of 24 to 27 6/7ths weeks who fail initial CPAP, with adequate power to determine if this approach is associated with significant benefits in terms of important short and longer term clinical outcomes.

Oxygen Saturation:

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality.³⁵ Pulmonary oxygen toxicity, through the generation of reactive oxygen/nitrogen species in excess-of antioxidant defenses, is believed to be a major contributor to the development of BPD.^{36,37,38} For example the preterm macrophage showed a significant increase in cytokine mRNA and protein after overnight incubation in 95% oxygen compared with cells from term animals. Only macrophages from premature animals had a significant increase in intracellular oxygen radical content, measured by 2', 7'-dichlorofluorescein analysis, after incubation in 95% oxygen. This enhanced inflammatory cytokine response to oxygen has been postulated to be a mechanism involved in the early development of chronic lung disease in premature infants.³⁹ Varsila et al noted that immaturity is the most important factor explaining free radical-mediated pulmonary protein oxidation in premature newborn infants and that oxidation of proteins is related to the development of chronic lung disease.⁴⁰

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported Infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen.^{41, 42} Vento et al also demonstrated that that infants resuscitated with oxygen demonstrated long lasting evidence of oxidative stress and activities of superoxide dismutase and catalase in erythrocytes that were 69% and 78% higher, respectively compared with control infants resuscitated with room air at 28 days of postnatal life.⁴³ A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal resuscitation in infants resuscitated with room air (6 vs 11%, $p < 0.005$ or 0.57 (95% CI $0.40 - 0.81$)).⁴⁴ While these studies described results of mostly term infants, some infants were premature and the premature infant is known to have decreased antioxidants which would increase their susceptibility to oxygen toxicity. In the only randomized prospective trial to evaluate room air compared with oxygen in preterm infants, Lundstrom et al resuscitated infants of less than 33 weeks gestation who were randomized to receive either 80% oxygen or room air and noted that 2 hours following delivery, the room air infants had a higher cerebral blood flow compared with oxygen resuscitated infants. (median (interquartile range)): 15.9 ($13.6-21.9$) v 12.2 ($10.7-13.8$) ml/100 g/minute).⁴⁵ They did not find any significant differences in short or long-term outcomes but did note that SpO₂ was lower in the room air infants with values at 5 and 7 minutes of 75% and 80% compared with 92% and 94% in the 80% oxygen group ($p < 0.001$). Current monitoring with pulse oximetry using limits of 95 to 96% will result in significant periods wherein the infants actual PaO₂ may increase to very high levels, as there are rapid increases in PaO₂ with very small increments in SpO₂ at this plateau portion of the hemoglobin dissociation curve.

Tin et al retrospectively reviewed outcomes for infants admitted to various neonatal intensive care units in northern England from 1990 to 1994 and managed with lower (70-90%) or higher SpO₂ ranges (88%-98%).⁴⁶ They reported that infants who were managed for at least the first 8 weeks of life with SpO₂s from 88-98% developed retinopathy of prematurity severe enough to be treated with cryotherapy four times as often as infants managed with the lower SpO₂ ranges. Infants managed with the lower SpO₂ ranges did not have increased risk of mortality or neurodevelopmental impairment. Bancalari et al using transcutaneous oxygen monitoring were able to show that infants who received continuous monitoring had a similar incidence of ROP to infants who were monitored by intermittent sampling had similar incidences of ROP, however for subgroup of infants \geq 1100gm, there was a decrease in the incidence of ROP.⁴⁷ The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO₂ less than 94% to two ranges of SpO₂ (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO₂ was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD.⁴⁸

Chow et al reported their observations following the institution in 1993 of a detailed oxygen management policy that included strict guidelines in the practices of increasing and weaning of fraction of inspired oxygen (FIO₂) and the monitoring of oxygen saturation parameters in the delivery room, during in-house transport of infants to the NICU, and throughout hospitalization.⁴⁹ The main objectives were to avoid hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. Their approach was initiated at birth, and included the avoidance of repeated increases and decreases of the FIO₂, and a change in previously used alarm limits. They reported that following the implementation of these new management strategies that the incidence of ROP Grades 3 to 4 decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001 and that the need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. They adopted an SpO₂ range of 85% to 95% for infants > 32 weeks gestation at birth, and a range of 85% to 93% for infants < 32 weeks. In addition some of their faculty used a range of 83% to 93%. This study did not provide any prospective values of the actual SpO₂ ranges that were actually achieved in their infants, and thus it is uncertain whether their observed reductions in ROP were related to the altered SpO₂ changes, or to overall changes in management over the period of the study. While these observations are encouraging, the authors did not report the complete neurodevelopmental outcomes for the infants cared for during the period of the new oxygen guidelines, and in the absence of contemporaneous controls, these results cannot be considered as proof that the SpO₂ ranges used by this group are beneficial in terms of significant longer-term neurodevelopmental outcomes.

The most recent trial conducted in Australia compared SpO₂ ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy. but resulted in an increased duration of oxygen supplementation.⁵⁰ They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months. Anderson et al have recently reported the results of a survey of pulse oximetry practices in 142 NICUs in the USA and noted a wide range of monitoring limits from 82% to 100%. They reported a lowered rate of ablative eye surgery in units that used lower maximal SpO₂ limits, with the lowest range seen in units that had a maximum SpO₂ of < 92%.⁵¹

In a recent review of oxygen toxicity in the premature infant Weinberger et al recommended that a strategy of limiting oxygen supplementation should be explored to reduce significant morbidities in the premature infant.⁵² No studies to date have prospectively randomized ELBW infants to differing oxygenation ranges from birth onwards to determine if there is a benefit of lower versus higher saturation ranges.

1.5 Recent Relevant Studies

We have recently evaluated an FDA approved device specifically designed to facilitate neonatal resuscitation (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand). This device has a t-piece that attaches to a mask and to a simple pressure generator. The inspiratory pressure can be set to a determined level, and a twist valve at the top of the t-piece determines the end-expiratory pressure. Most operators, with the exception of experienced respiratory therapists cannot routinely deliver a predetermined level of positive inspiratory pressures and PEEP⁵³ using an anesthesia-type manual bag and a neonatal manikin. In contrast, all operators could deliver the predetermined pressures with little intra-individual variation using the Neopuff®. The device operates identically using either a mask or endotracheal tube connection with or without PEEP/CPAP and the operator can adjust the positive inspiratory pressure (PIP) manually during resuscitation. At a flow of 10 liter per minute (lpm) or less, the maximum inadvertent CPAP/PEEP is 0.5 cm H₂O; which does not increase up to rates of 80 breaths per minute, the highest tested rate. The wave form is square, and is more similar to ventilator wave forms than to wave forms obtained using an anesthesia device. It should be noted, that the standard anesthesia devices used in delivery rooms may not deliver the desired CPAP/PEEP, depending on the operator's experience and skill, and may result in overshooting the desired PIP, even when the device is used by experienced operators. The Neopuff® device is now used as the standard resuscitation device in a number of hospitals in the USA, including at least two units in the NICHD Network.

There has been a recent trial evaluating earlier criteria for retinal laser ablative surgery for ROP, the ETROP study.⁵⁴ This study has demonstrated that using such criteria the visual outcomes are improved and reported that grating acuity results showed a reduction in unfavorable visual acuity outcomes with earlier treatment, from 19.5% to 14.5% (P=.01) and that unfavorable structural outcomes were reduced from 15.6% to 9.1% (P<.001) at 9 months. They recommend retinal ablative therapy for eyes with type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. While these results are likely to be integrated into Network practice, there is currently no baseline data regarding the number of infants who would meet these criteria, and thus we will utilize the presence of Stage 3 or greater ROP and/or the receipt of retinal surgery to power our current trial.

2.1 Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

- 1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (≤ 1 hour) surfactant and mechanical ventilation.
- 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.

The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial, a multicenter, multinational prospective trial to evaluate different SpO2 levels from birth.⁵⁵ The methodology described under oxygen monitoring (**Section 4.1B**) was developed for the current protocol to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters. These devices have been developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial, and the POST-ROP study group has agreed to use the ranges described in this protocol, and the methodology that will allow the oximeters to provide actual SpO2 values when the SpO2 is < 85% and > 95% (Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

Please see **Section 8.2** for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Treatment Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control Prophylactic/Early Surfactant	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2). We hypothesize that that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

2.3 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.

- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

3.1 Study Population

Study subjects are infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) will be enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. It is important to note that previous studies have included few, if any infants less than 25 weeks gestation and such infants are not included in the current COIN trial or the proposed Vermont Oxford Trial. Such infants will be enrolled in this trial because they are the group of infants with the highest mortality and morbidity. The feasibility trial demonstrated that the 5 NICHD centers involved could reduce intubation in the delivery room to less than 50% of such infants if they are not intubated for surfactant. We will exclude infants of 23 weeks or less in view of their extremely high mortality and morbidity, and their almost universal need for delivery room intubation for resuscitation. We have included Tables at the end of the protocol utilizing infants from 23 to 28 weeks to demonstrate that our sample size estimates will not be adversely affected if we should choose to include infants of 23 and/or 28 weeks.

Strata: There will be 2 randomization strata, infants of 24 0/7ths to 25 6/7ths weeks, and infants of 26 0/7ths-27 6/7ths weeks by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study will not be powered to detect outcome differences between strata.

3.2 Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

3.3 Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or \geq 28 weeks 0 days, completed weeks of gestation

3.4 Sampling Recruitment and Screening Procedures

Infants will be recruited for this study by approaching one or both parents at the time of admission to the hospital where there is deemed to be a risk of premature delivery at 27 6/7ths weeks or less.

3.5 Screening Procedures

All admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. We will inform our obstetrical colleagues at each involved institution of the nature of this study, and encourage them to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery

3.6 Other Procedures

A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology will be used at all sites for the delivery room administration of CPAP. A training video to explain the proper use of the Neopuff® will be provided to any site which wishes to use it and is not familiar with the device.

3.7 Randomization

Randomization will be stratified by gestational age group, will occur prior to delivery for consented deliveries, and will be performed by utilizing specially prepared double-sealed envelopes. Deliveries will be randomized as a unit, thus multiples, twins, triplets etc will be randomized to the same arm of the trial. We believe that this methodology will improve the percentage of consents, since in previous trials parents of multiple infants have expressed concern that their infants were being randomized to different treatment arms. We have made an appropriate sample size adjustment to account for this clustering effect.

Each randomization will indicate either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and either the Low (85%-89%) or High (91% - 95%) SpO₂ group. Parents will be approached for consent before delivery, but the randomization envelope will only be opened when delivery is imminent for a consented family.

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 Pulse Oximeter range, and an identification code for each site will be maintained by the PI/Site Coordinator should identification be required for patient safety. RTI will work with Masimo to ensure that the POs are labeled with unique identifiers, whose code will identify the

actual range of the individual PO. These would be affixed prior to shipping to the sites, and a copy of the labels sent to the site would be provided to RTI.

This methodology should reduce the work load to the sites at the time of randomization, providing the care team with the information needed for the infants' randomization, and will allow the study center to be notified within 24 hours of any randomization.

3.8 Informed Consent:

Parents will be approached prior to delivery for informed consent, and their infants enrolled at delivery. As previously noted we will randomize by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery.

3.9 Management and Retention of Study Population

All enrolled infants will be seen at follow-up at 18 to 22 months corrected age. We do not anticipate a significant loss other than death (13% in the first 12 hours, approximately 32% before discharge, based on year 2000 registry data), and will plan for a further 15% attrition.

4.1 A: Study Intervention: Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team. The conduct of the resuscitation will follow usual guidelines, and once stabilized, all Control infants in both strata will receive prophylactic/early surfactant (within 1 hour of age) whereas all Treatment infants will be placed on CPAP/PEEP following stabilization, and be intubated only for resuscitation indications.

The assignment to either a high or low SpO₂ by study oximeter assignment will be performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission.

TREATMENT: CPAP Group : Early Extubation and CPAP

Delivery Room Management

FiO₂:

Standard of care.

CPAP:

CPAP or ventilation with PEEP will be utilized if the infant requires positive pressure during resuscitation. CPAP will be continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial PPV will be at a PIP of 15-25 cm H₂O and a PEEP/CPAP of 5 cm cmH₂O.

Intubation:

Infants may not be intubated for surfactant only in the DR. Infants who require intubation for resuscitation will receive surfactant within 60 minutes of birth.

Intubation will be performed only for the standard NRP indications including failure to respond to PPV with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management

These infants will be managed on nasal CPAP, and intubation is never required by protocol. They *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 $\text{FiO}_2 > .50$ required to maintain an indicated $\text{SpO}_2 \geq 88\%$ (using the altered Pulse Oximeters) for one hour
- An arterial $\text{PaCO}_2 > 65$ torr (arterial or capillary samples, if venous $\text{PvCO}_2 > 70$ torr) documented on a single blood gas within 1 hour of intubation
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

These criteria will continue in effect for a minimum of 14 days of life.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

(e.g. - Upper airway obstruction (choanal atresia, micrognathia/glossoptosis)).

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 H_2O , ventilator rate ≤ 20 bpm, an amplitude $< 2X$ MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving inotropic/vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA

These criteria will continue in effect for the first 14 days of life.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted. (e.g. - PIE, air leak)

Reintubation

If a Treatment infant is extubated as per Protocol Criteria, and requires re-intubation for any indication, any further attempt at extubation may be delayed for 24 – 48 hrs based on the clinician's decision.

Re-intubation criteria are the same as those for Intubation for the CPAP infants. Thus, intubation is not required, but these infants **MAY** be reintubated if they meet **ANY** of the following:

Re-Intubation Criteria:

- An $\text{FiO}_2 > .50$ required to maintain an indicated $\text{SpO}_2 \geq 88\%$ (using the altered Pulse Oximeters) for one hour
- A $\text{PaCO}_2 > 65$ torr (arterial or capillary samples, if venous $\text{PvCO}_2 > 70$ torr) on a single blood gas.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

Re-intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be discontinued earlier and follow unit Standard of Care. CPAP may be restarted at any time in such infants.

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.

Surfactant

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant
Up to 4 surfactant administrations may be given if the FiO_2 is greater than 50% following manufacturers' recommendations for dose and dosing interval.

Explanation:

The purpose of the above criteria is to minimize the duration of intubation of Treatment infants. The Criteria for extubation are more severe than those of the Control Group infants, and extubation must be attempted for any infant who fulfills the stated criteria.

The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.

CONTROL- Prophylactic/Early Surfactant and Ventilation

Delivery Room Management:

Infants will be intubated in the delivery room and given surfactant or receive surfactant within 60 min minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management:

Extubation:

An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have Extubation attempted within 24 hours of fulfilling **ALL** of the following criteria documented on a single blood gas.

- PaCO₂ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO₂ = 35 with a SpO₂ = 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H₂O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving inotropic / vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size)

These criteria will continue in effect for a minimum of 14 days for all infants.

Failure to attempt to extubate an infant meeting all of the above criteria, or extubation prior to reaching criteria, will be recorded as a study protocol violation unless extenuating circumstances are noted.

Weaning

This protocol will not define strict weaning criteria for the Control infants, but it is to be understood that reasonable attempts should be made to extubate these infants. While it is understood that some centers may be using somewhat more severe FiO₂ and PaCO₂ criteria than those listed here as current practice, these Criteria are thought to reflect current Network practice and practice at 2 of the 3 Best practice centers.

Reintubation:

- Control Infants may be reintubated using Standard of Care.

Explanation:

Control infants are to be treated using an approach considered similar to current standards of care. Apparatus for resuscitation for Control Infants at each center will represent their usual equipment for the resuscitation of an ELBW infant. The Neopuff may be utilized for such infants as above, but this is not mandatory. It is anticipated that the majority of these infants will be intubated and receive surfactant in the delivery room.

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.⁴² 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%.

Low Range Infants:

These infants will be monitored with a target SpO2 range of 85% -89% with suggested indicated alarm limits of 85% and 95%, representing approximately a 10% span for alarms as long as the infants are receiving any ventilatory support, CPAP, and/or supplemental oxygen. **The study pulse oximeters will be applied to the infant within two hours following NICU admission.** The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

High Range Infants:

These infants will be monitored with a target SpO2 range of 91% -95% with suggested indicated alarm limits of 85% to 95% representing approximately 10% span for alarms as long as they are receiving any ventilatory support, CPAP and/or supplemental oxygen. The study pulse oximeters will be removed once the infant has been in room air for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

These interventions will be delivered using specially developed pulse oximeters whose displays (the actual readings seen by caretakers) will be adjusted so that the randomized range of SpO2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable. The target oxygen saturation (88-92%) of the display will be the same in both groups as indicated in Table1 below.

These POs will be able to display trend plots of the SpO2 display for a preceding interval to allow the caretakers to receive feedback regarding the actual SpO2 ranges of their baby.

The suggested alarms limits will be 84% and 96% for both groups.

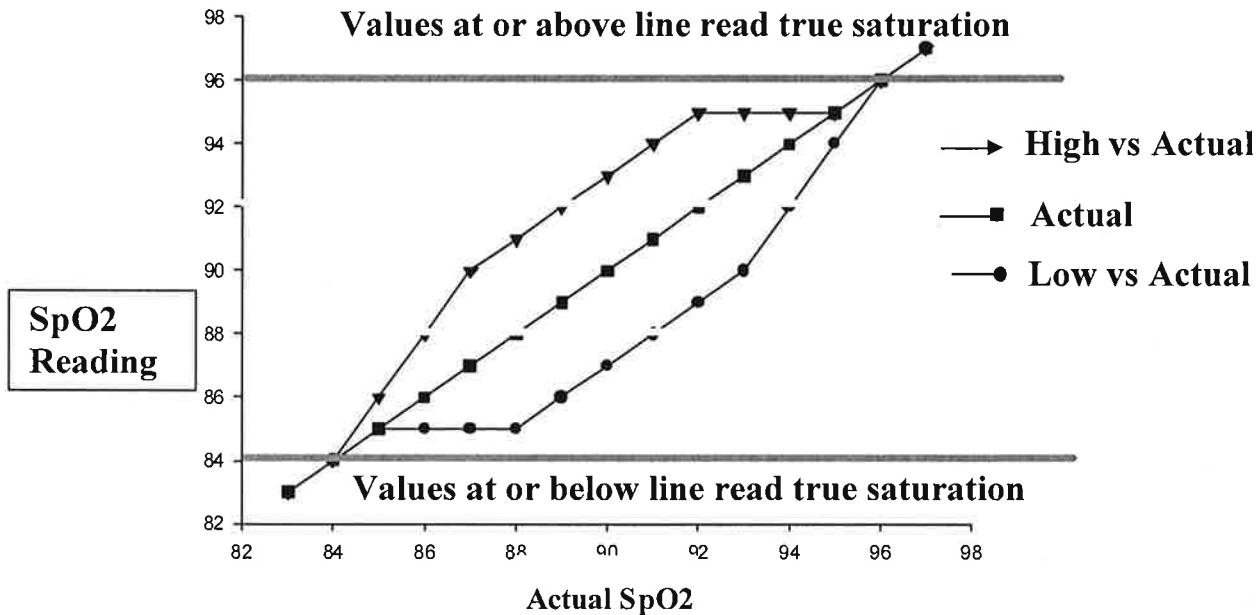
Table 1. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target	Actual Target	Alarm Values
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%

The pulse oximeters will display the actual reading when then the SpO2 is below 85% and above 95%. This will provide for an overall set of limits on actual SpO2 of 84% to 96% which we believe will avoid unacceptable levels of hypoxia, (< 85%) and hyperoxia (> 95%) **All data below 85% and above 95% will be unaltered on all oximeters.** An averaging time of 16 seconds will be applied in keeping with the settings used by POST-ROP. The preset alarm delay will be 10 seconds. The fail-safe alarm will alarm whenever the reading is 5% below the low alarm limit, in the study this will be at 80%. Some network centers use an averaging interval of 30 seconds, others use very short averaging times. This setting will allow for appropriate response times without unmasking the caretakers.

We believe that this methodology will provide an acceptable ethical design for this trial. The diagram below demonstrates how the pulse oximeter readings are altered between values of 85% to 95%. Readings below or above these levels will not be altered, and will represent actual SpO2 as determined by the pulse oximeter. Note that the entire range of actual SpO2 is altered to either a lower (Low SpO2 Group) value or higher value (High SpO2 Group) till the ends of the alarm ranges of 85% and 95% which will ensure that the infants SpO2 will be separated throughout this range.

Actual vs Low and Hi Reading SaO2



Every 30 days until 36 weeks PCA or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without losing significant data). These data points will be used to confirm that the infants were managed at the

target ranges and provide objective confirmation of the SpO₂ Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

Non-study pulse oximeters cannot be used on enrolled patients. If a second oximeter is required for such a patient, the site coordinator will provide an identical oximeter for the patient.

All ventilatory care after 14 days of age will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

4.2 Delivery of Interventions

CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece resuscitator, a neonatal ventilator or an equivalent device that is currently used by the site for the delivery of CPAP. (See 3.6).

Use of Nasal SIMV;

This approach is currently used by some Network units and has been previously established as being superior to CPAP following extubation in three prospective trials.^{56,57,58} For uniformity nasal SIMV may be used in place of CPAP **only following extubation for both Treatment and Control infants.**

Use of Caffeine:

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.⁵⁹

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers' recommendations for redosing intervals.

The protocol requires that at least one dose of surfactant be administered to any infant intubated within 48 hours of birth, with evidence of respiratory distress, who has not previously received surfactant.:

Postnatal Steroids

Postnatal steroids for the purpose of preventing or treating BPD/CLD will be prohibited for any infant in this trial in the first 21 days of life. Hydrocortisone for hypotension may be used as noted below.

