

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 not 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



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: _____

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: _____

From: [Bell, Edward \(Pediatrics\)](#)
To: [Wally Carlo](#); [Kurt Schibler](#); [Brenda Poindexter](#); [Kristi Watterberg](#); [Abhik Das](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: New draft
Date: Thursday, April 11, 2013 8:52:43 AM
Attachments: [NYT letter v4.doc](#)

I have revised this based on your suggestions and after perusing the reader comments to the NY Times. I'm not entirely happy with it yet, so further suggestions are welcome. The letter needs to clearly address the main concern of OHRP and the readers, that we failed to disclose predictable risks associated with study participation.

Ed

Notice: This UI Health Care e-mail (including attachments) is covered by the Electronic Communications Privacy Act, 18 U.S.C. 2510-2521, is confidential and may be legally privileged. If you are not the intended recipient, you are hereby notified that any retention, dissemination, distribution, or copying of this communication is strictly prohibited. Please reply to the sender that you have received the message in error, then delete it. Thank you.

April 10, 2013

Editors
New York Times

Dear Editors:

We are among the investigators of the SUPPORT study and authors of the resulting publications. Contrary to the determination of March 7, 2013 by the U.S. Office of Human Research Protection (OHRP), the press release today by Public Citizen, and the article by Ms. Sabrina Tavernise in today's Times, we disagree that the premature infants enrolled in the SUPPORT study were placed at increased risk because of their participation in the study and that the study findings were predictable. At the time the study was planned, there was limited evidence, based on studies done in the 1950s, that excessive levels of inhaled oxygen in premature infants increased the risk of retinopathy of prematurity (ROP, a common eye problem in premature infants) and that severe restriction of oxygen, regardless of the oxygen level in the blood, increased the risk of death. These old studies were done before it was possible to measure continuously the level of oxygen in the baby's bloodstream. In addition, by the time the SUPPORT study was being planned there had been so many changes in the way care is provided and improvements in the survival and health of premature infants that there was a compelling need for more information to guide the use of oxygen for premature infants in the modern era.

The American Academy of Pediatrics (AAP) recommended in 2007 that the oxygen level (measured as oxygen saturation by pulse oximetry) be kept between 85 and 95% as much as possible in premature babies. Several small, poorly controlled studies in recent years had shown that ROP risk could be reduced by aiming for lower oxygen saturation levels (as low as 70%) with no effect on death risk, and physicians were beginning to target lower oxygen levels for premature babies. The SUPPORT study was planned to compare the safety of using oxygen saturation targets toward the lower and upper ends of the range recommended by the AAP, 85-89% compared with 91-95%, ranges that had not been shown to result in differences in ROP or death.

Very premature babies have high risks of death, ROP, and a number of other health problems, whether or not they participate in research studies. The question at hand is whether it was known or anticipated that participation in the SUPPORT trial would increase these risks. If risks were known, they should have been explained to parents who gave consent for their babies to participate in the study.

Shown in the table below are the percentage of babies who had severe ROP, blindness, and death in both groups of the SUPPORT study, the babies who were eligible but not enrolled in the study, and a group of similar babies from before the SUPPORT study.

Patient group	Severe ROP(%)	Blindness (%)	Death (%)
Pre-SUPPORT (add range of years)			23.1
SUPPORT 85-89% oxygen saturation target	8.6		19.9
SUPPORT 91-95% oxygen saturation target	17.9		16.2
SUPPORT all patients			
Babies eligible but not enrolled in SUPPORT			24.1

Comment [efb1]: Should we add NDI?

Comment [WC2R1]: That is an excellent idea. It should be NDI/death as the increased survival may increase % of babies with NDI.

This table shows that the overall risks of severe ROP, blindness, and death were not increased by participation in the SUPPORT study. The babies in the lower oxygen saturation target group had lower risk of severe ROP but higher risk of death and no difference in blindness. Use of the higher oxygen saturation target resulted in 2 cases of severe ROP for each case of death prevented and 6 more survivors for each additional blind baby. This is vitally important information that was badly needed to help neonatologists decide the best target range to use for their very premature patients.

The press release of Public Citizen said that the standard care for non-participants was as follows: "The exact oxygen target level for a particular infant at any particular time would be based on the baby's individual medical needs and the wishes of the baby's parents." In fact, the target level varied among hospitals, based on the physicians' best guess from available evidence, but there was not enough information to guide an individualized approach to this aspect of care. We should add that, even now, we do not know if and how the target range should be adjusted for individual babies.

~~In retrospect, each participating investigator author can see ways that our consent forms might have been written in a clearer and more informative way, but these documents~~ Our consent forms were conscientiously drafted making full use of the information available at the time. If the comparative risks of the target oxygen saturation ranges used in the study had been known, there would have been no need for the study. We believe that the SUPPORT study provided valuable new evidence about the benefits and risks of using oxygen saturation targets toward the lower and upper ends of the range in common use.