If postnatal steroid use is considered after 21 days of life for any infant for the prevention/treatment of established lung disease the following guidelines should be followed:

1. The AAP statement and recommendations regarding Post-natal steroids should be adhered to.⁶⁰

2. The lowest dose of dexamethasone considered effective should be used and if ineffective after 24 – 48 hours they should be stopped.

3. Consider using hydrocortisone as a first therapy at a dose of 1 -2 mg/kg/day before using dexamethasone.

4. For hypotension, hydrocortisone in a dose of 1 mg/kg/dose should be given after fluid administration and standard doses of ionotropes/pressors have failed to correct the low blood pressure.

Head Ultrasound

If a Head ultrasound is done between days 4 and 21 the results will be recorded for this study. If one is not done for standard of care, the study requires that at least one HUS be completed during this window

4.3 Protocol Violations:

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. Intubation of a treatment group infant in the DR for the exclusive purpose of giving surfactant, in the absence of bradycardia (HR < 100 bpm) and/or poor color or an SpO₂ < 85-90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
2. Failure to continue CPAP on admission to the NICU for a treatment infant requiring supplemental oxygen
3. Intubation and surfactant administration of a treatment infant without meeting stated protocol criteria.
4. Failure to extubate a Treatment infant who fulfills all the extubation criteria.
5. Extubation of a Control infant who does not meet any of the Extubation criteria.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations.

4.4 Adverse Events

Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be 5% - 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.

4.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming⁶¹ boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock⁶² boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

5.1 Measurement Methods:

The PO stored data will be retrieved using a routine provided to all site coordinators, and the resultant data file will be sent electronically to RTI to be included as part of the study data collection.

5.2 Schedule of Data Collection: (See Data tables in Appendix A)

5.3 Primary and Secondary Outcome Measures

5.3.1 Primary Outcome Measure

The primary outcome will be the percentage of infants surviving without BPD (using the Physiologic Definition) or severe ROP (threshold disease or the need for surgery).

5.3.2 Secondary Outcome Measures

- The five minute Apgar score
- The percentage of infants with death or neurodevelopmental impairment at 18 months
- The total duration of mechanical ventilation during the entire NICU stay
- The percent of infants alive and off ventilation by day 7
- The proportion of infants receiving surfactant treatment
- The incidence of air leaks on admission and overall
- The incidence of BPD at 36 weeks using the physiologic definition of BPD
- The incidence of death
- The proportion of infants with severe IVH
- The proportion of infants with PVL
- The proportion of infants with threshold ROP and requiring surgery for ROP
- The proportion of infants requiring endotracheal intubation before 10 minutes of age
- The proportion of infants with of air leaks on admission and overall
- The duration of oxygen supplementation
- The percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- The proportion of infants who receive postnatal steroids to prevent or treat BPD
- The proportion of infants with who develop necrotizing enterocolitis (NEC)
- The proportion of infants with cerebral palsy at 18-22 month follow-up

6.1 Training Study Personnel

6.1.1 Job Descriptions of Study Personnel

The NICHD coordinators will assist the respiratory therapists in each unit regarding the set up the equipment for the delivery of CPAP in the delivery room, and in the NICU.

6.1.2 Training of Personnel

There will be a training session held in Cincinnati about the delivery of CPAP in the delivery room and in the NICU, and a review of available devices that may be used for this intervention.

7.1 Data Collection and Management

We will develop the required CRFs as per Network procedures. It will be our aim to minimize these to ensure that data is collected regarding the intervention, the adherence to the protocol for intubation, surfactant administration, and extubation, and the occurrence of the primary and secondary end-points. All remaining information will be extracted for the current data forms.

8.1 Statistical Analysis

8.1.1 Analysis Plan

The primary analyses of this factorial trial will be a logistic regression analysis of the percent of each Group (Treatment vs Control, High vs Low SpO₂) who developed their respective outcome measure (survival without BPD or ROP at 36 weeks respectively). An important analysis of a secondary outcome will determine if there is an effect of the interventions on the percent infants who survive without neurodevelopmental sequelae at 2 years. For all secondary outcomes, univariate analysis for continuous variables will be performed using parametric (e.g., Student t tests, ANOVA), and non-parametric (e.g., Mann-Whitney U) tests where appropriate; categorical variables including the primary outcome, feasibility, will be examined by Chi square analysis. Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of, various factors, (e.g., birth weight, gestational age, gender, treatment group, center, etc.) upon secondary outcomes (i.e., time to improvement in oxygen saturation, duration of positive pressure ventilation, five minute Apgar score, duration of mechanical ventilation, surfactant requirement, incidence of air leaks, and incidence of BPD).

8.2 Sample Size

As discussed above, there are two main outcomes for the factorial design: mortality or BPD; mortality or ROP. Mortality or NDI is a secondary outcome. For the cohort of infants born in 2000, 401-1000g birth weight, we have the following prevalence of outcomes for four subgroups of that cohort: Please note that we used population groupings to include or exclude infants of 23 and 28 weeks. These additional groups do not change the sample size estimates as the outcomes are essentially similar.

Subgroup	Death/BPD	Death/> Stage III ROP	Death/NDI
23-27 GA	70.6	53.1	65.7
24-28 GA	64.8	44.5	59.3
24-27 GA	66.6	46.8	60.7
23-28 GA	68.6	50.4	64.0

If the study is powered for the two outcomes, Death/BPD and Death/>Stage III ROP, then the sample size is driven by the prevalence nearest 50% for a given absolute percentage detectable change in the outcome. In this case it's the Death/>Stage III ROP outcome with a range of 44.5% to 53.1% across the subgroups. Furthermore, the sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially

50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

Hence, for any of the four groups the table below gives the total sample sizes required for a range of absolute percent changes, a two-tailed alpha level test of 5% and for powers of 80% and 90%. The N1 column powers the 2 x 2 factorial for the two primary outcomes and the N2 column assures comparable power for the Death/NDI outcome.

With regard to the power for detecting the interaction between the two factors in the factorial, a fourfold increase in the stated sample size would be required to detect an interaction effect as large or larger as that stated in the table (i.e. the Detectable Difference), assuming the same alpha level and power. The interaction effect referred to is the classical one where the difference in outcome for one of the treatments in the factorial differs according to the level of the other treatment (i.e. the treatment effects are not additive).

If the study is powered for the two primary outcomes and mortality/NDI is considered as a secondary outcome then the table below gives the total sample size required for a 5% overall level test at 80% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and a conservative outcome rate of 50% in making the calculations. These sample sizes are given in the N1 column and would also allow a 10% difference in NDI/death to be detected with a power of 73%. If an 80% power is desired for the NDI/mortality outcome this would result in sample sizes in the N2 column.

TOTAL SAMPLE SIZES REQUIRED

Detectable Difference (absolute %)	80% Power		90% Power	
	Total N1*	Total N2**	Total N1*	Total N2**
8%	1792	2096	2284	2676
9%	1388	1624	1792	2096
10% (multiples to same arm)	1120	1312	1456	1704
11%	940	1104	1208	1416
12%	784	920	1032	1208
13%	672	788	860	1008
14%	584	680	756	880
15%	504	588	652	768

* sample sizes to insure the appropriate power for the two primary outcomes (BPD/Death, ROP/Death)

** sample sizes to insure the appropriate power for the secondary outcome (NDI/Death)

We have increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduces a clustering effect into the design. The analysis of the GDB data base resulted in the 1.12 estimate. We also inflated the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This figure was also determined from the GDB data base. Thus the actual sample size for this trial would be 1310 for 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. This sample size is not sufficient to permit detection of interactive effects between the two treatments with reasonable power.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

When sample sizes were estimated for the SUPPORT trial the following base rates for the three outcomes (rounded) were calculated from the GDB:

- BPD/Mortality—67%
- ROP \geq Grade III/Mortality—47%
- NDI/Mortality—61%.

Sample sizes were calculated for a range of absolute treatment effects and 10% seemed to be the smallest plausible effect for the study. Rounding the above rates to 65, 45, and 60 percent the following tables show what the data would look like under the assumption of a 10% reduction in outcome and control rates of 65, 45, and 60 percent for the DRCPAP (No)/ SpO2 (High) group. Interactive effects are assumed to be zero. Tables are presented which show treatment effects when both treatments affect the BPD and the ROP outcomes and when only one of the treatments affects outcome. The NDI table is only for the case where both treatments affect outcome.

Table IA

Treatment Effects for SpO₂ (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO₂

		Low	High	Overall
CPAP	Yes	45	55	50
	No	55	65	60
	Overall	50	60	55

Table IB

Treatment Effects for SpO₂ (High, Low) and CPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for CPAP Only**—Table Entries are Outcome Rates (%)

SpO₂

		Low	High	Overall
CPAP	Yes	55	55	55
	No	65	65	65
	Overall	60	60	60

Table IIA

Treatment Effects for SpO₂ (High, Low) and DRCPAP (Yes, No) on ROP_≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO₂

SpO₂

		Low	High	Overall
CPAP	Yes	25	35	30
	No	35	45	40
	Overall	30	40	35

Table IIB

Treatment Effects for SpO₂ (High, Low) and CPAP (Yes, No) on ROP_≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO₂ Only**—Table Entries are Outcome Rates (%)

		SpO ₂		
		Low	High	Overall
CPAP	Yes	35	45	40
	No	35	45	40
	Overall	35	45	40

Table III

Treatment Effects for SpO₂ (High, Low) and CPAP (Yes, No) on NDI/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

		SpO ₂		
		Low	High	Overall
CPAP	Yes	40	50	45
	No	50	60	55
	Overall	45	55	50

9.1 Quality Control

The selection of personnel will be left to the site PI's. No specific job descriptions are required for this protocol. The actual duties of the individual who will perform the randomization will be detailed in the manual for the study. Protocol violations will be reviewed, and if frequent, may require a site visit and consideration for termination of a collaborating site.

10.1 Risks and Benefits

Potential risks to the use of CPAP and/or PEEP include pneumothoraces; however this is unlikely to be increased over the risk of PPV alone. The level of CPAP/PEEP will be set at 5-6 cmH₂O, a level that is not thought to increase the incidence of pneumothorax. Recent data from Dr Morley suggest that this level is probably the lowest effective level especially when the infant's mouth is open, and is well tolerated. Objections to use of PEEP or CPAP could be countered by the argument that the majority of neonatologists use PEEP in resuscitation, thus the standard of care at most centers probably include the administration of CPAP and/or PEEP. Another potential risk is the administration of CPAP in the DR to infants without respiratory distress, which could conceivably cause vagal stimulation and resultant bradycardia and gastric distension.

Perhaps the major risk of this trial is that the known benefit of early surfactant with a reduction of death and disease severity, and a reduction of BPD with natural surfactant may not be offset by the early use of CPAP. However, the increasing trend in the use of early CPAP without such evidence represents an even greater risk.

Appendix A

Study Tables

Table 1. Patient Description

	Treatment	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min < 3 Assigned			
Apgar 5 min < 3 Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			

Table 2. Other Outcomes

	Treatment	Control	P Value
Total Duration of Mechanical Vent (M +SD)			
Duration of Oxygen (Total days)			
Duration of CPAP			
Duration of nSIMV			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, %)			
Other air leaks (N, %)			
BPD at 36 weeks (O ₂ dependence)			
BPD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %)			
Number receiving PNS for BPD (N, % %)			
Alive without neurdevelopmental impairment at (18-22 months) years (N, %, +/-SD)			

Appendix B

Study Tables

Table 1. Patient Description

	Low Saturation	High Saturation	RR	CI	p value
Birth weight (grams) (M + SD)					
Gestation (weeks) (M + SD)					
Race (W, B, H, other) %					
Antenatal steroids (%)					
Apgars ≤ 3 at 5 min					

Table 2. Primary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Threshold ROP/Surgery or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					
BPD or Death by 36 weeks (%) \pm					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
BPD in alive infants at 36 weeks (%)					
IVH 3 or 4/PVL or death by 36 weeks (%)					
IVH 3 or 4 in alive infants at 36 weeks (%) \dagger					
Cystic PVL in alive infants at 36 weeks (%) \dagger					
Neurodevelopmental impairment or death by 18-22 months (%)					
Death by 18-22 months (%)					
Neurodevelopmental impairment at 18-22 months (%) \dagger					
Cerebral palsy at 18-22 months (%) \dagger					
MDI < 70 (%)					
PDI < 70 (%)					
Any blindness at 18-22 months (%) \dagger					
Unilateral blindness at 18-22 months (%) \dagger					
Deafness at 18-22 months \dagger					

\dagger Analyzed for survivors

Table 4. Other Outcomes

	Low Saturation	High Saturation	RR CI	P Value
Total Duration of Ventilation (M+SD)				
On ventilator or death by day 7 (%)				
Pneumothorax (%)				
Any air leak (%)				
Postnatal steroids for BPD (%)				
Necrotizing enterocolitis ≥ 2 (%)				
PDA requiring surgery				

	Early CPAP/Early Extubation	Prophylactic Surfactant
Delivery Room Management	Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. Transport on CPAP If intubated for resuscitation, give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	Intubate and give surfactant within 1 hour of age Transport with PPV according to SOC
Upon NICU Admission	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria	Not Required. May intubate for ANY of these criteria <ul style="list-style-type: none"> • $FiO_2 > .50$ required to maintain indicated $SpO_2 \geq 88\%$ (using the altered Pulse Oximeters) for one hour • $PaCO_2 > 65$ torr (art. or cap. samples, if venous $PaCO_2 > 70$ torr) documented on a single blood gas • Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated, give surfactant within the first 48 hrs if in respiratory distress	Reintubation Criteria Standard of Care
Extubation Criteria	Attempt extubation within 24 hours of fulfilling all of the following criteria: <ul style="list-style-type: none"> • $PaCO_2 < 65$ torr with a $pH > 7.20$ (arterial or capillary samples) • An indicated $SpO_2 \geq 88\%$ with an $FiO_2 \leq 50\%$ • Mean airway pressure (MAP) < 10 cm H_2O, vent rate ≤ 20 bpm, amplitude $< 2X$ MAP if on HFV • Absence of clinically significant PDA • Hemodynamically stable 	Keep intubated and ventilated until criteria met. Attempt extubation within 24 hours of fulfilling all of the following criteria <ul style="list-style-type: none"> • $PaCO_2 < 50$ torr and $pH > 7.30$ (arterial or capillary samples) • $FiO_2 \leq 35$ with $SpO_2 > 88\%$ • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 20 bpm, amplitude $< 2X$ MAP on HFV • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surf Doses	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
Intubation	Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery	
CPAP D/C	In room air for at least 1 hour	
CPAP Resumption	At any time	
Duration of Intervention	14 days	14 days

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Informed Consent

Title of Research: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Study) (Multicenter Network of Neonatal ICU's)

Title of Secondary Research: Neuroimaging and Neurodevelopmental Outcome (MRI Study)
Postnatal Growth of Infants Enrolled in SUPPORT Study (Growth Study)

UAB IRB Protocol Numbers: F040910010, X060418004 and F050922007

Investigators: Dr. Wally Carlo and Dr. Namasivayan Ambalavanan

Sponsor: National Institute of Child Health and Development (NICHD)

You are being asked to give your permission for your baby to participate in a study designed to determine if using positive airway pressure during resuscitation after birth helps decrease the severity of lung disease in premature babies. We will also be looking at the ranges of oxygen saturation that are currently being used with these same babies. You and your baby were selected as possible participants because you are less than 28 weeks pregnant and your baby may be born prematurely. The doctors at UAB, along with 15 other centers across the country, are participating in this project sponsored by the by the National Institute of Child Health and Human Development.

This consent form gives you information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risk of the procedures, and possible benefits. Once you are informed about this study, you will be asked if you want your baby to participate; if so, you will be asked to sign this form.

Introduction

If born prematurely, your baby is at risk for a breathing problem called **Respiratory Distress Syndrome (RDS)**. A baby's lungs are made up of tiny air sacs; each one is supposed to open and close as the baby breathes in and out. Oxygen is supposed to go in and carbon dioxide is supposed to come out. This works well in full term babies and adults; however, in premature babies, the lung sacs don't always work this way. Some lung sacs open and close normally; others collapse and stick together when the baby breathes out making it harder for the baby to breathe. Doctors treat this problem with expanding breaths and pressure to keep the lungs slightly inflated between those breaths. Keeping a little air pressure in the lungs after the baby

breathes out (resting pressure) makes it easier for the baby to take the next breath. Sometimes a medication called *surfactant* is given to try to help keep the lung sacs expanded. After your baby is born, if he/she needs help breathing, the doctor or nurse will place a resuscitation bag over the baby's nose and mouth to provide oxygen and manual breaths. The bag is squeezed to force air into the baby's lungs. The bag and mask may be used to give breaths or give just pressure to keep the lungs inflated between breaths. This resting pressure is called continuous positive airway pressure or CPAP or PEEP.

At the present time, there is no recommendation regarding the early use of CPAP/PEEP in the delivery room and continuing it in the nursery for premature infants. However, some studies have suggested that the use of early CPAP/PEEP may be associated with improved outcomes such as: fewer babies needing to be placed on a breathing machine, less oxygen use in babies at one month of age and longer, and less need for a medication given in the babies lungs called surfactant. This study will begin in the delivery room and continue into the nursery to compare the use of CPAP/PEEP and early placement on the breathing machine along with the early use of surfactant to see if we can help lessen the severity of and even possibly prevent long term lung problems in premature infants.

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

Expansion of Procedures

SUPPORT Study: If your baby is born before a gestational age of 28 weeks, he/she will randomly (like the flip of a coin) be placed into a group that receives early CPAP/PEEP use in the delivery room **or** early placement on the breathing machine (intubation) with the use of surfactant. Both ways are currently used in our hospital and we hope to determine which is the better way for these premature babies.

If your baby is in the Early CPAP group, he/she will be treated with CPAP/PEEP in the delivery room and will remain on it upon admission to the nursery. If, at any time, your baby shows signs of needing intubation for resuscitation purposes, then he/she will be intubated. If this happens within the first 48 hours he/she will also be given surfactant.

If your baby is in the Early Surfactant and Ventilation group, he/she will be placed on the breathing machine in the delivery room and will be given surfactant within the first hour of birth. For the first 14 days of life, there will be guidelines for the doctors in the nursery to follow. These guidelines help them decide when to place babies on the breathing machines and when to try and take them off the breathing machines. These guidelines will also help decide when to put babies on and take them off of CPAP/PEEP.

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

If your baby is still receiving oxygen close to the time of discharge (at approximately 36 weeks corrected age) a test will be done to determine the severity of lung disease that may be present. During this test, the oxygen your baby is receiving will be decreased gradually while continuously measuring oxygen saturation with the pulse oximeter. If the saturation falls below an acceptable range, your baby will then be returned to the prior oxygen level.

MRI Study: Part of your baby's regular care during the first few months after birth will include one or more head ultrasounds. The first one usually occurs during the first 2 weeks. There is also one done closer to the time of your baby's due date. In addition to the routine head ultrasound done close to your baby's due date, we would like to ask your permission to also do Magnetic Resonance Imaging (MRI) on your baby. The MRI is a common procedure that uses a magnetic field to make pictures of the inside of the head. It does this by taking a closer look at the tiny particles that are in the brain. Your baby will be placed on a narrow bed for about 20-30 minutes while the machine scans the brain and makes pictures. Your baby will not be exposed to any radiation when having the MRI done. The magnetic fields do not cause any known harmful effects at the levels used in the MRI machine. National and local guidelines have been developed for MRI machines, and these recommendations will be followed.

The ultrasound and MRI pictures of your baby's brain will be looked at by radiologists (doctors who are specialists in X-rays and other pictures of the body). Your doctors will tell you what they find. Because this study will be done in several hospitals across the United States, the ultrasound and MRI pictures from babies who participate will also be seen by other radiologists. They will look at all the pictures from all the babies.

Growth Study: It is routine care in the nursery to weigh and measure babies to watch their growth. With this secondary study to the SUPPORT Study, we will be collecting weight and measurements along with feeding information to take a closer look at how your baby grows.

Duration of Study

Your baby will be involved in the ventilation part of this study for the first 14 days after birth. After the first 14 days, he/she will still be monitored with the saturation monitor as long as he/she is receiving extra oxygen. Once your baby has been off of oxygen for 72 hours, then the saturation monitor may be discontinued. Information will be gathered from the medical record throughout your baby's hospitalization.

We expect to include about 1310 babies in this study from all the NICHD Neonatal Research Network hospitals over a two year period.

Long Term Follow-up

When your baby is 18-22 months old, he/she will be seen in the Newborn Follow Up Clinic for an evaluation. At this visit, we will ask you a few extra questions about your baby's health. It is also possible that you may be contacted in the future for further long term follow up for the study.

Possible Benefits

The investigators do not promise or guarantee that your baby will receive any direct benefit from participating in the SUPPORT Study or any of the secondary studies. Participation will, however, benefit the medical community by providing valuable information which may help us treat babies in the future.

SUPPORT Study: If he/she is in the group which receives CPAP/PEEP, he/she might benefit by not needing additional breathing support. He/she may not require surfactant to be given into the lungs.

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

MRI Study: There may be benefits to your baby directly, including findings of brain injury which will allow for earlier intervention than would normally occur.

Growth Study: There is no direct benefit to participating in this secondary study.