We provided parents with the information we had at the time, which did not indicate increased risk resulting from participation in the study nor from being assigned to either study group.

In conclusion, the OHRP determination, the Public Citizen press release, and the New York Times story wrongly accuse the SUPPORT investigators, their institutional review boards, the NICHD, the reviewers of the SUPPORT study proposal, and the Neonatal Research Network's independent Data Safety Monitoring Committee of conducting this important study without disclosing predictable, serious risks of study participation to the consenting parents.

Sincerely yours,

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Spong, Catherine \(NIH/NICHD\) \[E\]](#)
Cc: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Subject: RE: Letter regarding the SUPPORT study
Date: Thursday, April 11, 2013 8:42:00 AM
Attachments: [support background rdh.docx](#)
[Bullet points.docx](#)
[Re Support Bullet points.msg](#)

Cathy

WE had sent these late yesterday – Yvonne was working on this last night – I have not heard back from her yet

Let me know if you want to talk

I am at the NRN SC meeting but can break away

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, April 11, 2013 8:39 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: Letter regarding the SUPPORT study

Rose – given the front page story in the Washington Post today and the attached, can you please give me some bullets to address the attached as well

I have a meeting with Alan at 3 and I imagine this will come up

thanks

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 10:28 AM
To: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: Letter regarding the SUPPORT study

We should discuss.

Alan

From: Michael Carome [<mailto:mcarome@citizen.org>]
Sent: Wednesday, April 10, 2013 7:54 AM
To: Sebelius, Kathleen (HHS/OS)
Cc: Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Menikoff, Jerry (HHS/OASH); Borrer, Kristina C (HHS/OASH)
Subject: Letter regarding the SUPPORT study

Dear Secretary Sebelius,

Attached please find a letter from Public Citizen's Health Research Group expressing serious concern regarding the grossly inadequate corrective actions required by the Office for Human Research Protections in response to the egregious deficiencies in the consent forms for the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a multicenter study that tested two different experimental strategies for managing oxygen therapy in extremely premature infants and that was funded by the National Institutes of Health. The original hardcopy of our letter will follow by regular mail.

Thank you for your attention to this important matter.

Sincerely,

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

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

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Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0012 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0013 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: [Spong, Catherine \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Subject: FW: Letter regarding the SUPPORT study
Date: Thursday, April 11, 2013 8:39:07 AM
Attachments: [130410 Letter to HHS Secretary re SUPPORT trial FINAL Signed.pdf](#)

Rose – given the front page story in the Washington Post today and the attached, can you please give me some bullets to address the attached as well
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thanks

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Sent: Wednesday, April 10, 2013 10:28 AM
To: [Maddox, Yvonne \(NIH/NICHD\) \[E\]](#); [Spong, Catherine \(NIH/NICHD\) \[E\]](#)
Subject: FW: Letter regarding the SUPPORT study

We should discuss.

Alan

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Sent: Wednesday, April 10, 2013 7:54 AM
To: [Sebelius, Kathleen \(HHS/OS\)](#)
Cc: [Collins, Francis \(NIH/OD\) \[E\]](#); [Guttmacher, Alan \(NIH/NICHD\) \[E\]](#); [Menikoff, Jerry \(HHS/OASH\)](#); [Borrer, Kristina C \(HHS/OASH\)](#)
Subject: Letter regarding the SUPPORT study

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Thank you for your attention to this important matter.

Sincerely,

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

Tele: 202-588-7781
Fax: 202-588-7796
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PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

April 10, 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)

Dear Secretary Sebelius:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to express serious concern regarding the grossly inadequate corrective actions required by your department's Office for Human Research Protections (OHRP), as evidenced by the agency's March 7, 2013, compliance-oversight determination letter to the University of Alabama at Birmingham (UAB)¹ regarding the highly unethical, multicenter research study referenced above. The study involved the use of two different target ranges of oxygen levels (low, 85% to 89% saturation; and high, 91% to 95% saturation) to treat extremely premature infants, a most vulnerable group of human subjects.

This trial, funded by the National Institutes of Health (NIH) and ironically called the SUPPORT study, involved 23 major academic medical centers and exposed 1,316 extremely premature infants to increased risks of either death or retinal damage, depending on which oxygen group they were randomized to. Many, if not most, of the subjects' parents likely would have refused to let their newborn infants participate in the study had they been adequately informed of, and understood, the purpose and known risks of the research, as well as the differences in the experimental oxygen management for both SUPPORT study oxygen groups compared to usual individualized oxygen management for premature infants available at those same hospitals.

In its March 7 letter to the UAB, the Department of Health and Human Services' (HHS's) OHRP noted multiple serious deficiencies in the SUPPORT study consent form approved by the institutional review board (IRB, a committee charged with conducting an ethical review of human subjects research) at this trial center. The agency also noted similar serious deficiencies in consent forms approved by at least 22 other IRBs at major academic medical centers that reviewed this study. Referring to UAB's consent form, OHRP's letter reported the following key observations (bolded emphasis added):²

¹ Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_letters/YR13/mar13a.pdf. Accessed March 27, 2013.