Possible Risks

SUPPORT Study: The possible risks of using CPAP/PEEP include stomach bloating and a temporary slowing of the heart rate. Another possible risk is collapsing one or both of the lungs. Use of the CPAP/PEEP at the level used in this study does not increase the risk of collapsed lungs.

Like with the use of CPAP/PEEP, a possible risk of being intubated (placed on the breathing machine) may include a temporary slowing of the heart rate or possibly the collapse of one or

both lungs. Another risk is the possibility of the airway being punctured. Other possible risks include bruising or cutting of the tongue, gums, or airway.

Other potential risks during resuscitation after birth include; the need for chest compressions, rescue medications, and even death. It is not thought that the use of either of these ways of delivering oxygen to the baby's lungs increases these risks.

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

CPAP/PEEP, intubation, and pulse oximetry are commonly used in the newborn intensive care (NICU). Study participation should not increase these risks because all procedures are carried out by experienced NICU staff.

MRI Study: The risks of participating in this secondary study are minimal. The head ultrasound is a routine part of the care of a premature baby, and the way it is performed will not be changed for this study, nor does it cause any discomfort for the baby. The MRI is often done on babies whenever the doctor feels that it will give him information he needs to treat the baby. For this study, all participants who agree to participate will have an MRI done after getting the approval of the attending physician. The "tapping" noise that the MRI machine makes may agitate your baby. To minimize this, your baby's ears will be covered while the MRI is being done.

Your baby may also need to be given medicine to make him/her drowsy for the MRI. A possible risk of sedation is breathing difficulty. Your baby's heart rate and breathing will be closely monitored by an experienced baby nurse to reduce this risk.

Growth Study: There are no risks to participating in this secondary study.

Alternative Procedures

If you do not want your baby to participate in this study, he/she will receive the routine care given in the delivery room and nursery. The routine care may or may not include the use of CPAP and/or surfactant administration. He/she will most likely have oxygen saturation measured with a pulse oximeter as well. Routine care in the nursery may or may not include MRI.

Confidentiality

Information will be collected from your baby's chart by trained research personnel. It will be labeled with a code number and sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute (RTI) in North Carolina. The study log linking the code number to your baby's identity will be kept under lock and key in the UAB Division of Neonatology Research office. Any information that might identify your baby will not leave UAB. In addition, the NIH/NICHD, the UAB Institutional Review Board (IRB), the Food and Drug Administration (FDA), or the Office of Human Research Protections (OHRP) may monitor the

trial records and the individual conducting the review may see your name in the file folder. Otherwise, the records will remain confidential to the extent permitted by law.

Information relating to this study, including your name, medical record number, date of birth and social security number may be shared with the billing office of UAB and UAB Health System-affiliated entities so that claims may be appropriately submitted to either the study sponsor or your insurance company for clinical services and procedures provided to you during the course of this study. The results of the treatment may be published for scientific purposes; however, your baby's identity will not be revealed. If you or your baby receive services in University Hospital, or The Children's Health System as part of this trial, this informed consent will be placed in and made part of your baby's permanent medical record at these facilities.

If your baby is transferred to another hospital or discharged before his/her eyes have reached maturity, then we will call the hospital or eye doctor to find out the results of eye exams that are done after discharge.

Withdrawal Without Prejudice

Participation in this study is voluntary. If you do not wish to participate in this study, your baby will not lose benefits to which he/she is entitled. You are free to withdraw your consent and to discontinue your baby's participation in this project at any time without prejudice against future medical care he/she may receive at this institution. This means that withdrawing him/her will have no effect on the future care or treatment of your baby by physicians or by this institution.

In addition, if the study physician feels that it is in your baby's best interest to be withdrawn from the study, he will do so immediately.

Significant New Findings

Any significant new findings discovered during the course of this study, which may influence your decision to allow your baby to continue participation, will be made known to you.

Costs of Participation

The cost of your baby's standard medical care, including surfactant administration and head ultrasounds, will be billed to you and/or your insurance company in the usual manner. The costs of the study, including the MRI that will be done close to your baby's due date, will be covered by a research grant. If any other MRI's are ordered by your baby's doctor as part of clinical care, they will be billed to you or your insurance company. There will be no additional cost to you or your insurance company for expenses related to this study.

Payment for Participating in Research

There will be no payment to you or your baby for participating in this research study.

Payment for Research Related Injuries

If, as a result of your baby's participation, he/she experiences injury from known or unknown risks of the research procedures as described, immediate care and treatment, including

hospitalization if necessary, will be available. Neither UAB, The Children's Hospital of Alabama, nor the National Institutes of Health has made provision for monetary compensation in the event of injury resulting from the research, and in the event of such injury, treatment is provided, but is not free of charge. Further information regarding medical treatment can be obtained from Dr. Wally Carlo at 934-4680.

Questions

If you have questions about this study or experience any problems during the study, you should contact Dr. Wally Carlo at (205) 934-4680. You may also reach Monica Collins, RN, Shirley Cosby, RN, or Vivien Phillips, RN at (205) 934-5771. If you have questions about your baby's rights as a research participant, or concerns or complaints about the research, you may contact Ms. Sheila Moore. Ms. Moore is the Director of the Office of Institutional Review Board for Human Use (OIRB). Ms. Moore can be reached at (205) 934-3789 or 1-800-822-8816. If calling the toll-free number, press the option for "all other calls" or for an operator/attendant and ask for extension 4-3789. Regular hours for the Office of the IRB are 8:00 a.m. and 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

By signing this consent form, you are not waiving any of your or your child's legal rights.

Optional Participation in Secondary Studies

Please sign your choice below:

Neuroimaging and Neurodevelopmental Outcome (MRI Study)

_____	I agree to allow my baby to participate in the MRI Secondary Study.
_____	I Do Not agree to allow my baby to participate in the MRI Secondary Study.

Postnatal Growth of Infants enrolled in the SUPPORT Study (Growth Study)

_____	I agree to allow my baby to participate in the Growth Secondary Study.
_____	I Do Not agree to allow my baby to participate in the Growth Secondary Study.

Signatures

You are making a voluntary decision whether or not to let your baby participate in this study. Your signature below indicates that you have decided to let your baby participate, that you have read (or been read) the information provided above, that you were given the opportunity to ask questions and that they have been answered to your satisfaction. The consent form will remain in the files at UAB Division of Neonatology and a copy will be placed in your baby's medical record. You will receive a copy of this signed consent form.

WAIVER OF ASSENT

The assent of _____ (name of child) has been waived because of age.

Signature of Parent or
Legally Authorized Representative

Date

Signature of Person Obtaining Consent

Date

Signature of Witness

Date

UAB **University of Alabama at Birmingham** **irb**
Authorization for Use/Disclosure of Health Information
for Research

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant name: _____

UAB IRB Protocol Number: F040910010,
F050922007 and X060418004

Research Protocol: The Surfactant Positive Airway
Pressure and Pulse Oximetry Trial in Extremely Low
Birthweight Infants; Secondary Studies: Neuroimaging
and Neurodevelopmental Outcome and Postnatal Growth
of Infants Enrolled in SUPPORT Study
(Multicenter Network of Neonatal ICU's)

Principal Investigator: Wally Carlo, MD
Namasivayam Ambalavanan, MD;

Sponsor: National Institute of Child Health and
Development (NICHD)

What health information do the researchers want to use? All medical information and personal identifiers; including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of parent or _____
legally authorized representative

Date _____

Printed Name of parent/participant's representative: _____

Relationship to the participant: _____

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Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

ABSTRACT

BACKGROUND

Previous studies have suggested that the incidence of retinopathy is lower in preterm infants with exposure to reduced levels of oxygenation than in those exposed to higher levels of oxygenation. However, it is unclear what range of oxygen saturation is appropriate to minimize retinopathy without increasing adverse outcomes.

METHODS

We performed a randomized trial with a 2-by-2 factorial design to compare target ranges of oxygen saturation of 85 to 89% or 91 to 95% among 1316 infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation. The primary outcome was a composite of severe retinopathy of prematurity (defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab), death before discharge from the hospital, or both. All infants were also randomly assigned to continuous positive airway pressure or intubation and surfactant.

RESULTS

The rates of severe retinopathy or death did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3% and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06; $P=0.21$). Death before discharge occurred more frequently in the lower-oxygen-saturation group (in 19.9% of infants vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; $P=0.04$), whereas severe retinopathy among survivors occurred less often in this group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; $P<0.001$). There were no significant differences in the rates of other adverse events.

CONCLUSIONS

A lower target range of oxygenation (85 to 89%), as compared with a higher range (91 to 95%), did not significantly decrease the composite outcome of severe retinopathy or death, but it resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern, since a lower target range of oxygen saturation is increasingly being advocated to prevent retinopathy of prematurity. (ClinicalTrials.gov number, NCT00233324.)

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RETINOPATHY OF PREMATURITY IS AN important cause of blindness and other visual disabilities in preterm infants. The incidence of retinopathy of prematurity was increased with exposure to unrestricted oxygen supplementation in preterm infants in randomized, controlled trials performed in the 1950s.¹ In the 1960s, this increase resulted in the practice of restricting the fraction of inspired oxygen (FIO₂) to no more than 0.50, which was estimated to result in an excess of 16 deaths per case of blindness prevented.² More recent data suggest that levels of oxygen saturation previously thought to be at the upper end of the normal range may increase the risk of retinopathy of prematurity as compared with levels at the lower end of the normal range.³⁻⁵ Oxygen toxicity may also increase the risk of death,^{6,7} bronchopulmonary dysplasia,⁸⁻¹⁰ periventricular leukomalacia,¹¹ cerebral palsy,¹² and other conditions. Although a multicenter observational study did not show a significant association between higher values for the partial pressure of arterial oxygen and retinopathy, a single-center cohort study involving transcutaneous oxygen monitoring provided support for an association between an increased risk of retinopathy¹³ and exposure to arterial oxygen levels of 80 mm Hg or more.¹⁴

Pulse oximetry allows clinicians to continuously monitor levels of oxygen saturation and to target levels in a defined range. Associations between lower target levels of oxygen saturation and a lower incidence of retinopathy have been reported.¹⁻⁵ In a survey of 144 neonatal intensive care units (NICUs), the rate of retinal ablation surgery among very-low-birth-weight infants was increased among infants cared for in NICUs that used higher maximum target levels of oxygen saturation, as compared with infants in NICUs that used lower target levels. The rate of retinal ablation surgery was 3.3% in NICUs using target levels of 92% or higher and 1.4% in NICUs using target levels of less than 92%; the rate was 5.6% in NICUs using target levels of 98% or higher and 3.1% in NICUs using target levels of less than 98%.³ In a retrospective study comparing outcomes at five NICUs, the incidence of severe retinopathy requiring ablation therapy was 27% in NICUs where the target saturation level was 88 to 98% and only 6% in NICUs where the target level was 70 to 90%.³ Rates of death and cerebral

palsy did not differ significantly among these NICUs. In three studies with a before-and-after design, the implementation of a policy of target levels of oxygen saturation of approximately 83 to 95% was associated with a substantial reduction in the incidence of retinopathy, as compared with the period before implementation of the policy; however, the actual levels of oxygen saturation achieved, mortality, and neurodevelopmental outcomes were not reported.^{4,15,16} Although data from these studies suggest that maintenance of oxygenation at ranges lower than those previously used may decrease the incidence of retinopathy of prematurity, the safety of low target levels of oxygen saturation remains a concern.

We conducted the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a controlled, multicenter trial with a 2-by-2 factorial design, to compare two target levels of oxygen saturation and two ventilation approaches (continuous positive airway pressure [CPAP] initiated in the delivery room with a protocol-driven strategy of limited ventilation vs. intratracheal administration of surfactant with a protocol-driven strategy of conventional ventilation). The oxygen-saturation component of the trial tested the hypothesis that a lower target range of oxygen saturation (85 to 89%), as compared with a higher target range (91 to 95%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity or death among infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation. The ventilation part of this factorial-design trial, which was used to control the ventilation approach and test other hypotheses, is reported elsewhere in this issue of the *Journal*.¹⁷

METHODS

STUDY DESIGN

The study was conducted as part of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The study was approved by the institutional review board at each participating site and by RTI International, which is the independent data coordinating center for the Neonatal Research Network. Data collected at the study sites were transmitted to RTI International, which stored, managed, and analyzed the data for this

study. Written informed consent was obtained from the parent or guardian of each child before delivery.

PATIENTS

Infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation were eligible for enrollment at birth. Infants born in other hospitals and those known to have major congenital anomalies were excluded.

ENROLLMENT AND TREATMENT

Infants were enrolled from February 2005 through February 2009. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Using sealed, opaque envelopes, we randomly assigned infants before birth to a target range of oxygen saturation of 85 to 89% (the lower-oxygen-saturation group) or 91 to 95% (the higher-oxygen-saturation group). Infants who were part of multiple births were randomly assigned to the same group.

Blinding was maintained with the use of electronically altered pulse oximeters (Masimo Radical Pulse Oximeter) that showed saturation levels of 88 to 92% for both targets of oxygen saturation, with a maximum variation of 3%. For example, a reading of 90% corresponded to actual levels of oxygen saturation of 87% in the group assigned to lower oxygen saturation (85 to 89%) and 93% in the group assigned to higher oxygen saturation (91 to 95%). A previous trial used a fixed 3% absolute oxygen-saturation variation throughout the entire range of saturation levels to keep caregivers unaware of study-group assignments and to separate levels of oxygen saturation in preterm infants,¹⁸ but the algorithm used in the current trial differed, since the oxygen-saturation reading gradually changed and reverted to actual (non-skewed) values when it was less than 84% or higher than 96% in both treatment groups. Limits of 85% and 95% that would trigger an alarm in the delivery system were suggested, but they could be changed for individual patients.

Targeting of levels of oxygen saturation with altered pulse oximetry was initiated within the first 2 hours after birth and was continued until 36 weeks of postmenstrual age or until the in-

fant was breathing ambient air and did not require ventilator support or CPAP for more than 72 hours, whichever occurred first. Infants who were weaned to room air but who subsequently received oxygen supplementation before 36 weeks of postmenstrual age were placed back on the assigned study pulse oximeter. The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age. Adjustments in supplemental oxygen to maintain the target level of oxygen saturation between 88 and 92% were performed by the clinical staff rather than the research staff.

Data on oxygen saturation were electronically sampled every 10 seconds and downloaded by the data center. Readings of levels of oxygen saturation that were pooled (i.e., not separated according to treatment group) were provided quarterly to each center for feedback on compliance. Actual data on oxygen saturation were not provided to the clinicians or researchers but are used exclusively in this article. For the ventilation part of this trial with a 2-by-2 factorial design, participants were randomly assigned to CPAP with a protocol-driven limited ventilation strategy or to prophylactic early administration of surfactant with a protocol-driven conventional ventilation strategy.¹⁷

ASSESSMENTS

Research nurses recorded all data using standardized definitions included in the trial's manual of operations. Data collection, excluding examinations to detect retinopathy of prematurity, was completed at discharge. All surviving infants were followed by ophthalmologists trained in the diagnosis of retinopathy of prematurity. Examinations began by 33 weeks of postmenstrual age and continued until the study outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group^{19,20}) was diagnosed if any of the following findings were present: in zone 1, stage 3 retinopathy of prematurity, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of retinopathy of prematurity; in zone 2, plus disease with stage 2 retinopathy of prematurity or plus disease with stage 3 retinopathy of

prematurity. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. The primary outcome was death before discharge or severe retinopathy as defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy. The original study protocol specified a primary outcome of death before 36 weeks of postmenstrual age, but this was changed to death before discharge before any data analyses were performed. All other outcomes reported were prespecified, including assessment of the need for oxygen at 36 weeks of postmenstrual age²¹ and safety outcomes.

STATISTICAL ANALYSIS

The analysis for the oxygen-saturation part of this factorial trial compared the percentage of infants in each treatment group in whom the primary outcome of severe retinopathy or death occurred. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. We performed a post hoc survival analysis with the use of a Cox proportional-hazards model to compare mortality in the two oxygen-saturation groups, assuming that there were no subsequent deaths among the infants who were discharged. In the analysis of all outcomes, the results were adjusted, as prespecified, for stratification according to study center and gestational age, as well as for familial clustering due to random assignment of infants who were part of multiple births to the same treatment group. To compare the actual oxygen-saturation values in the two treatment groups, the median value during oxygen supplementation was determined for each infant. Those values were plotted according to treatment group, and the medians of the resulting distributions were compared with the use of a rank-sum test.

An absolute between-group difference of 10 percentage points in the rate of the composite primary outcome was considered clinically important. The sample-size calculations were based on the rate of death or threshold retinopathy of 47% in the Neonatal Research Network for the year

Figure 1 (facing page). Screening, Randomization, and Primary Outcome.

The numbers shown exclude infants of women who were screened during pregnancy but whose babies were not subsequently born at a study center between 24 weeks 0 days and 27 weeks 6 days of gestation. The outcome of severe retinopathy of prematurity (ROP) could not be determined in some infants because of loss to follow-up. CPAP denotes continuous positive airway pressure.

2000. We increased the sample size by a factor of 1.12 to allow for infants who were part of multiple births to be randomly assigned to the same treatment (since this introduced a clustering effect into the design), and we increased the sample size by an additional 17% to adjust for attrition after hospital discharge. We increased the sample size further to minimize type I error with the use of a conservative 2% level of significance. The result was a target sample of 1310 infants. The study was not powered to detect an interaction effect between the two factorial parts of the study.

Analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the 46 planned analyses of secondary outcomes according to treatment group, we would expect no more than three tests to have P values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for predefined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have P values of less than 0.05 on the basis of chance alone.

An independent data and safety monitoring committee appointed by the director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the data and safety monitoring committee, at the request of the investigators, evaluated the data on oxygen saturation to evaluate compliance with the protocol. The Lan-DeMets spend-

OXYGEN SATURATION AND OUTCOMES OF PREMATURITY

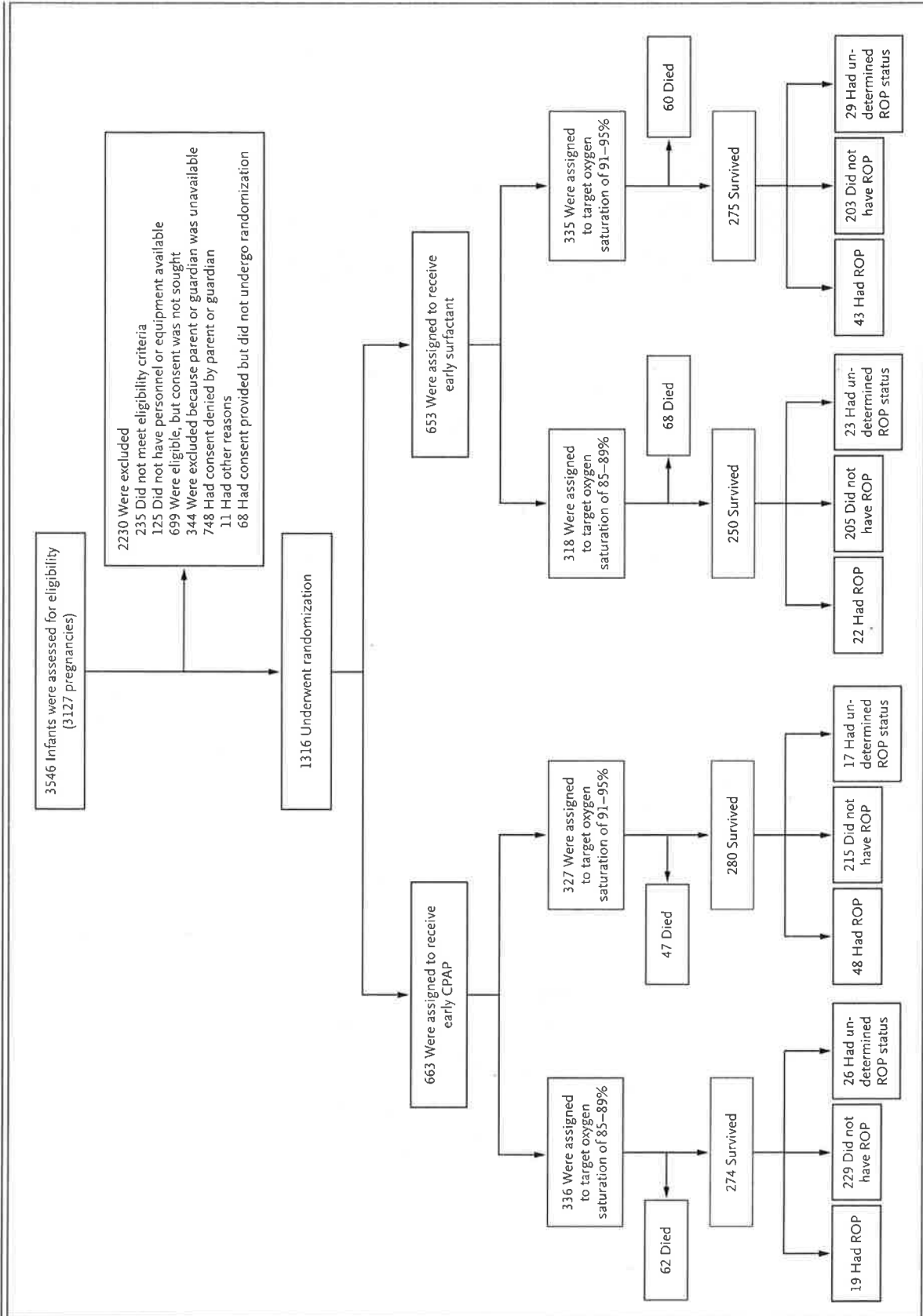


Table 1. Baseline Characteristics of the Patients.