² *Ibid.*

- 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 [oxygen] 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 [retinopathy — eye damage — of prematurity], 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 measure oxygen saturation levels] to the infant’s skin.”**

OHRP’s letter to UAB further stated (emphasis added):³

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.**

The institutions participating in the study were otherwise using a target oxygen saturation within the range of 85% to 95% for routine clinical care purposes. For infants whose parents chose not to be in the study, the oxygen would have been appropriately adjusted within this entire range to meet the specific individual needs of the infant, rather than attempting to confine the infant’s oxygen saturation to either the 85-89% range or the 91-95% range to meet the needs of the research, depending on the randomized group assignment of each infant.

Consistent with what had been known for decades, the SUPPORT study results demonstrated a statistically significant greater number of cases of serious retinal damage in the high-oxygen group compared with the low-oxygen group (see table below).⁴ In addition, as suspected for many years, the study revealed a statistically significant higher death rate in the low-oxygen group compared with those in the high-oxygen group.

As the table below shows, the absolute difference in the risk of serious retinal damage was 9.3% higher in the high-oxygen group compared with the low-oxygen group, representing an approximately 50% higher relative risk of serious retinal damage. On the other hand, the absolute difference in the risk of death was 3.7% higher in the low-oxygen group compared with the high-oxygen group, representing a 27% higher relative risk of death. These differences, particularly with respect to serious retinal damage, should have come as no surprise to anyone — except perhaps the uninformed parents of the subjects who participated in the research.

³ *Ibid.*

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.

Public Citizen

April 10, 2013, Letter to Secretary Sebelius

Table: Key Major Outcomes from SUPPORT Study

Outcome	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% Confidence Interval)
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)

Despite the egregious informed-consent omissions for the SUPPORT study, which caused parents to enroll their premature infants in this experiment under the false pretense that it was much safer for their infants than was known to be the case, OHRP has failed to demand adequate and meaningful corrective actions by HHS, the medical centers that conducted this research, and the IRBs that reviewed and approved it. At a minimum, such actions should have included:

- (1) A requirement that HHS issue a formal apology to the parents of all 1,316 infants who participated in the SUPPORT study. This apology should come directly from you and the NIH Director, and it should be accompanied by a complete divulgence of the information previously not disclosed about the (a) the purpose of the research; (b) the experimental nature of the oxygen interventions that were administered to the parents' babies; and (c) the real, substantial risks to their babies, some of whom subsequently may have died unnecessarily or suffered impairment of vision as a result of their participation in the study.
- (2) A requirement that each participating institution and reviewing IRB take corrective action to address the serious deficiencies identified by OHRP in the IRB-approved consent forms.

We urge you to promptly issue this apology and direct OHRP to immediately require additional corrective actions. In addition, further independent investigation is needed to understand how the HHS system for review and oversight of human subjects research failed so miserably during the process of reviewing, approving, and funding the SUPPORT study.

Below is a more detailed discussion of our concerns and requested actions.

Overview of the SUPPORT study

The SUPPORT study was a randomized, multicenter clinical trial that, in part, compared two target ranges of oxygen saturation, low (85% to 89% saturation) and high (91% to 95% saturation) in 1,316 extremely premature infants born between 24 weeks, 0 days and 27 weeks, 6 days of gestation.⁵ The primary outcome measure was a composite of severe retinopathy of prematurity (ROP) — a condition that frequently results in severe retinal damage and blindness

⁵ *Ibid.*

Public Citizen

April 10, 2013, Letter to Secretary Sebelius

— *death before discharge from the hospital, or both.*⁶ Subjects were enrolled in the study from 2005 to 2009.⁷

In commenting on the SUPPORT study protocol and consent form template, OHRP noted the following (emphasis added):⁸

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 [hypothetical] 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...**

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**

⁶ *Ibid.*

⁷ *Ibid.*

⁸ Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_letters/YR13/mar13a.pdf. Accessed March 27, 2013.

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 [and had gotten oxygen treatment suited to his or her individual clinical needs rather than the needs of the high or low oxygen groups in the study].**

Serious deficiencies of the IRB-approved SUPPORT study consent forms

In its March 7 letter to the UAB, OHRP stated the following regarding the IRB-approved consent forms for the SUPPORT study (emphasis added):⁹

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:

⁹ *Ibid.*

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At the front of the form:

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

In the section labeled “Introduction”:

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

In the section labeled “Procedures”:

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

In the section labeled “Possible Benefits”:

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

In the section labeled “Possible Risks”:

“There is no known risk to your baby from monitoring with the pulse oximeters used for this study. The possible risk of skin breakdown at the site will be

minimized by your baby's nurse moving the oximeter to another arm or leg a couple of times a day."

With regard to this information, OHRP notes the following:

- 1. The form does not say that there may be a greater or lesser risk of death depending on whether the infant is in the lower or upper range group.**
- 2. While the form says that being in the *lower* range group may result in the *benefit* of decreasing the chances of developing severe ROP, in the "Possible Risks" section it does not say that being in the *upper* range group may result in the greater *risk* of developing ROP.**
- 3. The only risk related to the part of the study involving the two ranges of oxygen levels described in the "Possible Risks" section is the risk of the pulse oximeter to the infant's skin.**

Based on the above facts, OHRP appropriately found that the IRB-approved consent form approved by the UAB IRB failed to adequately describe the risks of the research as required by HHS regulations at 45 C.F.R. 46.116(a)(2). In particular, OHRP noted the following (emphasis added):

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...

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**

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level they would have received had they not participated, could increase the risk of brain injury or death.

Although OHRP correctly determined that the IRB-approved consent forms for the SUPPORT study failed to disclose critically important information regarding the substantial, life-threatening risks of the research — and in fact misled parents of prospective subjects by essentially indicating that the research presented no risk — OHRP failed to identify other obvious, serious violations of the informed-consent requirements under HHS human subject protections regulations at 45 C.F.R. 46.116(a)(1). These regulations require that subjects or their legally authorized representatives (in this case, the parents of the premature infants) be provided, among other things, an explanation of the purpose of the research and identification of any procedures that are experimental.

- (1) With regard to the purpose of the research, the IRB-approved consent forms failed to disclose that one important purpose of the research was to determine whether the mortality rate of the infants would be different between the two experimental oxygen-management interventions.
- (2) With regard to identifying any experimental procedures, as explained clearly by OHRP, both subject groups received experimental interventions that altered the subjects' level of oxygen exposure in comparison to what they would have received as part of routine medical care, with one group receiving greater oxygen exposure and the other lower. Not only did the IRB-approved consent forms fail to identify these key experimental procedures, they instead clearly misrepresented the nature of the study interventions by stating that all subjects would receive oxygen treatments that maintained oxygen levels at "saturations ... considered normal ranges for premature infants."

As part of routine care for such infants outside the research context, oxygen therapy would have been individually titrated with a goal of maintaining oxygen saturation levels somewhere within the range of 85% to 95%. Such individualized care would have been based on the parents' wishes for balancing the risks of administering lower levels of oxygen (including neurologic injury and death from hypoxemia [oxygen deprivation]) with the risks of administering higher levels of oxygen (including severe retinal injury, lung injury, and death from oxygen toxicity). Decisions regarding which oxygen level to administer to an individual premature infant routinely would be based on the outcome of ongoing discussions between the parents of the infant and the physicians caring for that infant. Some parents may choose a level of oxygen therapy for their infant that lowers the risk of neurologic injury and death from hypoxemia at the expense of increased risk of serious retinal damage. Other parents may choose an oxygen-management strategy that minimizes the risk of severe retinal damage at the expense of increased risk of neurologic injury and death from hypoxemia. Thus, determining which level of oxygen to administer as part of routine care is based on what is in the best interests of that infant, as determined by the infant's parents in conjunction with the infant's physicians and other members of the health care team.

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Given the nature of the SUPPORT protocol as described by OHRP in its March 7 letter¹⁰ and by the investigators in published journal articles,^{11,12} these deficiencies in the IRB-approved consent forms regarding the research risks, purpose, and experimental procedures are extremely shocking. More disturbing is the fact that 23 IRBs at major academic medical centers all failed to recognize the deficiencies. Yet, it appears that UAB is the only institution required by OHRP to take corrective actions to address the consent-form deficiencies.

The failure to disclose such critically important information undoubtedly directly affected parents' decisions to enroll their premature infants in this study. It is highly likely that had they been appropriately informed about the nature of the research and its risks, many, if not most, parents would have declined to enroll their extremely premature infants in the SUPPORT study.

As a result of these deficiencies in the informed-consent process, the investigators of the SUPPORT study failed to obtain the legally effective informed consent from the subjects' parents, and the conduct of the study was highly unethical. Because this study was funded by NIH, the Department of Health and Human Services now has a moral obligation to formally apologize to the parents of all subjects enrolled in the study. This apology should come directly by you and the NIH Director, and it should be accompanied by a complete divulgence of the information previously not disclosed about (a) the purpose of the research; (b) the experimental nature of the oxygen interventions that were administered to the parents' babies; and (c) the real, substantial risks to their babies, some of whom subsequently may have died unnecessarily or suffered impairment of vision as a result of their participation in the study.

You also should direct OHRP to immediately take the following additional actions:

- (1) Expand its findings regarding the IRB-approved consent forms for the SUPPORT study to include the failure to accurately describe the purpose of the research and the failure to identify those research procedures that were experimental; and
- (2) Require substantive corrective action by each institution at which the IRB approved a seriously deficient consent form for the SUPPORT study. In addition to UAB, the institutions involved, according to the ClinicalTrials.gov registration¹³ for the trial and OHRP's March 7 letter, include:
 - Brown University
 - Case Western Reserve University
 - Duke University
 - Emory University School of Medicine

¹⁰ Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_letters/YR13/mar13a.pdf. Accessed March 27, 2013.