Characteristic	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)
Birth weight — g	836±193	825±193
Gestational age — wk	26±1	26±1
Male sex — no./total no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group — no./total no. (%)†		
Non-Hispanic white	242/654 (37.0)	279/662 (42.1)
Non-Hispanic black	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other or unknown	23/654 (3.5)	24/662 (3.6)
Maternal use of antenatal corticosteroids — no./total no. (%)		
Any	633/654 (96.8)	632/661 (95.6)
Full course	477/651 (73.3)	462/658 (70.2)
Apgar score <3 at 5 min — no./total no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant treatment — no./total no. (%)	531/653 (81.3)	558/660 (84.5)
Multiple birth — no./total no. (%)	161/654 (24.6)	176/662 (26.6)

* Plus-minus values are means ±SD. P>0.05 for all comparisons.

† Race or ethnic group was reported by the mother or guardian of each child.

ing functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. In the final analysis, the nominal level of significance was 0.05. The monitored safety outcomes included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

CHARACTERISTICS OF THE STUDY SAMPLE

We enrolled 1316 infants in the study (Fig. 1). When 247 infants had been enrolled, enrollment was temporarily suspended on the basis of the recommendation of the data and safety monitoring committee and the decision of the director of the National Institute of Child Health and Human Development because of concern that readings of levels of oxygen saturation often exceeded the target levels. Separation of the oximetry data according to whether patients were breathing ambient air or receiving oxygen supplementation addressed this concern, because infants who did not require supplemental oxygen accounted for a large proportion of the high saturation levels. Resump-

tion of enrollment was approved. The baseline characteristics of the two treatment groups were similar (Table 1).

PRIMARY OUTCOME

The rate of the composite primary outcome, severe retinopathy or death before discharge, did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3 and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21) (Table 2). Although the trial was not powered to detect an interaction between the level of oxygen saturation and the ventilation intervention, we prospectively planned to evaluate this interaction, and no significant interaction was found (P=0.57). Death before discharge occurred in 130 of 654 infants in the lower-oxygen-saturation group (19.9%) as compared with 107 of 662 infants in the higher-oxygen-saturation group (16.2%) (relative risk with lower oxygen saturation, 1.27; 95% CI, 1.01 to 1.60; P=0.04; number needed to harm, 27). The distribution of the major causes of death did not differ significantly between the two groups (see Table 1 in the Supplementary Appendix, available with the

OXYGEN SATURATION AND OUTCOMES OF PREMATURITY

Table 2. Major Outcomes.*

Outcome	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)	Adjusted Relative Risk (95% CI)
	<i>no./total no. (%)</i>		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76–1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37–0.73)
Death			
Before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01–1.60)
By 36 wk postmenstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99–1.63)
BPD, defined by use of supplemental oxygen, at 36 wk	203/540 (37.6)	265/568 (46.7)	0.82 (0.72–0.93)
BPD, defined by use of supplemental oxygen, or death by 36 wk	317/654 (48.5)	359/662 (54.2)	0.91 (0.83–1.01)
BPD, physiological definition, at 36 wk†	205/540 (38.0)	237/568 (41.7)	0.92 (0.81–1.05)
BPD, physiological definition, or death by 36 wk†	319/654 (48.8)	331/662 (50.0)	0.99 (0.90–1.10)
Intraventricular hemorrhage, grade 3 or 4‡	83/630 (13.2)	81/640 (12.7)	1.06 (0.80–1.40)
Intraventricular hemorrhage, grade 3 or 4, or death‡	179/653 (27.4)	156/661 (23.6)	1.18 (0.99–1.42)
Periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49–1.42)
Periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96–1.45)
Necrotizing enterocolitis, stage ≥2§	76/641 (11.9)	70/649 (10.8)	1.11 (0.82–1.51)
Necrotizing enterocolitis, stage ≥2, or death§	176/654 (26.9)	155/662 (23.4)	1.18 (0.98–1.43)
Pneumothorax	47/654 (7.2)	43/662 (6.5)	1.12 (0.74–1.68)
Postnatal corticosteroids for BPD	61/636 (9.6)	69/644 (10.7)	0.91 (0.67–1.24)
Death			
By 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72–1.72)
By 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84–1.70)
Late-onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89–1.18)
Late-onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94–1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86–1.07)
Treatment for patent ductus arteriosus			
Medical	219/634 (34.5)	233/645 (36.1)	0.95 (0.82–1.09)
Surgical	73/641 (11.4)	68/648 (10.5)	1.09 (0.80–1.48)
Any air leaks in first 14 days	51/654 (7.8)	42/662 (6.3)	1.23 (0.83–1.83)

* Values were adjusted for stratification factors (study center and gestational-age group) as well as for familial clustering. BPD denotes bronchopulmonary dysplasia.

† The physiological definition of BPD includes, as a criterion, the receipt of more than 30% oxygen or the need for positive pressure support at 36 weeks or, in the case of infants requiring less than 30% oxygen, the need for any oxygen at 36 weeks after an attempt at oxygen withdrawal.

‡ There are four grades of intraventricular hemorrhage; higher grades indicate more severe bleeding.

§ There are three stages of necrotizing enterocolitis; higher stages indicate more severe necrotizing enterocolitis.

full text of this article at NEJM.org). Similar results were observed for both gestational-age strata. Survival analysis with the use of the unadjusted Kaplan–Meier method (Fig. 2) and a Cox proportional-hazards model produced similar results (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07).

The rate of severe retinopathy among survivors who were discharged or transferred to another facility or who reached the age of 1 year was lower in the lower-oxygen-saturation group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; P<0.001; number needed to treat, 11). Although

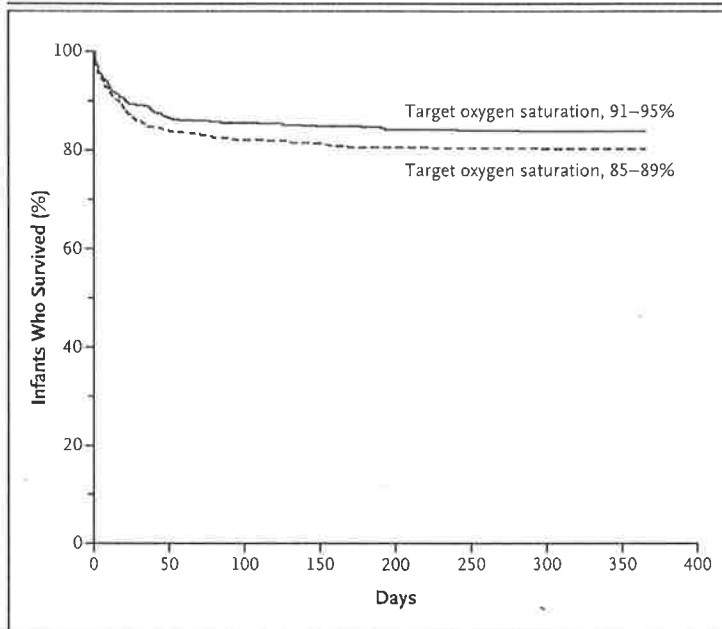


Figure 2. Kaplan-Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life.

Cox proportional-hazards analysis indicated that there was an increased hazard of death in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; $P=0.07$). The analysis assumed that infants who were discharged or transferred from the hospital survived to 1 year of age.

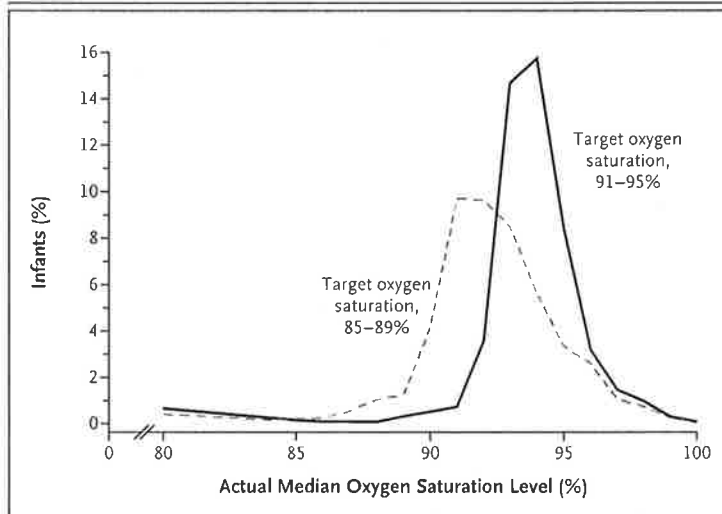


Figure 3. Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups.

The medians of the distributions were significantly different on the basis of a rank-sum test ($P<0.001$). The 80% level of oxygen saturation shown includes all values at or below 80%.

opathy or surgical intervention for retinopathy. Three ophthalmologists adjudicated results for the patients who did not meet the criteria for retinopathy, and the results were materially unchanged (Table 2 in the Supplementary Appendix).

SECONDARY OUTCOMES

The rate of oxygen use at 36 weeks was reduced in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group ($P=0.002$), but the rates of bronchopulmonary dysplasia among survivors, as determined by the physiological test of oxygen saturation at 36 weeks, and the composite outcome of bronchopulmonary dysplasia or death by 36 weeks did not differ significantly between the treatment groups. Other prespecified major outcomes also did not differ significantly between the two groups (Table 2).

The median level of oxygen saturation in infants who were receiving oxygen supplementation in the two treatment groups differed substantially but, as expected, there was considerable overlap (Fig. 3). The actual median levels of oxygen saturation were slightly higher than targeted levels in both treatment groups. The duration of oxygen supplementation was shorter in the lower-oxygen-saturation group, but the duration of mechanical ventilation, CPAP, and nasal synchronized intermittent mandatory ventilation did not differ significantly (Table 3 in the Supplementary Appendix). Other measures of resource use also did not differ significantly between the two groups.

DISCUSSION

In this multicenter, randomized trial, we found no significant difference in the primary outcome — severe retinopathy or death — between infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) and those assigned to a higher target range (91 to 95%). Assessment of the individual components of the primary outcome showed that the lower target range of oxygen saturation increased the risk of in-hospital death, whereas it reduced the risk of severe retinopathy among survivors. These results were observed even though there was substantial overlap of actual levels of oxygen saturation between the two treatment groups. Previous trials of targeting of levels of oxygen saturation have shown similar difficulties in maintaining levels of oxygen saturation within a narrow target range.^{18,22} Longer follow-up will be required to determine

use of bevacizumab was among the criteria for this outcome, only three infants received bevacizumab, and these infants also had threshold retin-

the effects of lower target ranges of oxygen saturation on functional visual and neurodevelopmental outcomes.

Despite the increase in mortality when restrictive oxygen supplementation was used in the 1950s and 1960s and the limited data from observational studies,^{3-5,15,16} it is becoming common practice to use lower target ranges of oxygen saturation with the goal of reducing the risk of retinopathy of prematurity.²³ The results of this large randomized trial to test the effect of lower versus higher target ranges of oxygen saturation, in conjunction with the results of previous studies, add to the concern that oxygen restriction may increase the rate of death among preterm infants. The combined risk difference observed in the trials from the 1950s was an absolute increase in in-hospital mortality of 4.9 percentage points in the oxygen-restricted group,¹ which is close to the absolute increase of 3.7 percentage points in the rate of death before discharge in the lower-oxygen-saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants at least 2 weeks after birth¹⁸ or after moderately severe retinopathy developed²² did not show an increased risk of death or a significantly reduced risk of retinopathy in the lower-oxygen-saturation groups. However, the lower target ranges of oxygen saturation in these trials — 91 to 94% in one trial and 89 to 94% in the other — were closer to the target range in our higher-oxygen-saturation group. The increase in mortality in our trial may be related to the lower target ranges of levels of oxygen saturation, the use of oxygen restriction started soon after birth, or both. A meta-analysis of early restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a reduction in severe retinopathy (relative risk, 0.19; 95% CI, 0.07 to 0.50) with a nonsignificant trend toward increased mortality.²⁴ These trials were performed by limiting the F_{iO_2} concentration usually to less than

0.50, at a time before the continuous monitoring of arterial oxygen saturation was possible. To our knowledge, no other randomized, controlled trials of different target ranges of oxygen saturation in supplementation initiated soon after birth have been performed since the availability of continuous transcutaneous monitoring of oxygen saturation. Like the meta-analysis²⁴ and most non-randomized studies,^{3-5,15,16} our trial confirmed that lower target ranges of oxygenation result in a large reduction in the incidence of severe retinopathy among survivors. However, our data suggest that there is one additional death for approximately every two cases of severe retinopathy that are prevented. Several ongoing trials across the world address the same intervention tested in the current trial.²⁵

In summary, a target range of oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, did not affect the combined outcome of severe retinopathy or death, but it increased mortality while substantially decreasing severe retinopathy among survivors. At the present time, caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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



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March 7, 2013

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

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

Dear Dr. Marchase:

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

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

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

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

Historical Background

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

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

¹ Much of the early history of retinopathy of prematurity recounted here is taken from W.A. Silverman, *Retrolental Fibroplasia: A Modern Parable*. Grune & Stratton, Inc., New York, N.Y. (1980), available at <http://www.neonatology.org/classics/parable>.

² E. Brown. Obituary for Arnall Patz. *Washington Post*, March 13, 2010.

³ L.K. Altman. Arnall Patz, a Doctor Who Prevented Blindness, is Dead at 89. *New York Times*, March 15, 2010.

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

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

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

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

⁴ V.E. Kinsey. Retrolental Fibroplasia: Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen. *Archives of Ophthalmology* 1956;56:481.

⁵ K.W. Cross. Cost of Preventing Retrolental Fibroplasia. *Lancet* 1973;302:954.

⁶ J.F. Lucey and B. Dangman. A Reexamination of the Role of Oxygen in Retrolental Fibroplasia. *Pediatrics* 1984;73:82.

⁷ National Eye Institute. Facts About Retinopathy of Prematurity (ROP). Available at <http://www.nei.nih.gov/rop>.

⁸ J.S. Greenspan, J.P. Goldsmith. Oxygen Therapy in Preterm Infants: Hitting the Target. *Pediatrics* 2006;118:1740. See also, e.g., an analysis of the literature performed for the Cochrane Collaboration. L.M. Askie, D.J. Henderson-

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

The Protocol

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

“Retinopathy of prematurity (ROP) remains a significant cause of morbidity among [extremely low birth weight] infants and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, but early trials were unable to pinpoint the actual level of arterial PaO₂ which was the threshold for triggering the pathophysiology of this disorder. . . . While retrospective cohort studies have suggested that the use of lower SpO₂ ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO₂ ranges for managing [such infants].” (p.2, “Statement of Problem,” 2004 protocol)

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

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

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

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

In particular, a non-invasive device known as a pulse oximeter, commonly used in clinical care, would be applied to the infant's foot or hand. That device measures the blood oxygen saturation (SpO₂), which is the percentage of hemoglobin in the infant's bloodstream that has oxygen bound to it. The amount of oxygen provided to the infant would then be adjusted to try to keep the SpO₂ within one of two discrete ranges of oxygen levels, *i.e.*, a "low" range of 85% to 89%, or a "high" range of 91% to 95%. Infants were randomly assigned to the low or the high range.

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

With regard to those possible differences in outcome, the researchers were specifically looking at both whether the infant survived, and whether the infant developed a fairly significant level of ROP (what is called "threshold" disease). As the protocol put it, the primary hypothesis they were testing was "that relative to infants managed with a higher SpO₂ range that the use of a lower SpO₂ range will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention."

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

The Consent Form Template

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

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

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

Several observations are appropriate with regard to this paragraph:

1. The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and ROP, and what that work indicates about how changing the oxygen range might affect whether an infant develops ROP.
2. The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and mortality and other forms of morbidity (apart from developing ROP).
3. The paragraph does not identify any specific risk relating to randomizing infants to a high or low range of oxygen.

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

Summary

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

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

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

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

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

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

The UAB Consent Form

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

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

At the front of the form:

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

In the section labeled “Introduction”:

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

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

In the section labeled "Procedures":

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

In the section labeled "Possible Benefits":

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

In the section labeled "Possible Risks":

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

With regard to this information, OHRP notes the following:

1. The form does not say that there may be a greater or lesser risk of death depending on whether the infant is in the lower or upper range group.
2. While the form says that being in the *lower* range group may result in the *benefit* of decreasing the chances of developing severe ROP, in the "Possible Risks" section it

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

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

A. Determinations Regarding the Consent Documents

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

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

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

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

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

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

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

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

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

⁹ W. Rich et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. *Pediatrics* 2012;129:480.

¹⁰ S.N. Whitney. The Python's Embrace: Clinical Research Regulation by Institutional Review Boards. *Pediatrics* 2012;129:576.

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

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

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

Results from the SUPPORT Study

The results of the SUPPORT study were published in the *New England Journal of Medicine* in 2010.¹¹ The rate of severe ROP among the infants who survived was significantly different between the low and high oxygen groups. Among the infants who were treated with low oxygen, only 41 out of 475 developed severe ROP, or 8.6%. In the high oxygen arm, more than double that percentage of infants developed severe eye disease: 91 out of 509, for a rate of 17.9%. The difference between these two groups was highly significant, with a P-value less than 0.001.

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

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

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

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

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

Requested Response

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

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

Sincerely,

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

cc:

Ms. Sheila D. Moore, Director, Office of the IRB, UAB

Dr. Ferdinand Urthaler, Chair, UAB IRBs

Mr. E. Ward Sax, V.P., Chief Risk Officer, Research Triangle Institute (RTI)

Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI

¹² Y.E. Vaucher et al. Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial. *New England Journal of Medicine* 2012;367:2495.

¹³ B. Stenson, P. Brocklehurst, and W. Tarnow-Mordi. Increased 36-Week Survival with High Oxygen Saturation Target in Extremely Preterm Infants. *New England Journal of Medicine* 2011;364:1680.

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March 7, 2013

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



Office of the Vice President for Research and Economic Development

March 22, 2013

Lisa R. Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight
Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

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

Dear Ms. Buchanan:

This letter is in response to your correspondence dated February 8, 2013 (and subsequent revision dated March 7, 2013) regarding the project referenced above. I am in receipt of a letter from the investigators of the NICHD Neonatal Research Network and authors of the SUPPORT Study Group. Allow me to provide an excerpt from that correspondence:

The investigators of the NICHD Neonatal Research Network and authors of the SUPPORT Study Group would like to first thank OHRP for presenting its concerns clearly and giving us an opportunity to share our thinking about these issues. The Neonatal Research Network investigators are committed to the highest standards of ethical conduct in our human subjects' research, especially where vulnerable participants are concerned. Please ... let us know if we can discuss any of the issues by conference call at your convenience. We welcome the opportunity to engage in a constructive dialogue with OHRP to ensure that if there are opportunities to improve our research practices, we will identify them and incorporate them into our program going forward.

OHRP's letter requested that UAB "provide a plan that the IRB will use to ensure that approved informed consent documents include and adequately address the basic elements of consent as required by HHS regulations at 45 CFR 46.116(a)". The following actions have already been implemented:

- The Office of the Institutional Review Board (OIRB) has revised the sample consent form (see Appendix I) provided to investigators. Information has been added to the Risks and Discomforts section to instruct investigators to include the specific risks of all arms even if those procedures fall within the parameters of standard of care.
- Checklists used by OIRB staff members to ensure both regulatory and institutional requirements are met prior to the IRB approval of a study have been refined to ensure inclusion of all of the basic elements of

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Lisa R. Buchanan – OHRP

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consent as required by HHS regulations at 45 CFR 46.116(a). The New Protocol Checklist is attached as Appendix II.

- OIRB staff members who coordinate the reviews of research protocols have been reminded that the risks of all study arms must be described in the consent document, even when those arms fall within the parameters of standard of care.

We believe the steps described above will ensure that approved informed consent documents will include and adequately address the basic elements of consent as required by HHS regulations at 45 CFR 46.116(a). The UAB OIRB continually seeks ways to improve its already strong program of human research protection and is appreciative of OHRP's recommendations and guidance.

Please do not hesitate to contact me if OHRP has questions or suggestions in this regard.

Sincerely,

A handwritten signature in cursive script that reads "Richard B. Marchese".

Richard B. Marchese, Ph.D.

Vice President for Research and Economic Development

cc: Ferdinand Urthaler, MD, Chair, UAB IRBs
Jonathan Miller, Director, UAB Office of the IRB

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Appendix I – UAB IRB Sample Informed Consent Document

Sample Consent Form

It is impossible to address all scenarios for the many types of research protocols conducted by UAB researchers. This sample is designed to assist you in the preparation of consent forms. It is intended to show language preferred by the UAB IRB to address the essential elements of informed consent. In many cases, the sample language will need to be modified, deleted, or expanded for the particular study.

Shaded paragraphs like this one are Instructions for you, the writer. Do not include them in the consent form you submit. If the instructions indicate that specific language applies to your protocol, the specific language will be shown below the instructions outside of the shaded paragraph.

Use this sample consent form as a guide for obtaining consent and/or assent from participants 14 years of age and older.

Formatting Instructions

- Use a 12 pt font for the consent form.
- Write the consent form in the 2nd person (i.e., you) and keep the pronoun usage consistent throughout.
- Use *Page X of Y* numbering on each page.
- Leave an area approximately 1 inch by 2 inches on the bottom of the first page for the IRB approval stamp.

Use understandable, non-technical language at an 8th-grade or lower reading level.

- Readability statistics can be displayed in Microsoft Word. Search Microsoft Office Help for "readability statistics" for further instructions.