¹¹ 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.

¹² 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.

¹³ 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.

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- Indiana University School of Medicine
- Sharp Mary Birch Hospital for Women and Newborns
- Stanford University School of Medicine
- Tufts Medical Center
- University of California, San Diego
- University of Cincinnati
- University of Iowa
- University of Miami Miller School of Medicine
- University of New Mexico Health Sciences Center
- University of Rochester School of Medicine and Dentistry
- University of Tennessee
- University of Texas Health Science Center, Houston
- University of Texas Southwestern Medical Center
- University of Utah School of Medicine
- Wake Forest University School of Medicine
- Wayne State University
- Women and Infants Hospital of Rhode Island
- Yale University School of Medicine

Unresolved ethical questions about the design of the IRB-approved SUPPORT study

In addition to the clear deficiencies regarding the informed-consent process for the SUPPORT study, there also are important unresolved ethical questions about the design of the study.

In particular, it appears that the study as designed failed to satisfy the requirements of 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 any anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

The SUPPORT study involved extremely premature infants whose clinical status was critically ill, requiring customized neonatal intensive care unit management. As discussed above, as part of routine care for such infants, oxygen therapy would have been individually titrated within an oxygen saturation range of 85% to 95%.

As OHRP noted, the study involved randomization to two experimental groups that involved attempting to confine oxygen saturation levels at either the high end or the low end of the range routinely used to manage such patients, but it did not include a control group. Through randomization, subjects were changed from what would have been individualized oxygen

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management had they not participated in the study to different fixed target levels of oxygen management, independent of perceived clinical need or an individualized assessment of risks and benefits.

Based on research conducted long before the SUPPORT study and summarized by OHRP, it was highly plausible that targeting oxygen saturation at the high end of the usual range in premature infants would increase the risk of ROP, whereas targeting oxygen saturation at the low end of the usual range might increase the risk of neurological damage and death related to hypoxemia.

Given the available information, a strong argument can be made that any study comparing the two experimental target levels of oxygen saturation would be both unethical and not compliant with requirements of HHS regulations at 45 C.F.R. 46.11(a)(1) and (2).

We therefore urge you to direct OHRP to expand its compliance-oversight investigation of the SUPPORT study to include a careful re-assessment of the unresolved questions concerning the ethics of the study design.

Conclusions and summary of requested actions

In conclusion, the egregious deficiencies in the informed-consent process alone resulted in indefensible, highly unethical research involving vulnerable premature infants. While OHRP appropriately documented the serious informed-consent deficiencies related to the lack of disclosure of the risks of the research, the scope of OHRP's compliance-oversight findings for this research and the corrective actions being required by the agency are grossly inadequate.

In addition, the failure of at least 23 IRBs at major academic medical centers to recognize and correct the serious deficiencies in the sample consent form for the SUPPORT study is very troubling.

To ensure that the SUPPORT study deficiencies are meaningfully and adequately addressed and to prevent similar failures in the future, we again urge you to immediately take the following actions:

- (1) Issue a formal apology from you and the NIH Director to the parents of all 1,316 subjects enrolled in the SUPPPORT study. This apology should be accompanied by a complete divulgence of the previously undisclosed information regarding the nature, purpose, and risks of the research.
- (2) Direct OHRP to take the following actions:
 - (a) Expand the agency's findings regarding the IRB-approved consent forms for the SUPPORT study to include the failure to accurately describe the purpose of the research and the failure to identify those research procedures that were experimental;
 - (b) Require substantive corrective action by each institution at which the IRB approved the SUPPORT study;

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- (c) Expand its compliance-oversight investigation of the SUPPORT study to include a careful re-assessment of the unresolved questions concerning the ethics of the design of the study.
- (3) Initiate an independent investigation of the HHS system for review and oversight of HHS-funded human subjects research to understand how the system failed so miserably in the case of the SUPPORT study. This investigation should include an assessment of all entities within NIH and other HHS agencies that played a role in the review, approval, and funding of the SUPPORT study. In addition, given the widespread failures across multiple IRBs that reviewed and approved the SUPPORT study, HHS should determine what system-wide actions are needed to prevent such failures from recurring.
- (4) Identify and suspend any similarly unethical research involving premature infants that is funded by NIH or any other HHS agency.

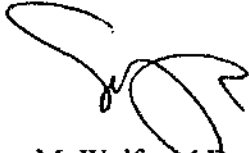
Finally, this is another disturbing situation that may warrant the attention of the Secretary's Advisory Committee on Human Research Protections.

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

Sincerely,



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



Sidney M. Wolfe, M.D.
Director
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cc: 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

From: Willinger, Marian (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Don't give out this statement yet
Date: Thursday, April 11, 2013 8:03:50 AM

I have been (b)(6) but have been following the emails. The articles are clear.

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 2:29 PM
To: Bock, Robert (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: Re: Don't give out this statement yet

Tx bob. Having a hard time reasing much at this moment sounds like a good plan however

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 02:25 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Don't give out this statement yet

Yes. We will likely (b)(5) I'm going to work with the material Rose provided to develop a standard response, if NICHD is directly asked to comment.

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 2:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Don't give out this statement yet

The New York Times article is clear. I think before we could invite (b)(5) (b)(5) we would need to talk to Bldg 1. Bob, have you spoken to the communications folks at OD, yet?

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 2:16 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Don't give out this statement yet

Here are bullet points:

Bullet points

(b)(5)

(b)(5)



(b)(5)



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From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 2:11 PM
To: Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Don't give out this statement yet

This is a well thought (b)(5) Do we all agree? If so, I think we should consider (b)(5)

(b)(5)

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From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 1:39 PM
To: Willinger, Marian (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Don't give out this statement yet

I just checked the University's site and did a Google Search and this statement does not appear to be public.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 1:20 PM
To: Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: FW: NRN SC Agenda and Materials

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srhintz@stanford.edu<mailto:srhintz@stanford.edu>; Susan Gunn; Tarah Colaizy; Yvonne Vaucher;
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ewoldt@med.wayne.edu<mailto:ewoldt@med.wayne.edu>; Joan Merzbach; Karen Murray;
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dale_phelps@urmc.rochester.edu<mailto:dale_phelps@urmc.rochester.edu>; Wrage, Lisa Ann; McDonald, Scott
A.; Tan, Sylvia; Becky Brazeel; Brenda Vecchio; Garcia, Deborah;
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lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>;
Nancy.M.Smith@uth.tmc.edu<mailto:Nancy.M.Smith@uth.tmc.edu>; Theresa Banker; Penelope Bradley
Subject: RE: NRN SC Agenda and Materials

This is the UAB response to multiple media outlets calls.

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, April 09, 2013 1:13 PM
To: Prem Fort, M.D.; Valerie Y-L Chock;
Gloria_Pryhuber@URMC.Rochester.edu<mailto:Gloria_Pryhuber@URMC.Rochester.edu>; Erika Fernandez;
alexis.davis@stanford.edu<mailto:alexis.davis@stanford.edu>; [SCRN] Stoll, Barbara;
alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill
Truong; bpoindex@iu.edu<mailto:bpoindex@iu.edu>; Carl D'Angio; Das, Abhik; Gantz, Marie;
goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Higgins, Rosemary (NIH/NICHD) [E];
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kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; Leif Nelin;
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sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; Uday Devaskar;
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Huitema, Carolyn Petrie; Janice Bernhart;
janice_wereszczak@med.unc.edu<mailto:janice_wereszczak@med.unc.edu>; Joanne R Finkle; Johnson, Karen;
Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu<mailto:Kimberley.fisher@duke.edu>;
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Fananoff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu<mailto:dstevenson@stanford.edu>; Eugenia
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Keszler, Martin; Lina.Yossef@nationwidechildrens.org<mailto:Lina.Yossef@nationwidechildrens.org>; Luc
Brion; Meena Garg; Michael Cotten; Namasivayam Ambalavanan;
rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Ronnie Guillet; Sood, Beena; Sudarshan Jadcherla; Abbey
Hines; Andrea Duncan; Athina Pappas; bvoehr@wihri.org<mailto:bvoehr@wihri.org>; Christopher Timan;
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srhintz@stanford.edu<mailto:srhintz@stanford.edu>; Susan Gunn; Tarah Colaizy; Yvonne Vaucher; afurey@tuftsmedicalcenter.org<mailto:afurey@tuftsmedicalcenter.org>; Andrea Halbrook; BRODSKYN@email.chop.edu<mailto:BRODSKYN@email.chop.edu>; bss5@cwru.edu<mailto:bss5@cwru.edu>; Corri DeDomenico; diane-eastman@uiowa.edu<mailto:diane-eastman@uiowa.edu>; elaine.romano@yale.edu<mailto:elaine.romano@yale.edu>; Elizabeth Paulsen; ewoldt@med.wayne.edu<mailto:ewoldt@med.wayne.edu>; Joan Merzbach; Karen Murray; karen.osborne@hsc.utah.edu<mailto:karen.osborne@hsc.utah.edu>; Kathy Johnson; Margaret.Poundstone@uth.tmc.edu<mailto:Margaret.Poundstone@uth.tmc.edu>; Teresa.Gratton@uc.edu<mailto:Teresa.Gratton@uc.edu>; Victoria Watson; Vivien Phillips
Cc: vwilli4@emory.edu<mailto:vwilli4@emory.edu>; monica@bocaner.net<mailto:monica@bocaner.net>; dale_phelps@urmc.rochester.edu<mailto:dale_phelps@urmc.rochester.edu>; Wrage, Lisa Ann; McDonald, Scott A.; Tan, Sylvia; Becky Brazeel; Brenda Vecchio; Garcia, Deborah; gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Heidi Kleinbart; jwaidne@emory.edu<mailto:jwaidne@emory.edu>; Kristie Smiley; lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>; Nancy.M.Smith@uth.tmc.edu<mailto:Nancy.M.Smith@uth.tmc.edu>; Theresa Banker; Penelope Bradley
Subject: NRN SC Agenda and Materials