DELETE THIS FIRST PAGE OF INFORMATION
IF YOU ARE USING THIS DOCUMENT
TO CREATE YOUR CONSENT FORM.

CONSENT FORM

TITLE OF RESEARCH: Evaluation of the Safety and Efficacy of Trimycin vs. Hydrochlorothiazide in the Treatment of Hypertension

IRB PROTOCOL: F#####

INVESTIGATOR: John Doe, Ph.D.

SPONSOR: If the protocol is being sponsored by UAB departmental funds or is unfunded, put the name of the department here (e.g., UAB Department of Medicine). For student research, include the student's departmental affiliation.

If additional or other support is being provided, include this information with a heading such as "**SUPPORTED BY:**" After the SPONSOR line.

SPONSOR: Wise Drug Company, Inc.

RESEARCH INVOLVING CHILDREN:

- When a parent or guardian is providing consent for only the child participant who will sign the assent section of the consent form, do not use "you/your child" throughout the form. Instead, use "you" and insert the following text after the SPONSOR line and before the Purpose of the Research section:

For Children (persons under 19 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").

- When a parent or guardian is providing consent for only the child participant who will sign a separate assent form or who will not provide written assent, use "your child" throughout the form.
- When a parent or guardian is providing consent for both him/herself and the child participant, specify throughout the consent form when you are referring to the parent and when you are referring to the child. This would allow for the use of "you," "your child," and "you and your child" throughout the form.

Purpose of the Research

- Explain the purpose of the study in nontechnical language.
- Describe why the participant is being asked to join.
- State that the study involves research.
- If drugs or devices are used, indicate whether they are FDA approved or investigational.
- If applicable, explain what a Pilot, Phase I, II, III, or IV drug study is.
- State the total planned number of participants (e.g., individuals, records, specimens) to be enrolled by the UAB investigator, and studywide for multicenter studies.

We are asking you to take part in a research study. This research study will test how well a new drug lowers blood pressure. The new drug, Trimycin, is investigational and not yet approved by the U.S. Food and Drug Administration (FDA). People who enter into the study will take either the new drug, Trimycin, or Hydrochlorothiazide (water pill). Hydrochlorothiazide is the FDA approved drug that most people take now to lower blood pressure. Trimycin is approved in Europe, but has not been approved in the United States. More than 200 people in other research studies in the United States have safely used Trimycin. This is a Phase III study. A Phase III study is a research study that looks at a large number of patients receiving a common or routine treatment. This study will enroll 200 participants nationwide, and 20 of them will come from UAB.

Explanation of Procedures

- Describe the procedures to be followed, identifying which procedures are for research and which procedures are standard of care.
- Identify which procedures are experimental.
- Estimate the amount of time involved in study participation.
- If specimens (e.g., blood, tissue, body fluids) will be collected as part of the research procedures, describe the collection in this section. If the specimens will be stored for future research, describe the storage procedures under "Storage of Specimens for Future Use."

If you enter the study, all your current blood pressure medicines will be stopped for 1 month. During this time, you will be given pills called placebos. A placebo does not have any active medicine, so it should not have any effect on your blood pressure. However, this placebo might cause your blood pressure to lower. The study staff will need to watch your blood pressure closely while you are not on any medicine for your blood pressure. Your blood pressure will be watched to make sure it does not rise so high that you need immediate treatment. You will need to come for office visits three times during the first week. You will need to come for office visits two times per week during Weeks 2, 3, and 4. If your blood pressure is in the range required after Week 4, you will be entered into the study. If your blood pressure is not in the range required after Week 4, you will not be entered into the study and will receive standard care for your blood pressure. If you are entered and complete the entire study, you will be in the study for 6 months. If you qualify for the study, you will be randomly picked (like the flip of a coin) by a computer to receive either Trimycin or Hydrochlorothiazide. You will take the medicine once a day by mouth. This will be a double-blind study. This means neither you nor your doctors will know which medicine you are taking. If medically necessary, the doctor can find out which drug you are taking.

These tests will be made during the study: lab blood tests, urine tests, weight measures, resting electrocardiogram, heart rate, and blood pressure. (An electrocardiogram measures the electrical activity of the heart.) You will be asked to come back to the clinic for 20 weekly visits. At each visit you will be asked if you have had any bad reactions and how you are feeling on the drug.

If drug screening is part of the protocol, include a statement such as:

If you have used any illicit (street) drug(s) within the past 3 months, we ask that you not participate in this project.

Where HIV testing is conducted, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling before and after the testing.

Where other protocol testing for reportable diseases is conducted, individuals will be informed of the results and told where to obtain counseling and referred to their primary care physician or the state health department.

Incidental Findings

If research-only imaging studies are part of the protocol, address whether or not the images will be read for incidental findings. If the images will not be read for incidental findings, include the following:

We are performing imaging solely for the research purposes described above. It is not a clinical scan intended for diagnostic or therapeutic purposes. Under no circumstance will the investigator, research staff, or imaging staff interpret the scan as normal or abnormal. They are unable to make any medical comments about your scan. The scan will not be looked at or read for any healthcare treatment or diagnostic purpose. If you want your scan to be reviewed by a physician so that the physician can look for medical issues, you can request a copy of your scan. We will provide an electronic copy at no charge.

Risks and Discomforts

- Include any foreseeable risks or discomforts to the participant (e.g., physical, social, financial, loss of employability, reputation, and breach of confidentiality).
- When possible, quantify the risks involved (e.g., *common, rare, percentages*).
- If the study involves a placebo,
 - define placebo (not as *treatment or medication*; see paragraph above that begins "*If you enter the study...*")
 - describe what complications may result
 - describe the precautions that will be taken to protect the participant during this time.
- Do not include risks or discomforts associated with drugs or interventions that are not being administered or performed as part of this study.

You may have some side effects from taking these drugs. The side effects of Trimycin are headaches, feeling drowsy, and feeling tired. About forty percent (40%) of people who take Trimycin have reported feeling drowsy and tired. About twenty percent (20%) of people who take Trimycin have headaches. Hydrochlorothiazide can cause the following side effects: low blood potassium; a rise in blood uric acid and blood sugar; and a lowering of red and white blood cells. About eighty percent (80%) of people who take Hydrochlorothiazide have these problems. There may also be risks that are unknown at this time. You will be given more information if other risks are found.

Randomization: If your protocol involves randomization, include a paragraph on risks of randomization. Ensure the risks of all study arms are described in detail in this section, even if the procedures in those arms would be standard of care if the participant was not in the study. For example:

You will be assigned to a treatment group by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

Information for Women of Childbearing Potential and/or Men Capable of Fathering a Child

If applicable, include this section and address the precautions that should be taken by women of childbearing potential and/or by men capable of fathering a child before, during, and/or after participation. List the specific acceptable methods of birth control for participants involved in the study. Use only the information that is applicable to the study population.

We do not know if the study drug will affect mother's milk or an unborn fetus. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time. Women who can become pregnant must take a pregnancy test before the start of the study.

You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex.

Unless you cannot have children because of surgery or other medical reasons, you must have been using an effective form of birth control before you start the study. You must also agree to continue to use an effective form of birth control for 6 months after taking the study drug. Effective birth control includes birth control pills, patch, IUD, condom, sponge, diaphragm with spermicide, or avoiding sexual activity that could cause you to become pregnant.

Benefits

- State any potential benefits to the participant or to others that may reasonably be expected from the research.
- Do not overstate benefits.
- If there is no potential for direct benefit to the participant, that should also be stated.
- **Do not include** medication, treatment, devices, or compensation information.

You may not benefit directly from taking part in this study. However, this study may help us better understand how to treat high blood pressure in the future.

Alternatives

- Include appropriate alternative procedures or courses of treatment that may be advantageous to the participant.

- One alternative may be to not participate in the study.

There are many other drugs that are used to treat high blood pressure. Some examples of these drugs are Betaspan, Enalapril, and Lisinopril. The investigator or research staff will discuss these other drugs with you.

Confidentiality

- Include information regarding anyone who will receive identifiable data (e.g., through subcontracts or other agreements).
- Include the US Food and Drug Administration (FDA) if the research involves a drug, device, or biologic subject to FDA oversight.

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of [ADD SPONSOR NAME] and the Office for Human Research Protections (OHRP). The results of the treatment may be published for scientific purposes. These results could include your [ONLY INCLUDE APPLICABLE] lab tests and X-rays. However, your identity will not be given out.

Permanent Medical Record: If the consent form will be placed in the participant's permanent medical record at University of Alabama Hospital and/or The Children's Hospital of Alabama, include the following:

If any part of this study takes place at

[UAB ONLY] University of Alabama Hospital

[TCHA ONLY] The Children's Hospital of Alabama

[UAB & TCHA] University of Alabama Hospital and The Children's Hospital of Alabama

this consent document will be placed in your file at that facility. The document will become part of your medical record chart.

Billing Compliance Language: Only if "clinical billable services" will be provided at a UAB Health System location (i.e. HSF Clinics, UAB Hospital, UAB Highlands, or Callahan Eye Foundation) or The Children's Hospital of Alabama, include the language below, as applicable. If you have questions about UAB's clinical trial billing, contact the Fiscal Approval Process (FAP) staff at FAP@uab.edu. For details on submission requirements, go to <http://www.uab.edu/osp/fiscal-approval-process-fap>. If you have questions about clinical trial billing for studies conducted at The Children's Hospital of Alabama, contact Pam Barlow at pam.barlow@chsys.org or 558-2452.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of

[UAB ONLY] UAB and UAB Health System affiliated entities

[TCHA ONLY] The Children's Hospital of Alabama and its billing agents

[UAB & TCHA] UAB and UAB Health System affiliated entities, along with The Children's Hospital of Alabama and its billing agents

so that claims may be appropriately submitted to the study sponsor or to your insurance company for clinical services and procedures provided to you during the course of this study.

International Protocols: Only if the study is conducted outside the United States or sponsored by a company based outside the United States and foreign regulatory agencies will have access to identifiable research records, include the following:

Monitors, auditors, the Institutional Review Board for Human Use, and regulatory authorities will be granted direct access to your original medical records for verification of trial procedures and/or data without violating confidentiality.

ClinicalTrials.gov: For applicable clinical trials, include the statement below. It is the responsibility of the sponsors and investigators to determine if their clinical trial meets the definition of an "applicable clinical trial" and to ensure compliance with the most current applicable statutory and regulatory requirements. If you have any questions regarding registering a study on ClinicalTrials.gov, contact Penny Jester at 934-2424 or pjester@uab.edu.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Reportable Diseases/Conditions: Only if the investigator will be testing for any reportable diseases/conditions, include a statement specifying what reportable diseases/conditions are being tested and that positive results will be reported to the county or state health department.

Screening for Drugs, Observations of Abusive Behavior: Only if the investigator will conduct drug screening or inquire about abusive behavior (e.g., child or elder abuse or neglect, or harm to self) as part of the protocol, include the following statement:

Information obtained during the course of the study which, in the opinion of the investigator(s), suggests that you may be at significant risk of harm to yourself or others will be reportable to a third party in the interest of protecting the rights and welfare of those at potential risk.

Genetic Research: Only if the research involves genetic testing, describe the protections provided to the participant under GINA. For questions regarding GINA, see the IRB Guidebook. The following may be used for the description:

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.

- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

Voluntary Participation and Withdrawal

- Include the consequences of a participant's decision to withdraw from the research.
- Include procedures for orderly termination of participation by the participant.
- If applicable, include anticipated circumstances under which the PI without regard to the participant's consent may terminate the participant's participation (see second paragraph below).

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

You may be removed from the study without your consent if the sponsor ends the study, if the study drug is approved by the FDA, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

If students or employees of UAB may participate in the study, the IRB recommends using the following language in the consent form:

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll, or withdraw after enrolling at any time before the study is over, with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

Cost of Participation

- If any costs to the participant or the participant's health insurance might result from the research (e.g., for tests, drugs, biologics, devices, or copayments), describe those costs. Include information about any financial assistance that may be available, such as how to consult a social worker.
- If there is no cost to the participant, this should be stated.

There will be no cost to you for taking part in this study. All drugs, exams, and medical care related to this study will be provided to you at no cost during the 6-month study period.

If standard medical care may be provided during the study include the following statement:

The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

If participants may be enrolled in Medicare Advantage and will have study related services billed to their Medicare Advantage Insurance, include the following statement. If you have questions regarding the inclusion of this statement, contact the Fiscal Approval Process (FAP) staff at FAP@uab.edu.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

Payment for Participation in Research

- Note: Payment may not be based upon successful completion of the protocol.
- Specify the amount and type/method of compensation a participant will receive for participating OR that there is no compensation for participation.
- If applicable, include the payment schedule.
- Describe prorated payments for participants who withdraw before the end of the study.
- If children are involved, specify whether the child or parent is being paid.

You will be paid \$10 for each study visit, including the placebo phase of the study. If you quit the study, you will be paid \$10 for each study visit made to the clinic. Payments will be made after 3 months and 6 months if you complete the entire study. Payments will be made by check sent to you in the mail. If you do not finish the entire study, you will be paid at the time you decide to stop taking part in the study. If you complete the entire study, you will receive a total of \$290.

If a participant is to earn \$600 or more in a calendar year from their participation in research, include the following language:

You are responsible for paying any state, federal, Social Security or other taxes on the payments you receive. You will receive a form 1099 in January of the year following your participation in this study. This form is also sent to the IRS to report any money paid to you. No taxes are kept from your check.

Payment for Research-Related Injuries

- Include this section only if the research involves (a) greater than minimal risk or (b) procedures or interventions that could result in harm or injury.
- If the section is to be included, include the UAB statement below.

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

In addition, if the research is sponsored, include language that addresses whether or not the sponsor(s) will provide compensation for research-related injuries.

- For sponsored research where the sponsor(s) **will not** pay for compensation to injured research participants or pay for medical treatment of research-related injuries, list the names of all sponsors after "UAB".

UAB and Wise Drug Company, Inc. have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

- For sponsored research where the sponsor(s) **will** pay participants for either compensation or treatment for research-related injuries, include the specific language provided by the sponsor(s) regarding injury compensation. The IRB must be provided with "sponsor verification" either in the form of a letter signed by the sponsor(s) with the same wording given in the consent form or a model consent form included in the protocol and listed in the Table of Contents of the protocol with the same wording. Do not submit a copy of the indemnification letter as the verification. Include information regarding what medical treatment will consist of if injury occurs and where further information may be obtained.

Significant New Findings

Indicate that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided to the participant by the principal investigator or his/her staff.

You will be told by your doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Genome-Wide Association Studies (GWAS)

For protocols that are considered Genome-Wide Association Studies (GWAS), UAB must certify that plans for the submission of genotype and phenotype data from GWAS to the NIH meet the expectations of the policy. See the IRB Guidebook for more information on what should be submitted for this certification. For applicable protocol, include the following:

The DNA that composes your genes will be analyzed and that data, which is referred to as your genotype or complete genetic makeup, will be compared to your phenotype, which consists of your observable traits, characteristics, and diseases. Your genotype and phenotype data will be shared for research purposes through the National Institutes of Health (NIH) Genome-Wide Association Studies (GWAS) data repository. The aim of this research is to discover genetic factors that contribute to the development, progression, or therapy for a particular disease or trait.

Questions

- Include the name of the Principal Investigator and his/her contact number for participants to contact regarding the research and research-related injuries.
- Include the names of additional contact personnel, if applicable.

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, you may contact Dr. John Doe. He will be glad to answer any of your questions. Dr. Doe's number is 205-934-3810. Dr. Doe may also be reached after hours by paging him at 205-934-3411 (beeper 9999).

Include for the Office of the IRB contact information.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Storage of Specimens for Future Use

If specimens (e.g., blood, tissue) obtained for the research may be stored for research not specifically defined in the protocol, place this section after Legal Rights and before Signatures. At a minimum, address the following points and include lines for participants to initial (do not use checkboxes):

- What kind of specimens will be collected and the means of collection.
- What type of research will be done with the specimens.
- Whether the specimens will be shared with other investigators
- Whether the specimens will be coded or anonymized (no way of tracing back to participant/uncoded or code destroyed).
- Whether the participant may be contacted for additional consent.
- How long, if known, the biological specimens will be stored. (Short-term: current protocol only or other current research; Long-term: future studies on disease or condition, repository, etc.).
- Foreseeable risks or benefits to participants in the collection, storage, and subsequent research use of specimens.
- What will be done with the biological specimens if the participant refuses permission.
- What will be done with the research results. (Research results should not be placed in the individual participant's medical record.)
- Potential for commercial use of the subject's specimen(s).
- How to withdraw consent for future use.

As part of this study, we would like to store some of the blood and urine specimens collected from you for future research on hypertension. The future research may be conducted by Dr. John Doe or by other researchers that obtain IRB approval for their research. The specimens will be

labeled with a code that only Dr. John Doe can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur.

You do not have to agree to allow your blood and urine specimens to be stored in order to be part of this study.

You may request at any time that your research samples be removed from storage and not be used for future research. If you decide you want your samples removed, you may contact Dr. John Doe at the University of Alabama at Birmingham at 205-934-3810. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial your choice below:

I agree to allow my samples to be kept and used for future research on hypertension.

I do not agree to allow my samples to be kept and used for future research.

Signatures

It is impossible to address all scenarios for signature requirements that may be needed for various types of research. These instructions and samples are designed to assist you in the preparation of the Signatures section. In many cases, the Signatures section will need to be customized for the particular study population.

- The requirements for signature lines depend upon the consent process described in the Human Subjects Protocol.
- Each signature-date line included in the Signatures section, as applicable to the research, must be signed and dated.
- All signatures must appear on the same page, but that page does not need to be a separate page with no other information.
- Each person who signs the consent form must include the date of his/her signature.
- If the research involves children (i.e., individuals younger than 19 years of age for research conducted in the state of Alabama), see "Children" under General Information in the IRB Guidebook and see Example Signatures for Research Involving Children, below.
- If the research involves pregnant women, see "Pregnant Women, Fetuses, Neonates" under General Information in the IRB Guidebook.
- A signature-date line for the participant must be included. The three acceptable options are shown and described below.

Your signature below indicates you agree to participate in this study. You will receive a copy of this signed consent form.

Option 1

Signature of Participant

Date

Option 2

Signature of Participant or Legally Authorized Representative

Date

Option 3

Signature of Participant

Date

Signature of Legally Authorized Representative

Date

Legally Authorized Representatives (LAR)

- If the research proposes to obtain consent from the participant **or** the LAR, add "(or Legally Authorized Representative)" after "Signature of Participant."
- If the research proposes to obtain consent from the participant **and** the LAR, include a separate signature-date line for each person.
- If an individual is not capable of providing informed consent, the IRB allows that it may be obtained from the individuals listed below in priority order:
 - Judicially appointed guardian or individual named in a durable power of attorney;
 - Spouse;
 - Sons or daughters 19 years of age or older;
 - Either parent;
 - Brother or Sister 19 years of age or older;
 - Other nearest kin 19 years of age or older.

Signature of Principal Investigator

Date

- All persons who discuss or obtain informed consent must be listed in the HSP.
- If the principal investigator is not the only person who will conduct informed consent discussions and obtain signatures, add "or Other Person Obtaining Consent" after "Signature of Principal Investigator."
- If the Principal Investigator will never obtain informed consent, this signature-date line should be labeled "Signature of Person Obtaining Informed Consent."

Signature of Witness

Date

- Include this line unless the PI requests and justifies, and the IRB approves a waiver of the witness requirement.
- The person administering the consent (e.g., study coordinator) cannot sign as the witness.

Reviewed by:

Signature of Principal Investigator Reviewing Consent Document

Date

Include this line **only if** the HSP specifies that the principal investigator will not obtain informed consent but will only review signed consent documents.

Signatures for Research Involving Children

You are making a decision whether or not to have your child participate in this study. Your signature indicates that you have read (or been read) the information provided above and decided to allow your child to participate.

- The requirements for signature lines depend upon the consent process described in the Human Subjects Protocol. See the instructions and options below.
- The UAB IRB usually recommends the following:
 - Waiver of assent needs to be documented for participants under 7 years of age, but these participants should be included in the consent process if possible.
 - A separate assent form should be prepared for use with, and to document the assent of, participants who are 7-13 years old.
 - Participants 14-18 years old document their assent by signing the main consent form.
- If the IRB determines the permission of only one parent or guardian is necessary, only include one line for "Signature of Parent or Guardian" below.
- A parent, for purposes of consent, means either a child's biological or adoptive parent. In some instances, the consent of a guardian may be used in lieu of parental consent. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. For purposes of research conducted in Alabama a *guardian* is:
 1. A person appointed guardian of a child pursuant to the Alabama Uniform Guardianship and Protective Proceedings Act (Code of Alabama, Title 26) as documented by a valid court order;
 2. A person having legal custody of a child and as documented by court order;
 3. A person acting *in loco parentis*, regardless of whether such is documented by a court order. A person acts *in loco parentis* of a child where the individual voluntarily assumes responsibility for the child's custody, care, and maintenance even though no court order exists formally appointing the person as the guardian, legal custodian, or adoptive parent of the child. If such individuals may provide permission for the enrollment of children, the Human Subjects Protocol must explain how the investigator will confirm the *in loco parentis* relationship.

You will receive a copy of this signed informed consent document.