Hi All,

Attached you will find a revised (and hopefully final this time!) agenda for this week's meeting. All handouts and concepts are now posted on the private gateway of the website following these links:

Administration<[https://neonatal.rti.org/index.cfm?](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.home)

[CEID=2220051&CFTOKEN=90695570&fuseaction=administration.home](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.home)> >

Minutes<[https://neonatal.rti.org/index.cfm?](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes)

[CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes)> > Steering

Committee<[https://neonatal.rti.org/index.cfm?](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering)

[CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering)> >

2013<[https://neonatal.rti.org/index.cfm?](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering_2013)

[CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering_2013](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering_2013)> >

April<[https://neonatal.rti.org/index.cfm?](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering_2013_april)

[CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering_2013_april](https://neonatal.rti.org/index.cfm?CEID=2220051&CFTOKEN=90695570&fuseaction=administration.minutes_steering_2013_april)> > Handouts

Safe travels and see you soon!

Meg

Meg Cunningham, CCRP
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
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fax: 202-728-2095
www.rti.org<<http://www.rti.org>>

From: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE:
Date: Thursday, April 11, 2013 7:58:07 AM

I've been reading the emails -is anyone from HHS coming to the meeting?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 11, 2013 7:56 AM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re:

Yes and tomorrow also
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

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

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Thursday, April 11, 2013 07:54 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:

Rose- do you still have NRN today?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 3:07 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject:

<http://washpost.bloomberg.com/Story?docId=1376-ML0DZQ6JLIVW01-4CPE0JNAV9BLHE37LDEHPPE0AQ>

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov <<mailto:higginsr@mail.nih.gov>>

From: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#)
Subject: RE:
Date: Thursday, April 11, 2013 7:35:52 AM

ok story

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 3:07 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject:

<http://washpost.bloomberg.com/Story?docId=1376-ML0DZQ6IIVW01-4CPE0JNAV9BLHF37LDEHPPE0AQ>

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From: Pablo Sanchez
To: Susan Partridge
Cc: Diana Vasil; Diane Sheppard; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: NY Times article
Date: Thursday, April 11, 2013 5:50:17 AM

Yes - we know- am at the neonatal research meeting and discussing it - many statements incorrect - sound familiar? I have been in contact with Utsw IRB as well - study conducted at pmh with follow up at Cmc Lbw clinic - the NIH is said to be drafting some talking points - but the trial was conducted appropriately and the fact is that what they are claiming was only known after the trial - and by the way, blindness was not 18% - more like 1% - and the study was to reduce its occurrence - anyway could go on - I am out of the office and don't know the IRB number - will try to get it for you

Pablo
214-(b)(6) (cell)
972-(b)(6) (beeper)
214-648-3903 (office)

Sent from iPhone.

On Apr 10, 2013, at 7:06 PM, "Susan Partridge" <SUSAN.PARTRIDGE@phhs.org> wrote:

Dear Diana

Our CEO has asked me to provide him with a briefing about this study. We are getting inquiries from the press. Can you help me or direct me to the right person? Can you give me the IRB number?

Thanks very much,

Susan

Sent from my iPhone

Begin forwarded message:

From: Robert Smith <ROBERTL.SMITH@phhs.org>
Date: April 10, 2013, 4:15:45 PM CDT
To: Susan Partridge <SUSAN.PARTRIDGE@phhs.org>
Subject: FW: NY Times article

FYI

From: April Foran
Sent: Wednesday, April 10, 2013 4:05 PM
To: Robert Smith; Ronald Laxton; Ted Shaw; Mary Eagen; Christopher

Madden; Sharon Phillips; Paul Leslie; Michael Malaise; Joe Householder
(Purple Strategies) (Joe.householder@purplestrategies.com)

Subject: NY Times article

http://www.nytimes.com/2013/04/11/health/parents-of-preemies-werent-told-of-risks-in-study.html?hp&_r=0

The New York Times ran an article today stating that lead investigators on a large study of the effects of oxygen levels on extremely premature babies failed to inform the infants' parents that the risks of participating could involve increased chances of blindness or death. Representatives from University of Alabama, Birmingham were the lead researchers but UT Southwestern was one of the 23 sites in the clinical trials – which means that Parkland was a participant in the clinical trials since we have the premature babies (along with St. Paul). Per Mike Berman, Director of External Communications at UT Southwestern, they are not commenting on anything, he just wanted to give us a heads up that the story is out there. UT is not mentioned in the story.

April Foran
Director of Corporate Communications & PIO
Parkland Health & Hospital System
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<image003.jpg>

UT Southwestern Medical Center
The future of medicine, today.