Signature of Participant 14-18 Years of Age

Date

Signature of Parent or Guardian

Date

Signature of Parent or Guardian

Date

Signature of Investigator or Person Obtaining Consent

Date

Signature of Witness

Date

If the assent of any child participant may be waived, include the following section with the applicable reason(s) for walver of assent marked:

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:

Age _____ Maturity _____ Psychological state of the child _____

Signature of Parent or Guardian

Date

Signature of Parent or Guardian

Date

Signature of Investigator or Person Obtaining Consent

Date

Signature of Witness

Date

University of Alabama at Birmingham
**AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION
FOR RESEARCH**

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant Name: _____
Research Protocol: Evaluation of the Safety and Efficacy of Trimycin vs. Hydrochlorothiazide in the Treatment of Hypertension

UAB IRB Protocol Number: F#####
Principal Investigator: John Doe, Ph.D.
Sponsor: Wise Drug Company, Inc.

What health information do the researchers want to use? All medical information and personal identifiers, including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____

Date: _____

or participant's legally authorized representative: _____

Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Appendix II – New Protocol Checklist

New Protocol Checklist

Full Convened Research no more than minimal risk (Expedited Category # _____)

Principal Investigator: _____ FAX: _____ IRB Protocol #: _____

Contact Person: _____ PHONE: _____ IRAP Created

Protocol Title: _____

Faculty Sponsor: _____ Training Complete: Y N - Needed for: _____

Sponsor: _____ DOD DOE DE DOJ/NIJ/Bureau of Prisons ICH/GCP applies

OSP Proposal # _____ Funding App/Grant Subcontract MTA CDA DUA FFS

HSP Sponsor Protocol (date) _____

PORF or CTCR Titles Match – Grant/Sponsor Protocol HSP ICF

1572 IB, Package Insert, or Device Manual _____

Waiver of IC Waiver of Auth & IC Waiver of IC Documentation

Consent/Assent Form(s) # _____ Sponsor Sample CF ICH/GCP criteria met (if applicable)

<input type="checkbox"/> Title, IRB Protocol #, Investigator, & Sponsor/Support	<input type="checkbox"/> Alternatives	<input type="checkbox"/> Payment for Participation
<input type="checkbox"/> Version Date	<input type="checkbox"/> Confidentiality	<input type="checkbox"/> UAB Injury Statement
<input type="checkbox"/> Page #s	<input type="checkbox"/> Permanent Medical Record	<input type="checkbox"/> Sponsor Injury Statement
<input type="checkbox"/> You/your child box	<input type="checkbox"/> UAB <input type="checkbox"/> TCHA	<input type="checkbox"/> Sponsor Verification
<input type="checkbox"/> Purposes of the Research	<input type="checkbox"/> Billing Compliance	<input type="checkbox"/> New Findings
<input type="checkbox"/> Statement re: research	<input type="checkbox"/> UAB <input type="checkbox"/> TCHA	<input type="checkbox"/> GWAS
<input type="checkbox"/> Explanation of Procedures	<input type="checkbox"/> International Protocol	<input type="checkbox"/> Name/Number (Research/Injury)
<input type="checkbox"/> Identify experimental procedures	<input type="checkbox"/> Clinical Trials.gov	<input type="checkbox"/> Name/Number (Participant Rights)
<input type="checkbox"/> Expected duration of participation	<input type="checkbox"/> Reportable Diseases/Conditions	<input type="checkbox"/> Legal Rights
<input type="checkbox"/> Incidental Findings	<input type="checkbox"/> Screen Drugs/Observe Abuse Behavior	<input type="checkbox"/> Storage of Specimens
<input type="checkbox"/> Risks and Discomforts	<input type="checkbox"/> Genetic Research/GINA	<input type="checkbox"/> Signatures
<input type="checkbox"/> Randomization risks	<input type="checkbox"/> Voluntary Participation & Withdrawal	<input type="checkbox"/> Assent of Child/Waiver of Assent
<input type="checkbox"/> Childbearing &/or Fathering	<input type="checkbox"/> Student/Employees	<input type="checkbox"/> HIPAA
<input type="checkbox"/> Benefits	<input type="checkbox"/> Cost of Participation	
	<input type="checkbox"/> Cost of SMC	<input type="checkbox"/> FAP
	<input type="checkbox"/> Medicare Advantage language	

Pharmacy Release TKC, notif attached - Y N

Radiation Safety Approval UH, notif attached - Y N

Infection Control Approval UAB Highlands, notif attached - Y N

Pathology Release TCHA, notif attached - Y N

IBC Approval EFH, notif attached - Y N

CIRB Conflict Identified CRU, notification attached - Y N

Include CIRB Language Other UAB sites _____

FERPA Applies Non UAB sites _____

PPRA Applies Engaged in Research: Y N If yes, IRB approvals Y N

Children - CRL# _____ Pregnant Women & Fetuses Nonviable or UV Neonates Decisionally Impaired

Prisoners - Cat# _____ Student/Employees Non-English Speakers

Recruitment Materials _____ Partial Waiver of Authorization

SAE Log submitted. Date/numbers _____ Screening Script/Questionnaire

Other Questionnaires _____

Phase: _____ DSMB Int. Analysis Sponsor/PI Monitoring Plan Plan Described

Describes alternate plan for SAE reporting Board approved at meeting?

Requests waiver of 24 hour "think it over" Board approved at meeting?

Drugs/Devices Name and IND/IDE Number _____

IRB pre-start up visit taken place, if Investigator is both sponsor and holder of IND/IDE IRAP Approved

WRITE REVIEWER NOTES ON BACK OF THIS PAGE.

OHRP Media Quotes, Statement, Talking Points and Q&A

New York Times

April 15, 2013

Crucial Studies, Fragile Subjects

By SABRINA TAVERNISE

The study's designers agreed that the risk of blindness should have been more clearly explained, but said that the infants were within the standard band of care, and therefore facing the same steep odds as any premature infant not in the study.

Dr. Menikoff disagreed.

"To be told that this was all standard care — it wasn't," he said. "It was taking a child and flipping a coin and giving them 50 percent chance of being at the higher end and 50 percent chance of being at the lower end. They were changing what happened to all of the children."

Washington Post

Watchdog agency criticizes ethics of study of premature infants

By David Brown, Published: April 10

"The consent form was written in a slanted way," said Jerry A. Menikoff, director of the Office for Human Research Protections (OHRP), which found that the study was "in violation of the regulatory requirements for informed consent" required by federal law.

"They went out of their way to tell you that your kid might benefit," he said in an interview. "But they didn't give the flip side, which is that there is a chance your kid might end up worse off. You can't have it both ways."

"You're intentionally shoving [the babies] into one end or the other of the range. And they were studying very real consequences in the kids," Menikoff said.

OHRP's proposed comment from Jerry Menikoff (4/18 for response to WSJ):

Protecting human subjects in research studies is our top priority. The SUPPORT study was indeed an important one, but its consent form was seriously flawed. It inadequately apprised the infant subjects' parents of reasonably foreseeable risks of severe retinopathy and death. Participating in the study would, in many cases, have altered the oxygen level a child received, compared to what a child would have received had he or she *not* participated in the study. And, accepting the hypothesis put forth by the researchers in the study's protocol, changes in oxygen levels could increase the risks that some children would develop severe retinopathy or even die. A consent form that clearly lays out the possible risks and benefits would have given parents better information to help them make a truly informed choice for their child.

OHRP Statement:

Cleared on Fri., April 12

Attribute to Jerry Menikoff, MD, JD, Director, HHS Office for Human Research Protections

The Office for Human Research Protections (OHRP) was created to ensure that human subjects are appropriately protected in the course of their participation in research. Fully informed consent is one of the bedrock ethical protections for research involving human subjects.

OHRP maintains that the SUPPORT study inadequately apprised the infant subjects' parents of reasonably foreseeable risks of blindness, neurological damage and death.

It is the responsibility of the investigators who conduct the research, and the institutional review boards that approve the research, to ensure that consent is adequate. When they fail to ensure proper consent – as was the case with the SUPPORT study – OHRP requires institutions to take appropriate corrective actions. Those corrective actions could involve, among other things, informing the parents of the inadequacy of the consent process used when enrolling subjects for this study.

OHRP does not take issue with the research design. The study asked an important question that needs to be answered. OHRP's exclusive concern is whether the parents of children entered into the study were appropriately informed of related risks—and with preventing a future occurrence of this nature.

OHRP Talking Points:

Talking points

- Fully informed consent is one of the bedrock ethical protections for human subjects involved in research.
- For research posing more than minimal risk to subjects, Federal rules governing human subjects research require that prospective subjects or their representatives be apprised of risks, benefits, and alternatives to research participation in order that they may gauge the advisability of participating in the study. In application, however, processes and forms for obtaining consent vary widely.
- It is the responsibility of principal investigators and of the Institutional Review Boards that approve and monitor research to ensure that consent is adequate. Today's complex research enterprise argues for improving the process of informed consent to emphasize essential consent elements.
- Findings regarding the SUPPORT study speak to the need to reexamine current systems and procedures of Institutional Review Board research review and, especially, informed consent.

OHRP Q&A:

1). OHRP maintains that the SUPPORT study inadequately apprised the infant subjects' parents of reasonably foreseeable risks or discomforts to the subjects. If both interventions were within the "standard of care," as suggested in the consent form, why was it even necessary to inform the subjects' parents about possible risks of the interventions?

The purpose of the SUPPORT trial was to ascertain the preferred range of treatment *within* the current standard of care. Consequently, infants were assigned to either the upper or the lower extreme of that range, thereby altering the level of actual risk. From more than 50 years of previous research and from clinical experience, it was well known that infants at lower levels of

oxygen were at decreased risk of retinopathy of prematurity (ROP, or blindness) but increased risk of impaired neurological development and even death, whereas infants at higher oxygen levels were at increased risk of blindness. Indeed, the purpose of the study was to determine the optimal oxygen level within the range of treatments customarily used.

As noted in OHRP's determination letter, the SUPPORT study protocol included the usual section entitled "Risks and Benefits." The section did not identify any risks relating to randomizing subjects to the low or high range of oxygen. Similarly, the consent form template did not identify any specific risk related to randomizing infants to a high or low range of oxygen; neither did it include information about prior research and analyses related to the relationship between oxygen level and ROP or between oxygen level and mortality or morbidity other than ROP.

To adequately portray risk, the SUPPORT study should have apprised prospective participants or their representatives (parents) that actual risks associated with the specific study interventions were yet to be determined by this and possible future studies. Nor did the investigators fully convey the findings of more than 50 years of previous research into this question.

- 2) Describe the essential elements of informed consent.

Federal regulations require that consent forms include

- a statement that the study involves research
- an explanation of the purpose of the research
- a description of procedures
- identification of any experimental procedures
- a description of any foreseeable risks or discomforts
- a description of any benefits to the subjects or others
- disclosure of appropriate alternative procedures or courses of treatment that may be advantageous to the subject.

- 3) What were the consequences of the SUPPORT study to participants and their families?

Significantly fewer infants in the lower-oxygen arm of the study experienced ROP; however, significantly more infants died before discharge. Results from a longer-term followup study indicate that, among infants who survived, there was no difference between the two groups in neurological development.

OHRP concluded that the researchers had sufficient available information before initiating the study to know that participation might lead to differences in whether an infant survived or developed blindness, compared with what that infant might have experienced had that infant not been enrolled in the study.

- 4) If consent forms at all sites were inadequate, why was OHRP's determination letter addressed only to UAB?

The principal investigator in charge of this research is based at UAB. OHRP deemed a single letter, copied to other trial sites, sufficient to the purpose of notifying all involved.

- 5) What are next steps for imposing sanctions on the institutions involved?

Involved institutions are required to propose corrective actions. HHS has the authority to accept or reject those proposals and may, in the most extreme case, deny the institutions' ability to receive federal funding for research.

OHRP has required UAB to propose corrective actions appropriate to address the regulatory noncompliance found by OHRP. This could involve a plan to enhance oversight by its IRB when reviewing

research in the future, it may include requiring investigators, IRB staff, and IRB members to receive additional training and education, and it may also include notifying subjects' parents of OHRP's findings. OHRP has the authority to accept or reject an institution's proposed corrective actions and, in the most extreme instances, could suspend an institution's ability to conduct federally funded human subjects research.

6) If consent forms at all sites were inadequate, why was OHRP's determination letter addressed only to UAB?

The principal investigator in charge of this research is based at UAB. OHRP deemed a single letter, copied to other trial sites, sufficient to the purpose of notifying all involved.

7) What are next steps for imposing sanctions on the institutions involved?

Involved institutions are required to propose corrective actions. HHS has the authority to accept or reject those proposals and may, in the most extreme case, deny the institutions' ability to receive federal funding for research.

OHRP has required UAB to propose corrective actions appropriate to address the regulatory noncompliance found by OHRP. Appropriate corrective actions when the research at issue is no longer ongoing could involve a plan to improve IRB oversight when reviewing research in the future, including additional training and education of investigators, IRB staff, and IRB members. Another corrective action institutions may consider is whether subjects, subject's parents or guardians, or subject's legally authorized representatives should be notified of information that OHRP determined should have been included in informed consent. OHRP has the authority to accept or reject proposed corrective actions and could, in the most extreme case, restrict or terminate an institution's ability to receive federal funding for human subjects research.

From: Myles, Renate (NIH/OD) [E]
To: Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: FW: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story
Date: Thursday, April 18, 2013 1:28:19 PM

Hi all:

(b) (5)

Renate

From: Bray, John P (OS/ASPA)
Sent: Thursday, April 18, 2013 1:25 PM
To: Daniels, Carla (HHS/ASPA/News Division); Gianelli, Diane M (OASH); HHS/OS Interviews; Salcido, Dori (HHS/ASPA); Sye, Tait (OS/ASPA)
Cc: Rosenberg, Jenny (OS/OASH); Broido, Tara (HHS/OASH); Migliaccio, Kate (HHS/OASH); Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story

(b)(5) - deliberative process

From: Daniels, Carla (HHS/ASPA/News Division)
Sent: Thursday, April 18, 2013 1:19 PM
To: Gianelli, Diane M (OASH); OS - Interviews; Salcido, Dori (HHS/ASPA); Bray, John P (OS/ASPA); Sye, Tait (OS/ASPA)
Cc: Rosenberg, Jenny (OS/OASH); Broido, Tara (HHS/OASH); Migliaccio, Kate (HHS/OASH); Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story

(b)(5) - deliberative process

Carla L. Daniels
Public Affairs Specialist
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs
Washington, DC
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From: Gianelli, Diane M (OASH)
Sent: Thursday, April 18, 2013 1:14 PM
To: Daniels, Carla (HHS/ASPA/News Division); OS - Interviews; Salcido, Dori (HHS/ASPA); Bray, John P (OS/ASPA); Sye, Tait (OS/ASPA)
Cc: Rosenberg, Jenny (OS/OASH); Broido, Tara (HHS/OASH); Migliaccio, Kate (HHS/OASH); Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]

Subject: RE: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story

(b) (5)

From: Daniels, Carla (HHS/ASPA/News Division)
Sent: Thursday, April 18, 2013 12:22 PM
To: Gianelli, Diane M (OASH); OS - Interviews; Salcido, Dori (HHS/ASPA); Bray, John P (OS/ASPA); Sye, Tait (OS/ASPA)
Cc: Rosenberg, Jenny (OS/OASH); Broido, Tara (HHS/OASH); Migliaccio, Kate (HHS/OASH); Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story

(b)(5) - deliberative process,

Carla L. Daniels
Public Affairs Specialist
U.S. Department of Health and Human Services
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From: Gianelli, Diane M (OASH)
Sent: Thursday, April 18, 2013 12:08 PM
To: OS - Interviews; Salcido, Dori (HHS/ASPA); Bray, John P (OS/ASPA); Sye, Tait (OS/ASPA)
Cc: Rosenberg, Jenny (OS/OASH); Broido, Tara (HHS/OASH); Migliaccio, Kate (HHS/OASH); Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story

Reporters: Thomas Burton

Publications: Wall Street Journal

Topic: Wants OHRP comment on NEJM editorial on SUPPORT study

Type of interview: Email response from OHRP press officer, attributed to Jerry Menikoff, MD, JD, OHRP director

Deadline: Immediate

Additional information: Please see http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf;
http://www.nejm.org/doi/full/10.1056/NEJMc1304827?query=featured_home;
http://www.nejm.org/doi/full/10.1056/NEJMe1304996?query=featured_home

Expected place of publication: WSJ, possibly only online

Expected date of publication/airing: Now. It will update current story online.

Expected prominence: High

Background: WSJ ran an online article last night, highlighting the New England Journal of Medicine's editorial defending the SUPPORT study and criticizing OHRP for finding fault with its consent process. The WSJ asked OHRP for a response to the editorial (see below).

OHRP's proposed comment from Jerry Menikoff:

(b) (5)



Today's WSJ story online:

WSJ Blogs

Real-time commentary and analysis from The Wall Street Journal

WASHINGTON WIRE

By Thomas M. Burton

An editorial by three senior editors of the New England Journal of Medicine came out against a federal government office that questioned the ethics of a study on how much oxygen premature babies need.

At issue is a study involving about 1,300 premature infants, conducted between 2004 and 2009, and published in 2010. Run by doctors at the University of Alabama at Birmingham, the research sought to discover the right levels of oxygen needed to sustain very premature infants.

Over earlier years, doctors had learned that high levels of oxygen could lead to a serious and often-blinding eye condition called retinopathy of prematurity.

The study, conducted at about 20 major hospitals, randomly assigned infants to lower or higher oxygen levels to see if blindness could be reduced.

Last month, the Office for Human Research Protections of the federal Department of Health and Human Services criticized the study for, among other things, allegedly not informing

parents of a potentially greater risk of death.

In an editorial released Wednesday, the prestigious New England Journal took issue with the federal office's criticism.

The premature-baby study was "critical in informing treatment decisions for extremely pre-term infants," the editorial said. It added that such children's "chances of survival to adulthood are greatly improved" as a result of the research. The editorial was written by the New England Journal's editor-in-chief, Jeffrey M. Drazen, and by a deputy editor, Caren G. Solomon, and an associate editor, Michael F. Greene.

The study researchers, and the New England Journal editorial, said both groups were treated in ways consistent with clinical practice at the time.

However, when the results came in, not only did babies with more oxygen have more of the eye illness, but babies with less oxygen died at a slightly higher rate.

Doctors who ran the study have said in interviews that they were extremely surprised by that slightly higher death rate (19.9% in the low-oxygen group versus 16.2% in the higher-oxygen babies). Thus, they say, they couldn't have warned of a completely unexpected risk

Diane M. Gianelli
Office of Communications
Office of the Assistant Secretary for Health
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202-690-7169
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From: Hudson, Kathy (NIH/OD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Myles, Renate (NIH/OD) [E]
Subject: FW: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story
Date: Thursday, April 18, 2013 1:23:41 PM

Rose,

Can you take a look at the OHRP statement below and share your thoughts with me?

Thanks

kathy

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, April 18, 2013 12:16 PM
To: Hudson, Kathy (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: FW: OASH: OHRP response to WSJ story on NEJM editorial on SUPPORT story

FYI

From: Gianelli, Diane M (OASH)
Sent: Thursday, April 18, 2013 12:08 PM
To: HHS/OS Interviews; Salcido, Dori (HHS/ASPA); Bray, John P (OS/ASPA); Sye, Tait (OS/ASPA)
Cc: Rosenberg, Jenny (OS/OASH); Broido, Tara (HHS/OASH); Migliaccio, Kate (HHS/OASH); Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
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Topic: Wants OHRP comment on NEJM editorial on SUPPORT study

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Deadline: Immediate

Additional information: Please see http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf;
http://www.nejm.org/doi/full/10.1056/NEJMc1304827?query=featured_home;
http://www.nejm.org/doi/full/10.1056/NEJMe1304996?query=featured_home

Expected place of publication: WSJ, possibly only online

Expected date of publication/airing: Now. It will update current story online.

Expected prominence: High

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(b) (5)

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WSJ Blogs

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Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, April 18, 2013 10:50 AM
To: Corr, Bill (HHS/IOS)
Subject: SUPPORT study issue really heating up
Attachments: 130418_Letter to ASH and OHRP Director re Neonatal Research Network Tria....pdf

Hi Bill,

I just met with a dozen NIH folks to go over the situation with the SUPPORT study. There's a new letter from Public Citizen this morning, demanding that enrollment in seven other studies be stopped. (b) (5)

(b) (5)

I gather from Rose that you are booked until 6 PM today, but I'd be glad to talk anytime – call when you have a minute.

FC



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

April 18, 2013

Howard K. Koh, M.D., M.P.H.
Assistant Secretary for Health
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

RE: Neonatal Research Network Randomized Clinical Trials – Demand for OHRP Investigation and Suspension of Enrollment

Dear Assistant Secretary Koh and Dr. Menikoff:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to request emergency action by the Office for Human Research Protections (OHRP) — a program office within the Office of the Assistant Secretary for Health — to ensure that newborn premature and term infants are being adequately protected in seven current randomized trials being conducted by the Neonatal Research Network (NRN).

As you are aware, on April 10 we sent a letter to Secretary of Health and Human Services Kathleen Sebelius condemning the highly unethical Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) funded by the National Institutes of Health (NIH) and conducted by 23 academic medical institutions from the NRN.¹ Our letter highlighted egregious deficiencies in the SUPPORT study consent forms regarding the purpose, nature, and risks of the research that were uncovered by OHRP. Because the NRN researchers failed to disclose these critical pieces of information in the consent forms used in the SUPPORT study, there is reason for concern that the same inadequacies may exist in consent forms for the current, ongoing NRN clinical trials.

This situation is urgent: As each week goes by without assurances that parents of highly vulnerable subjects are being adequately informed about the nature and risks of these newer

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 12, 2013.

Public Citizen

April 18, 2013, Letter to the Assistant Secretary for Health and OHRP

experimental studies, more parents are potentially being deprived of information critical to making an informed decision regarding enrollment of their babies. As we pointed out in the case of the SUPPORT study, it is likely that many, if not most, parents would not have consented had they been fully informed about the purpose, nature, and risks of the research.

Our search of the ClinicalTrials.gov website reveals that the following randomized clinical trials funded by NIH and conducted by the NRN are either actively (six trials) or imminently (one trial) enrolling babies:

- (1) Evaluation of Systemic Hypothermia Initiated After 6 Hours of Age in Infants \geq 36 Weeks Gestation With Hypoxic-Ischemic Encephalopathy: A Bayesian Evaluation (primary endpoints: death or moderate or severe disability);²
- (2) A Multi-center Randomized Trial of Laparotomy vs. Drainage as the Initial Surgical Therapy for Extremely Low Birth Weight Infants With Necrotizing Enterocolitis or Isolated Intestinal Perforation (primary endpoints: death or neurodevelopmental impairment);³
- (3) Optimizing Cooling Strategies at $<$ 6 Hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy (primary endpoints: death or moderate-to-severe disability);⁴
- (4) A Randomized Controlled Trial of the Effect of Hydrocortisone on Survival Without Bronchopulmonary Dysplasia and on Neurodevelopmental Outcomes at 22-26 Months of Age in Intubated Infants $<$ 30 Weeks Gestation Age (primary endpoints: improvement in survival without physiologically defined moderate-to-severe bronchopulmonary dysplasia, and survival without moderate or severe neurodevelopmental impairment);⁵
- (5) Neurodevelopmental Effects of Donor Human Milk vs. Preterm Formula in Extremely Low Birth Weight Infants (primary endpoint: neurodevelopmental outcome; death is one of the secondary endpoints);⁶
- (6) Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy? (primary endpoints: death or significant neurodevelopmental impairment);⁷ and
- (7) A Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Hypoxic-Ischemic Encephalopathy in Premature

² <http://clinicaltrials.gov/ct2/show/NCT00614744>. Accessed April 12, 2013.

³ <http://clinicaltrials.gov/ct2/show/NCT01029353>. Accessed April 12, 2013.

⁴ <http://clinicaltrials.gov/ct2/show/NCT01192776>. Accessed April 12, 2013.

⁵ <http://clinicaltrials.gov/ct2/show/NCT01353313>. Accessed April 12, 2013.

⁶ <http://clinicaltrials.gov/ct2/show/NCT01534481>. Accessed April 12, 2013.

⁷ <http://clinicaltrials.gov/ct2/show/NCT01702805>. Accessed April 12, 2013.

Public Citizen

April 18, 2013, Letter to the Assistant Secretary for Health and OHRP

Infants 33-35 Weeks Gestational Age (primary endpoints: death or moderate or severe disability).⁸

A brief overview of these studies is enclosed. The total planned enrollment for these seven studies, six of which are currently enrolling infants, is more than 4,500 newborn infants.

Given the glaring deficiencies identified in the consent forms for the SUPPORT study discussed in our April 10 letter — forms apparently approved by the institutional review boards (IRBs) at 23 NRN medical centers participating in the study — there clearly is sufficient reason for the Department of Health and Human Services (HHS), OHRP, and the public to seriously doubt whether adequate and appropriate informed consent will be or was obtained from the parents of all newborn infants enrolling in these newer ongoing interventional trials also conducted by the NRN. Indeed, the public's confidence in the ethical integrity of human experimentation funded by HHS has been understandably shaken by the revelations about lack of informed consent in the SUPPORT study.

We therefore call on OHRP, using its authority to conduct compliance oversight investigations, to immediately obtain the IRB-approved protocols and consent forms from all institutions conducting all seven of these clinical trials, as well as any other ongoing NRN randomized trials not listed above. OHRP should ensure that each trial meets all requirements for IRB approval under HHS regulations for the protection of human subjects at 45 C.F.R. 46.111 and that the IRB-approved consent forms satisfy the informed consent requirements of HHS regulations at 45. C.F.R. 46.116.

Please note that in addition to concerns about the adequacy of consent in these studies, we also have serious concerns that the designs of some of the NRN studies listed above are unethical and violate the following provisions of the HHS human subjects protection regulations:

- (1) 45 C.F.R. 46.111(a)(1), which requires that, as a condition of approval, the IRB must determine that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
- (2) 45 C.F.R. 46.111(a)(2), which requires that, as a condition of approval, the IRB must determine that risks to subjects are reasonable in relationship to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

For example, the Transfusion of Prematures (TOP) Trial is comparing two different strategies for treating anemia (low red blood cell count/hemoglobin level) in extremely premature infants (birth weight of less than 2.2 pounds). The infants are randomly divided into two groups. Babies in one group receive blood transfusions whenever their red blood cell counts (hemoglobin levels) reach a moderately low target threshold ("liberal" transfusion group), and babies in the other group receive blood transfusions only when their red blood cell counts reach a severely low target threshold ("restricted" transfusion group). The researchers will then determine whether

⁸ <http://clinicaltrials.gov/ct2/show/NCT01793129>. Accessed April 12, 2013.

Public Citizen

April 18, 2013, Letter to the Assistant Secretary for Health and OHRP

one group of babies has higher rates of death or long-term neurologic damage compared with the other group.

The TOP Trial as designed does not have a well-defined hypothesis. Through randomization in the study, subjects' clinical care with respect to anemia and blood transfusion management is being changed from the usual individualized care that is titrated based on the neonates' needs and a wide range of comorbid conditions, to experimental transfusion management based on different fixed levels of hemoglobin targets independent of perceived clinical need or an assessment of comorbid conditions. Because (a) the subjects are vulnerable premature infants struggling for life; (b) mortality is one of the primary outcomes of interest; and (c) the experimental study interventions for both groups have a risk of increasing patient mortality, minimization of risks to subjects necessitates inclusion of a control group that receives the usual routine transfusion management. The absence of an appropriate control group in the TOP trial precludes effective safety monitoring. For both experimental groups, increased rates of harm, including increased mortality, in comparison to patients receiving routine transfusion management may go undetected. As a result, the TOP Trial design fails to minimize risks to subjects.

Furthermore, such a study design almost certainly will result in harmful practice misalignments for a subset of subjects randomized to each group, a phenomenon well-described in the critical care and transfusion medicine literature.^{9,10,11,12,13,14} Such practice misalignments predictably may result in worse outcomes for the misaligned subjects in either experimental group in comparison to outcomes that would occur if the babies were managed according to usual, individualized blood transfusion management. Such treatment misalignments can seriously confound the results of a study, rendering the data uninterpretable. When this occurs, risks to subjects could *not* be reasonable in relationship to anticipated benefits, if any, to subjects, nor to the importance of the knowledge that may reasonably be expected to result.

Finally, OHRP should immediately order the suspension of new enrollment in the NRN studies listed above and in any other ongoing NRN randomized clinical trials not listed above until the agency completes its compliance oversight investigation. Enrollment in any particular trial should not be allowed to resume until OHRP confirms that the protocol, consent form content, and plan for obtaining consent are ethical and satisfy all HHS regulatory requirements.

⁹ Deans KJ, Minneci PC, Eichacker PQ, Natanson C. Defining the standard of care in randomized controlled trials of titrated therapies. *Curr Opin Crit Care*. 2004;10(6):579-82.

¹⁰ Deans KJ, Minneci PC, Suffredini AF, et al. Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols. *Crit Care Med*. 2007;35(6):1509-1516.

¹¹ Minneci PC, Eichacker PQ, Danner RL, et al. The importance of usual care control groups for safety monitoring and validity during critical care research. *Intensive Care Med*. 2008;34(5):942-947.

¹² Deans KH, Minneci PC, Klein HG, Natanson C. The relevance of practice misalignments to trials in transfusion medicine. *Vox Sang*. 2010;99(1):16-23.

¹³ Deans KJ, Minneci PC, Danner RL, et al. Practice misalignments in randomized controlled trials: identification, impact, and potential solutions. *Anesth Analg*. 2010;111(2):444-450.

¹⁴ Deans KJ, Minneci P, Eichacker PQ, et al. Walk a mile in whose shoes? *Anesth Analg*. 2010;111(2):576-577.

Public Citizen

April 18, 2013, Letter to the Assistant Secretary for Health and OHRP

In the wake of the disturbing revelations about the highly unethical SUPPORT study, agreeing to take these critically important actions would begin the surely lengthy process of restoring the public's confidence in the ethical integrity of HHS-funded research. Your refusal to take these urgently needed actions would only heighten the concerns millions of people in this country now have about the adequacy of HHS surveillance over human experimentation and, more important, would allow further recruitment of babies into potentially unethical, ongoing trials.

Please note that you may share this complaint letter with anyone. We will be posting it on our website and announcing it to major media outlets.

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

Sincerely,



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



Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

cc: The Honorable Kathleen Sebelius, Secretary of Health and Human Services
Dr. Francis Collins, Director, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Development, NIH
Dr. Kristina Borrer, Director, Division of Compliance Oversight, Office for Human Research Protections

Enclosure

Overview of Neonatal Research Network Randomized Clinical Trials Currently or Imminently Enrolling Newborn Infants

Evaluation of Systemic Hypothermia Initiated After 6 Hours of Age in Infants \geq 36 Weeks Gestation With Hypoxic-Ischemic Encephalopathy: A Bayesian Evaluation¹

This study is assessing the safety and effectiveness of cooling the body (hypothermia) for 96 hours in infants (born at 36 weeks gestational age or older) who have evidence of hypoxic-ischemic encephalopathy (brain injury due to insufficient oxygen) at birth. The infants are randomly divided into two groups. Babies in one group have their body temperature lowered to 33.5°C for 96 hours starting between 6 and 24 hours after birth (hypothermia group). Babies in the other group have their body temperature maintained at a normal level (37°C). The researchers will determine whether one group of babies has higher rates of death or moderate-to-severe disability compared with the other group. The study began in April 2008 and is expected to continue until approximately March 2014. The researchers plan to enroll 168 infants.

A Multi-center Randomized Trial of Laparotomy vs. Drainage as the Initial Surgical Therapy for Extremely Low Birth Weight Infants With Necrotizing Enterocolitis (NEC) or Isolated Intestinal Perforation²

This study is comparing the effectiveness of two surgical procedures — laparotomy or drainage — commonly used to treat NEC or isolated small intestine perforation (a hole through the wall of the small intestine) in extremely premature infants (birth weight of less than 2.2 pounds). NEC, a common disorder in premature infants, causes necrosis (tissue death) in parts of the small intestine. It can progress to peritonitis (infection throughout the abdominal cavity) and shock. Babies with suspected NEC or isolated small intestine perforation who require surgical treatment are randomly divided into two groups. Babies in one group undergo laparotomy surgery, which involves making a relatively large incision in the wall of the abdomen, examining the intestines and abdominal cavity, and removing dead small-bowel tissue. Babies in the other group only have a drainage tube placed through a very small incision in the abdominal wall to drain fluid from the abdominal cavity. The researchers will determine whether one group of babies has higher rates of death or long-term neurologic damage compared with the other group. The study began in January 2010 and is expected to continue until approximately September 2015. The researchers plan to enroll 300 extremely premature infants.

Optimizing Cooling Strategies at $<$ 6 Hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy³

This study is assessing the safety and effectiveness of four different hypothermia treatment strategies based on target temperature and time in infants (born at 36 weeks

¹ <http://clinicaltrials.gov/ct2/show/NCT00614744>. Accessed April 12, 2013.

² <http://clinicaltrials.gov/ct2/show/NCT01029353>. Accessed April 12, 2013.

³ <http://clinicaltrials.gov/ct2/show/NCT01192776>. Accessed April 12, 2013.

gestational age or later) who have evidence of hypoxic-ischemic encephalopathy at birth. The infants are being randomly assigned to receive one of four cooling treatments:

- Cooling to 33.5°C for 72 hours
- Cooling to 33.5°C for 120 hours
- Cooling to 32.0°C for 72 hours
- Cooling to 32.0°C for 120 hours

The researchers will determine the rates of death or moderate-to-severe disability for each group. The study began in September 2010 and is expected to continue until approximately March 2017. The researchers plan to enroll 726 infants.

A Randomized Controlled Trial of the Effect of Hydrocortisone on Survival Without Bronchopulmonary Dysplasia and on Neurodevelopmental Outcomes at 22-26 Months of Age in Intubated Infants < 30 Weeks Gestation Age⁴

This study is testing the safety and effectiveness of a 10-day course of treatment with the drug hydrocortisone for premature infants (estimated gestational age of less than 30 weeks) who are intubated (on a mechanical ventilator) at 14-28 days of life. The infants are randomly divided into two groups. Babies in one group receive hydrocortisone, and babies in the other group receive placebo. The researchers will determine whether infants in one group are more likely to survive without having moderate-to-severe bronchopulmonary dysplasia, a type of lung disease commonly seen in premature infants who need prolonged mechanical ventilation. They also will determine whether infants in one group are more likely to survive without having moderate-to-severe neurologic damage compared with the other group. The study began in September 2011 and is expected to continue until October 2016. The investigators plan to enroll 800 premature infants.

Neurodevelopmental Effects of Donor Human Milk vs. Preterm Formula in Extremely Low Birth Weight Infants⁵

This study is comparing the safety and effectiveness of nonmaternal human milk versus preterm baby formula. The infants are randomly divided into two groups. Babies in one group receive pasteurized donated human breast milk, and babies in the other group receive formula milk developed for preterm babies. The researchers will determine whether babies in one group are more likely to die or have abnormal neurologic development compared with the other group. The study began in August 2012 and is expected to continue until June 2018. The researchers plan to enroll 670 premature infants.

⁴ <http://clinicaltrials.gov/ct2/show/NCT01353313>. Accessed April 12, 2013.

⁵ <http://clinicaltrials.gov/ct2/show/NCT01534481>. Accessed April 12, 2013.

Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy?⁶

This study is comparing two different strategies for treating anemia (low red blood cell count or hemoglobin level) in extremely premature infants (birth weight of less than 2.2 pounds). The infants are randomly divided into two groups. Babies in one group receive blood transfusions whenever their red blood cell counts (hemoglobin levels) reach a moderately low target threshold (“liberal” transfusion group), and babies in the other group receive blood transfusions only when their red blood cell counts reach a severely low target threshold (“restricted” transfusion group). The researchers will then determine whether one group of babies has higher rates of death or long-term neurologic damage compared with the other group. The study began in December 2012 and is expected to continue until August 2017. The researchers plan to enroll more than 1,800 extremely premature babies.

A Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Hypoxic-Ischemic Encephalopathy in Premature Infants 33-35 Weeks Gestational Age⁷

This study will assess the safety and effectiveness of cooling the body for 72 hours in premature infants (born at 33-35 weeks gestational age) who have evidence of moderate-to-severe hypoxic-ischemic encephalopathy at birth. The infants will be randomly divided into two groups. Babies in one group will have their body temperature lowered to 33.5°C (hypothermia group). Babies in the other group will have their body temperature maintained at a normal level (37°C). The researchers will then see whether one group of babies has higher rates of death or moderate-to-severe disability compared with the other group. The study is expected to begin in May 2013 and continue until May 2018. The researchers plan to enroll 168 premature babies.

⁶ <http://clinicaltrials.gov/ct2/show/NCT01702805>. Accessed April 12, 2013.

⁷ <http://clinicaltrials.gov/ct2/show/NCT01793129>. Accessed April 12, 2013.

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, April 17, 2013 9:45 PM
To: Corr, Bill (HHS/IOS)
Subject: NEJM Correspondence: Oxygen Saturation Targets in Extremely Preterm Infants

More...

NEW ENGLAND JOURNAL OF MEDICINE

CORRESPONDENCE

Oxygen Saturation Targets in Extremely Preterm Infants

April 17, 2013 DOI: 10.1056/NEJMc1304827

To the Editor:

Questions have been raised about the consent process for the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).¹ The SUPPORT study was designed, in part, to test the hypothesis that a lower target range of oxygen saturation (85 to 89%), as compared with a higher target range (91 to 95%), would reduce the incidence of retinopathy of prematurity or death among very preterm infants (between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation).² Death was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected. The American Academy of Pediatrics recommended oxygen-saturation levels of 85 to 95%,³ and both treatment groups had targets within that range.

Some persons have compared the SUPPORT study with studies in the 1950s in which oxygen delivery was restricted without measurement of oxygenation status; this restriction probably created hypoxia and was associated with a trend toward higher mortality. Today, levels of oxygen saturation are monitored continuously and adjusted within limits. Thus, it is inappropriate to compare these older studies with the SUPPORT study. 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.⁴ 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.

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. When the analysis was adjusted for characteristics of the nonenrolled infants, the infants in the study were still at no higher risk for death. The rates of survival and retinopathy² without increased blindness were higher among infants in the higher-oxygen-saturation group than among those in the lower-oxygen-saturation group. Other rigorous trials using the same intervention as the SUPPORT study also have shown higher rates of survival in the higher-oxygen-saturation groups.⁵

Clinical research improves the health of babies and patients of all ages. Ill-informed allegations create unwarranted apprehension that serves no one. Our consent forms were conscientiously drafted according to the Code of Federal Regulations

and were based on the best available evidence. We provided parents with the information known at the time, which did not indicate an increased risk of death resulting from assignment to either treatment group.

We have adhered to the highest ethical principles, and we will continue to work to ensure that known potential risks are described in our consent forms. We thank the families of our patients for their trust in us; we will continually strive to maintain that trust.

Waldemar A. Carlo, M.D.

University of Alabama at Birmingham, Birmingham, AL

Edward F. Bell, M.D.

University of Iowa, Iowa City, IA

Michele C. Walsh, M.D.

Rainbow Babies and Children's Hospital, Cleveland, OH

for the SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on April 17, 2013, at NEJM.org.

5 References

1. Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. N Engl J Med 2013. DOI: 10.1056/NEJMe1304996.
2. 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;362:1959-1969
[Free Full Text](#) | [Web of Science](#) | [Medline](#)
3. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2007:260-2.
4. 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
[CrossRef](#) | [Web of Science](#) | [Medline](#)
5. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. N Engl J Med 2011;364:1680-1682
[Free Full Text](#) | [Web of Science](#) | [Medline](#)

Bartok, Lauren (NIH/OD) [C]

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, April 17, 2013 9:44 PM
To: Corr, Bill (HHS/IOS)
Subject: NEJM Editorial: Informed Consent and SUPPORT

Hi Bill,

I thought you might want to see this.

(b) (5)

(b) (5)

Perhaps we can discuss again in our call on Friday.

FC

NEW ENGLAND JOURNAL OF MEDICINE

EDITORIAL

Informed Consent and SUPPORT

Jeffrey M. Drazen, M.D., Caren G. Solomon, M.D., M.P.H., and Michael F. Greene, M.D.

April 17, 2013 DOI: 10.1056/NEJMe1304996

In the summer of 1963, the nation watched in sadness as Patrick Bouvier Kennedy, the youngest child of President John F. Kennedy and First Lady Jacqueline Bouvier Kennedy, was born prematurely and then died of lung disease 2 days later at Children's Hospital in Boston. Even now, it is common knowledge that children born prematurely are at high risk for death.

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. Decades of study and refining practice have resulted in major improvements in the care of premature infants; now most babies weighing a kilogram or more, and many weighing less than this, survive. This progress has come through careful research in multiple aspects of neonatal care, but many questions remain regarding practice that will maximize survival and minimize the long-term sequelae resulting from surviving severe prematurity. Without research studies your neonatologist would simply be guessing about what is best rather than knowing what is best for your child.

The physicians in the nursery ask you to allow your very premature baby to participate in a research study, called the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), part of which is focused on the amount of supplemental oxygen they will give to your baby. They orally explain the study to you and ask you to sign an informed-consent document; it is six pages of single-spaced typescript.

Premature babies often require supplemental oxygen; what was not known in 2005 was exactly how much oxygen to give. The doctors knew that maintaining very high oxygen levels in the blood might cause retinopathy of prematurity (ROP), or abnormal growth of blood vessels in the eyes, which can damage the retinas and impair vision. The informed-consent form notes the higher risk of ROP that is associated with prolonged exposure to supplemental oxygen but states that “the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known” and also notes that “the use of lower saturation ranges may result in a lower incidence of severe ROP.” Clinical practice at the time (and that recommended in the 2002 and 2007 guidelines of the American Academy of Pediatrics,^{1,2} on whose guidelines committee one of us served) was to target values for the partial pressure of arterial oxygen anywhere between 50 and 80 mm Hg, consistent with oxygen saturations measured by pulse oximetry between 85% and 95%. Among the clinical questions addressed by SUPPORT was whether targeting the upper or lower end of this range might result in better outcomes for very preterm infants.

The study was conceived in 2003, initiated in 2005, and completed in 2009. Trials addressing the same clinical question were initiated in 2006 in the United Kingdom, Australia, and New Zealand (Benefits of Oxygen Saturation Targeting [BOOST II]), indicating the importance of the question.³ 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.

The consent document for SUPPORT that you have been handed spells this out clearly and succinctly: “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.” You sign the form, and your child enters the study. The same process was also taking place with parents of newborn extremely premature infants at multiple centers across the country.

After 5 years and more than 1300 babies studied, the data from SUPPORT are published in 2010 in the *Journal*.⁴ The data show that, even within the recommended oxygen saturation range, babies with a higher oxygen saturation target had a higher risk of ROP, and those with a lower saturation target had a higher risk of death. With this new information, the investigators in the BOOST II trials in the United Kingdom and Australia review their preliminary data and discover that lower oxygen saturations in their trials are also associated with a higher rate of death.³ These findings changed medical practice at many centers.

There was no way for you as a parent of a child in SUPPORT to know what the answer would be before your child participated. The study made clear that higher oxygen saturations within the then-recommended range increased the risk of retinopathy but decreased the risk of death. This is how new medical knowledge is gained. The story should have ended there, but it didn't.

In 2011, the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services began an investigation into the informed-consent process used when newborns were enrolled in SUPPORT. Their investigation concluded with a 13-page letter of determination sent to the SUPPORT lead center on March 7, 2013 (provided with a sample informed-consent form in the [Supplementary Appendix](#), available with the full text of this article at NEJM.org). The OHRP reached the following conclusion: “It was alleged, and we determine, that the IRB [institutional review board] approved informed consent documents for this study failed to include or adequately address the following basic element required by HHS [Health and Human Services] regulations at 45 CFR 46.116(a): Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts.”

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. At the time, as explained in the principal investigator's response to the allegations and in a related letter to the editor in the *Journal*⁵ there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent from parents of participating infants. Through hindsight (and essentially faulting investigators for not informing parents up front of a risk later uncovered by the trial itself), the OHRP investigation has had the effect of damaging the reputation of the investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice.

Clinical research is crucial if we are to advance medical science. Clinical investigators acted in good faith to design a trial to address an important question. An informed-consent document was drafted and approved by institutional review boards of participating centers before the work was begun. The OHRP has a duty to investigate questions of research impropriety, but we strongly disagree with their determination of inadequate informed consent in this case.

The results of SUPPORT have been critical in informing treatment decisions for extremely preterm infants. When babies like Patrick Bouvier Kennedy are born today, their chances of survival to adulthood are greatly improved, thanks to research made possible by thousands of parents and their children. We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article was published on April 17, 2013, at NEJM.org.

Source Information

From the Massachusetts General Hospital, Boston (M.F.G.).

From: Buchanan, Lisa (HHS/OASH)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT Trial enrolling sites
Date: Wednesday, April 17, 2013 4:06:00 PM

Hi Rose,

When we spoke earlier this year, you indicated that the list of reviewing IRB's could be found at the end of the NEJ article, but somehow I had the impression that there may be more hospitals/sites that enrolled subjects than the institutions listed in the article. If so, would you please provide a list of any sites that enrolled subject in the SUPPORT trial beyond those listed in the article?

Thanks,
Lisa

Lisa Buchanan, MAOM
Public Health Analyst
Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Ph: 240-453-8298
Fax: 240-453-6909

Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 16, 2013 2:07 PM
To: Hudson, Kathy (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]
Subject: Heads-Up RE OHRP Determination letter posting

Kathy and Sally,

Just an FYI: various people at NICHD were notified about the determination letter over 6 weeks ago, when it was posted (see below). And I've determined that since the issue "blew up" a few days ago, NIH public affairs personnel have also actively been involved at the outset (from 11:59 am on April 10th, just hours after we received the first emailed letter from Public Citizen that morning).

And as I indicated, I would welcome sending an HHS message that we all are comfortable with. I agree that it is in our mutual interest.

Jerry

From: Bradley, Ann (HHS/OASH)
Sent: Tuesday, February 26, 2013 11:04 AM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Tillman, June (NIH/NICHD) [E]
Subject: Heads-Up RE: OHRP Determination letter posting

Hi, Mona and Bob.

I tried to telephone just now but June told me that you are in a meeting. I wanted to apprise you that OHRP yesterday posted to our web site the determination letter regarding the NICH-supported SUPPORT study. Dr. Maddox and others at NICHD I believe received the letter by email, shortly after it was mailed to UA-B. You may access it at http://www.hhs.gov/ohrp/detrm_lettrs/YR13/feb13a.pdf.

I have informed the ASH Communications Office and they, in turn, will notify ASPA, in case we receive media inquiries. OHRP's position will be that our director, Dr. Jerry Menikoff, takes interview questions on the OHRP determination, current regulations, and essential aspects of informed consent; (b) (5)

(b) (5) We propose to refer to (b) (5) (b) (5) about real-world consequences of the trial. Please let me know whether you agree with this plan?

In addition, I note on the determination letter that (b) (5) is involved. Can you let me know if they or others also provided funding support?

I will be at 240-453-8130 most of the day if you wish to speak.

Best,
Ann

Ann M. Bradley
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
tel. 240/453-8130, bb 202/495- (b) (6)
ann.bradley@hhs.gov

Bock, Robert (NIH/NICHD) [E]

From: Bradley, Ann (HHS/OASH)
Sent: Tuesday, February 26, 2013 11:20 AM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Gianelli, Diane M (OASH)
Subject: RE: Heads-Up RE: OHRP Determination letter posting

CORRECTION: I just learned that my ASH Comms colleague Diane Gianelli independently reached out to Renate Miles, who plans with Amanda Fine to handle incoming media requests. You may wish to touch base with them—or they you.

Best to all my former NIH Colleagues!

From: Bradley, Ann (HHS/OASH)
Sent: Tuesday, February 26, 2013 11:04 AM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Tillman, June (NIH/NICHD) [E]
Subject: Heads-Up RE: OHRP Determination letter posting

Hi, Mona and Bob.

I tried to telephone just now but June told me that you are in a meeting. I wanted to apprise you that OHRP yesterday posted to our web site the determination letter regarding the NICH-supported SUPPORT study. Dr. Maddox and others at NICHD I believe received the letter by email, shortly after it was mailed to UA-B. You may access it at http://www.hhs.gov/ohrp/detrm_lettrs/YR13/feb13a.pdf.

I have informed the ASH Communications Office and they, in turn, will notify ASPA, in case we receive media inquiries. OHRP's position will be that our director, Dr. Jerry Menikoff, takes interview questions on the OHRP determination, current regulations, and essential aspects of informed consent; (b) (5)

(b) (5) We propose to refer to (b) (5) (b) (5) about real-world consequences of the trial. Please let me know whether you agree with this plan?

In addition, I note on the determination letter that (b) (5) is involved. Can you let me know if they or others also provided funding support?

I will be at 240-453-8130 most of the day if you wish to speak.

Best,
Ann

Ann M. Bradley
Office of the Assistant Secretary for Health
U.S. Department of Health and Human Services
tel. 240/453-8130, bb 202/495-(b) (6)
ann.bradley@hhs.gov

From: [Buchanan, Lisa \(HHS/OASH\)](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: SUPPORT Determination Letter 020813
Date: Friday, February 15, 2013 10:22:41 AM
Attachments: [SUPPORT Trial determination letter .pdf](#)

Rose,

Attached is the determination letter for the SUPPORT Trial.

Thanks,

Lisa

Lisa Buchanan, MAOM
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February 8, 2013

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

Addressee not involved in the study.

RE: Human Research Protections under Federalwide Assurances (FWA) 5960 and 3331

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

Dear Dr. Marchase and

Addressee not involved in the study.

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

The SUPPORT study was a randomized multi-site study conducted at approximately twenty-two sites and reviewed by at least twenty-three institutional review boards (IRBs). Approximately 1,300 infants were enrolled in this study from 2004 to 2009. The study was designed to 1) learn more about treatment with continuous positive airway pressure (CPAP)

Page 2 of 14

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

Addressee not involved in the study.

February 8, 2013

which is positive pressure applied with a face mask to help keep the lungs inflated, and 2) to learn the appropriate levels of oxygen saturation in extremely low birth weight infants by comparing a lower versus a higher range of levels of oxygen saturation in such infants. The University of Alabama, Birmingham (UAB) was the lead site for the portion of the study relating to the second purpose. The CPAP portion of this study raised no concerns for OHRP and therefore will not be discussed in this letter.

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

Historical Background

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

The results of this trial and others showed that infants receiving low oxygen had a much lower incidence of ROP than those receiving the then-standard higher oxygen levels. Within

¹ Much of the early history of retinopathy of prematurity recounted here is taken from W.A. Silverman, *Retrolental Fibroplasia: A Modern Parable*. Grune & Stratton, Inc., New York, N.Y. (1980), available at <http://www.neonatology.org/classics/parable>.

² E. Brown. Obituary for Arnall Patz. *Washington Post*, March 13, 2010.

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

Addressee not involved in the study.

February 8, 2013

a couple of years, medical practice had dramatically changed, with a large drop in the acceptable level of oxygen used to treat premature newborns. This change resulted in "an immediate 60 percent reduction in the number of blind children in the United States."³ Among the concerns addressed by these early trials was the possibility that even if lower oxygen led to less ROP, it might also produce other bad consequences for the health of a very premature infant, including possibly death. One of the largest such trials specifically looked at this question, concluding that this was not a problem.⁴

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

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

The significance of this ongoing problem is underscored by the number of relatively recent calls in the scholarly literature for doing the clinical trials needed to determine the appropriate amount of oxygen to use in treating premature infants. As one commentary noted, "[l]owering oxygen saturation targets in preterm infants in the first few weeks of life has been shown to reduce the incidence of certain complications; however, prolonged periods

³ L.K. Altman. Arnall Patz, a Doctor Who Prevented Blindness, is Dead at 89. New York Times, March 15, 2010.

⁴ V.E. Kinsey. Retrolental Fibroplasia: Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen. Archives of Ophthalmology 1956;56:481.

⁵ K.W. Cross. Cost of Preventing Retrolental Fibroplasia. Lancet 1973;302:954.

⁶ J.F. Lucey and B. Dangman. A Reexamination of the Role of Oxygen in Retrolental Fibroplasia. Pediatrics 1984;73:82.

⁷ National Eye Institute. Facts About Retinopathy of Prematurity (ROP). Available at <http://www.nei.nih.gov/rop>.

Page 4 of 14

Richard B. Marchese, Ph.D. -- University of Alabama at Birmingham

Addressee not involved in the study.

February 8, 2013

of hypoxemia may result in poor growth, cardiopulmonary complications of chronic lung disease, neurodevelopmental disabilities, or increased mortalities. . . . Although maintaining ranges of hemoglobin oxygen saturation in the vulnerable preterm population in the proximity of 85% to 90% is gaining increasing acceptance, marked variability in opinion exists.”⁸ In short, the research and data analyses that had occurred prior to the SUPPORT study demonstrated that the use of higher versus lower levels of oxygen could significantly affect the likelihood of a premature infant developing ROP and other aspects of morbidity and mortality.

The Protocol

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

“Retinopathy of prematurity (ROP) remains a significant cause of morbidity among [extremely low birth weight] infants and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, but early trials were unable to pinpoint the actual level of arterial PaO₂ which was the threshold for triggering the pathophysiology of this disorder. . . . While retrospective cohort studies have suggested that the use of lower SpO₂ ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO₂ ranges for managing [such infants].” (p.2, “Statement of Problem,” 2004 protocol)

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

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

⁸ J.S. Greenspan, J.P. Goldsmith. Oxygen Therapy in Preterm Infants: Hitting the Target. *Pediatrics* 2006;118:1740. See also, e.g., an analysis of the literature performed for the Cochrane Collaboration. L.M. Askie, D.J. Henderson-Smart, H. Ko. Restricted Versus Liberal Oxygen Exposure for Preventing Morbidity and Mortality in Preterm or Low Birth Weight Infants. *Cochrane Database of Systematic Reviews* 2009(1), available at <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001077.pub2/pdf> (looking at whether the level of oxygen affects “mortality, [ROP], lung function, [and] growth or development.”).

Page 5 of 14

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

Addressee not involved in the study.

February 8, 2013

brain development and result in impaired neurologic outcome.” (p.2 “Background,” 2004 protocol)

The SUPPORT study was thus an important clinical trial designed to generate knowledge that could help physicians determine exactly how much oxygen to provide to extremely low birth weight infants in order to minimize ROP without contributing to undue increases in other problems (such as impaired brain development or even death). Infants enrolled in the study would be randomized to one of two levels of oxygen. The amount of oxygen provided to the infant would be measured not by looking at the absolute quantity of oxygen provided to the infant, but instead by providing sufficient oxygen to maintain a specified level of oxygen in the infant’s blood.

In particular, a non-invasive device known as a pulse oximeter, commonly used in clinical care, would be applied to the infant’s foot or hand. That device measures the blood oxygen saturation (SpO₂), which is the percentage of hemoglobin in the infant’s bloodstream that has oxygen bound to it. The amount of oxygen provided to the infant would then be adjusted to try to keep the SpO₂ within one of two discrete ranges of oxygen levels, *i.e.*, a “low” range of 85% to 89%, or a “high” range of 91% to 95%. Infants were randomly assigned to the low or the high range.

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

With regard to those possible differences in outcome, the researchers were specifically looking at both whether the infant survived, and whether the infant developed a fairly significant level of ROP (what is called “threshold” disease). As the protocol put it, the primary hypothesis they were testing was “that relative to infants managed with a higher SpO₂ range that the use of a lower SpO₂ range will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.”

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

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Addressee not involved in the study.

February 8, 2013

The Consent Form Template

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

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

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

Several observations are appropriate with regard to this paragraph:

1. The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and ROP, and what that work indicates about how changing the oxygen range might affect whether an infant develops ROP.
2. The paragraph does not include any information about the prior research and analyses that had been done looking at the relationship between oxygen and mortality and other forms of morbidity (apart from developing ROP).
3. The paragraph does not identify any specific risk relating to randomizing infants to a high or low range of oxygen.

Although the consent form did not identify a single specific risk relating to the randomization to high or low oxygen ranges, it did include a section that was quite specific in noting possible benefits to participating infants from the change in oxygen ranges. That paragraph

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

Addressee not involved in the study.

February 6, 2013

observed that “[t]here may be benefits to your child directly, including . . . a decrease in the need for eye surgery as a result of exposure to oxygen.” It did go on to point out that since it was not known in advance which treatment a particular child would be randomized to, it was “possible that your baby will receive no direct benefit.”

Summary

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

- a. The relationship between oxygen and development of severe retinopathy of prematurity had been examined for over 50 years. While the details of that relationship were not fully known, it was well recognized that changing a premature infant’s amount of exposure to oxygen could have an impact on a number of important health outcomes, including the development of severe eye disease (and possibly blindness); reduced neurologic development, including brain damage; chronic lung disease; and could even lead to death.
- b. The SUPPORT study was designed as an interventional study. It specifically enrolled very premature infants and randomized them to one of two levels of oxygen. For many of those infants, the level of oxygen they received was different from what they would have received had they not participated in the study. A major purpose for doing this was to increase the likelihood that there would be a measurable difference in the outcomes of the two groups. The primary outcome of interest for the researchers was whether the infants would develop severe eye disease or would die before being discharged from the hospital.
- c. The template for the consent form used in this study did not mention any risks relating to the randomization between the higher and lower levels of oxygen, instead suggesting that this was a low risk study, noting that all of the treatments in the study were “standard of care,” and that there was “no predictable increase in risk for your baby.”
- d. While it would have been unwarranted to predict, ahead of time, specific outcomes (*i.e.*, which infants developed which outcomes), the researchers had sufficient available information to know, before conducting the study, that participation might lead to differences in whether an infant survived, or developed blindness, in comparison to what might have happened to a child had that child not been enrolled in the study.

The UAB Consent Form

We reviewed the UAB IRB records, including the study protocol, informed consent documents and data safety monitoring committee (DSMC) reports. We also reviewed

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consent documents approved by 23 IRBs, and found problems with all of them similar to those described above with regard to the template consent form.

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

At the front of the form:

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

In the section labeled “Introduction”:

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

In the section labeled “Procedures”:

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

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In the section labeled "Possible Benefits":

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

In the section labeled "Possible Risks":

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

With regard to this information, OHRP notes the following:

1. The form does not say that there may be a greater or lesser risk of death depending on whether the infant is in the lower or upper range group.
2. While the form says that being in the *lower* range group may result in the *benefit* of decreasing the chances of developing severe ROP, in the "Possible Risks" section it does not say that being in the *upper* range group may result in the greater *risk* of developing ROP.
3. The only risk related to the part of the study involving the two ranges of oxygen levels described in the "Possible Risks" section is the risk of the pulse oximeter to the infant's skin.

A. Determinations Regarding the Consent Documents

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

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

OHRP is concerned that the failure to disclose adequately the risks of the research derives in part from the belief that participation in the research study did not involve an appreciable amount of risk, because the lower and upper ranges of oxygen saturation utilized in the research fall within the range of values that doctors were using as standard care at the participating institutions. OHRP asked UAB for information regarding the oxygen levels that were being used as standard care prior to commencing this study, and UAB confirmed that standard care was to keep infants

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somewhere in the range between 85% and 95%, without any greater specificity, and the consent form also described this as the normal range.

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

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

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

⁹ W. Rich et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. *Pediatrics* 2012;129:480.

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

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

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

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

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

Results from the SUPPORT Study

The results of the SUPPORT study were published in the *New England Journal of Medicine* in 2010.¹¹ The rate of severe ROP among the infants who survived was significantly different between the low and high oxygen groups. Among the infants who were treated with

¹⁰ S.N. Whitney. The Python's Embrace: Clinical Research Regulation by Institutional Review Boards. *Pediatrics* 2012;129:576.

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

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low oxygen, only 41 out of 475 developed severe ROP, or 8.6%. In the high oxygen arm, more than double that percentage of infants developed severe eye disease: 91 out of 509, for a rate of 17.9%. The difference between these two groups was highly significant, with a P-value less than 0.001.

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

Thus, it appeared that while low oxygen produced fewer cases of severe ROP in the infants who survived, this was being accomplished at the cost of fewer infants surviving. In their discussion of these results, the authors noted how this in many ways echoed results from earlier studies. For example, they observed that the increase in mortality seen in the 1950s, when oxygen restriction was first begun, was 4.9 percentage points, which was not all that different from the 3.7 percentage points difference seen between the two groups in this study. Moreover, with regard to the rate of development of ROP, they also saw confirmation of prior results: like "most non-randomized studies, our trial confirmed that lower target rates of oxygenation result in a large reduction in the incidence of severe retinopathy among survivors. However, our data suggest that there is one additional death for approximately every two cases of severe retinopathy that are prevented." They ended their discussion with the conclusion that "caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality." (A subsequent publication analyzing the results from longer-term follow-up did show that among the infants that did survive, there was no difference in neurological development between the infants who received low oxygen and those who received higher oxygen.¹²)

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

¹² Y.E. Vaucher et al. Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial. *New England Journal of Medicine* 2012;367:2495.

¹³ B. Stenson, P. Brocklehurst, and W. Tarnow-Mordi. Increased 36-Week Survival with High Oxygen Saturation Target in Extremely Preterm Infants. *New England Journal of Medicine* 2011;364:1680.

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Addressee not involved in the study.

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oxygen group that was statistically significant with a P-value of 0.015. As a result of these findings, both the U.K. and Australia trials were terminated early.

Requested Response

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

We appreciate the continued commitment of your 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:

Ms. Sheila D. Moore, Director, Office of the IRB, UAB
Dr. Ferdinand Urthaler, Chair, UAB IRBs
Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI
Mr. David Borasky, Chair IRB#1, RTI
Ms. Angela Greene, Chair IRB#2, RTI
Dr. Juesta M. Caddell, Chair IRB#3, RTI
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Dr. Yvonne Maddox, Deputy Director, NICHD
Dr. Rosemary Higgins, Program Scientist, NICHD
Dr. Robert H. Miller, Case Western Reserve University
Dr. Nancy C. Andrews, Duke University
Dr. Janice D. Wagner, Wake Forest University School of Medicine
Mr. Thomas Hughes, Women and Infants Hospital of Rhode Island
Dr. Clyde L. Briant, Brown University

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February 8, 2013

Dr. Thomas N. Parks, University of Utah, School of Medicine
Dr. Jane Strasser, University of Cincinnati
Ms. Susan Blanchard, BBA, Tufts Medical Center
Ms. Angela Wishon, University of Texas Southwestern Medical Center
Dr. David Wynes, Emory University School of Medicine
Dr. Gary Chadwick, MPH, University of Rochester, School of Medicine and Dentistry
Dr. Jorge Jose, Indiana University School of Medicine
Ms. Nancy J. Lee, Stanford University School of Medicine
Dr. John L. Bixby, University of Miami, Miller School of Medicine
Dr. Hilary H. Ratner, Wayne State University
Dr. James C. Walker, University of Iowa
Dr. Andrew Rudczynski, Yale University School of Medicine
Dr. Gary S. Firestein, University of California, San Diego
Dr. Daniel L. Gross, Sharp Mary Birch Hospital for Women and Newborns
Dr. Paul B. Roth, University of New Mexico Health Sciences Center

From: [Buchanan, Lisa \(HHS/OASH\)](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: SUPPORT
Date: Friday, February 01, 2013 10:51:53 AM

Thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, February 01, 2013 10:15 AM
To: Buchanan, Lisa (HHS/OASH)
Subject: RE: SUPPORT

Lisa

Here is one additional manuscript from the SUPPORT study.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Buchanan, Lisa (HHS/OASH)
Sent: Wednesday, January 30, 2013 10:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Got it. Thanks!

Lisa Buchanan, MAOM
Public Health Analyst
Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
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Fax: 240-453-6909

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Wednesday, January 30, 2013 10:57 AM
To: Buchanan, Lisa (HHS/OASH)
Subject: SUPPORT

Hi

Here are the publications from the SUPPORT Trial. (b) (5), (b) (6)

(b) (5), (b) (6) I have asked that the UCSD site forward their consent form.

Please confirm receipt.

Thanks for your help

Rose

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