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Pablo Sanchez
Subject: FW: Recent OHRP finding of consent violations in component of SUPPORT trial
Date: Thursday, April 11, 2013 5:49:46 AM
Attachments: [OHRP Support Study HSP violation letter Mar 2013.pdf](#)

Rose;

FYI.

Diane Shephard is Director of Research Regulations at UTSW.

Simon Lee reviewed Jackie's paper on changes in process of care at Parkland during SUPPORT

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The
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From: Simon Lee
Sent: Wednesday, April 10, 2013 3:18 PM
To: Luc Brion; Jaclyn Levan
Cc: Diane Sheppard
Subject: Recent OHRP finding of consent violations in component of SUPPORT trial

Dear colleagues,

This may well have already come to your attention given your active areas of research but I wanted to share with you the federal finding letter (attached) regarding the violation of informed consent despite UAB's IRB approved documents.

Further information is also available here: [Compliance Watch](#) and [DHHS OHRP](#)

Simon

Simon J. Craddock LEE, PhD MPH
Assistant Professor of Clinical Sciences (Medical Anthropology)
Department of Clinical Sciences
and
~~Population Sciences & Cancer Control~~, Simmons Cancer Center
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Committee on Ethics, *presidential appointment*
American Anthropological Association

NCI·CC

A Cancer Center Designated by the National Cancer Institute

UT Southwestern Medical Center
The future of medicine, today.

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

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: 240-453-8298
FAX: 240-453-6909
E-mail: Lisa.Buchanan@HHS.gov

March 7, 2013

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

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

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

Dear Dr. Marchase:

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

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

Page 2 of 13

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

March 7, 2013

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.

Page 3 of 13

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

March 7, 2013

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

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.”).

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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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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

From: [Einer, Neil](#)
To: [William Tarnow-Mordi](#)
Cc: [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: SUPPORT and NYT
Date: Thursday, April 11, 2013 4:21:49 AM

Thanks William
Did your consent mention an increased risk of death?
Be well and see you soon
Neil

Sent from my iPhone

On Apr 11, 2013, at 8:32 AM, "William Tarnow-Mordi" <williamtm@med.usyd.edu.au> wrote:

> Dear Wally, Neil and Rose
>
> Just to let you know our thoughts are with you at this incredibly
> difficult time following the NY Times article. I look forward to
> meeting you in Washington next month.
>
> Illegitimi non carborundum!
>
> best wishes
>
> William
> --
> William Tarnow-Mordi
> Professor of Neonatal Medicine, Westmead Hospital
> NHMRC Clinical Trials Centre, University of Sydney,
> Foundation Director
> Westmead International Network for Neonatal Education and Research
> WINNER Centre - working together to win healthy survival.
>
>
>
>
>
>
>

From: [Bell, Edward \(Pediatrics\)](#)
To: [Michele Walsh](#); [Abbot Laptook](#); [Abhik Das](#); [Kurt Schibler](#); [Pablo Sanchez](#); [Brenda Poindexter](#); [Cotten, Mike](#); [Krisa P Van Meurs \(vanmeurs@stanford.edu\)](#); [Kristi Watterberg](#); [Goldberg, Ron](#); [Marie Gantz](#)
Cc: [Wally Carlo](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Draft letter and op-ed commentary for NY Times
Date: Thursday, April 11, 2013 12:44:56 AM
Attachments: [NYT letter v3\(s\).doc](#)
[NYT letter v2wc.doc](#)

Here are drafts of a letter (150-word limit) and commentary (if the editors are interested) that Wally and I have drafted for the NY Times. The longer document needs some more numbers to complete the table. Should we also include NDI and/or NDI/death? I don't know if they will even allow a table. We welcome your comments and editorial suggestions. Let us know if you would like to be co-signators.

Ed and Wally

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April 10, 2013

Editors
New York Times

Dear Editors:

We are among the investigators of the SUPPORT study and authors of the resulting publications. Contrary to the determination of March 7, 2013 by the U.S. Office of Human Research Protection (OHRP), the press release today by Public Citizen, and the article by Ms. Sabrina Tavernise in today's Times, we disagree that the premature infants enrolled in the SUPPORT study were placed at increased risk because of their participation in the study. At the time the study was planned, there was limited evidence, based on studies done in the 1950s, that excessive levels of inhaled oxygen in premature infants increased the risk of retinopathy of prematurity (ROP) and that severe restriction of oxygen, regardless of the oxygen level in the blood, increased the risk of death. These old studies were done before it was possible to measure continuously the level of oxygen in the baby's bloodstream. In addition, by the time the SUPPORT study was being planned there had been so many changes in the way care is provided and improvements in the survival and health of premature infants that there was a compelling need for more information to guide the use of oxygen for premature infants in the modern era.

The American Academy of Pediatrics (AAP) recommended in 2007 that the oxygen level (measured as oxygen saturation by pulse oximetry) be kept between 85 and 95% as much as possible in premature babies. Several small, poorly controlled studies in recent years had shown that ROP risk could be reduced by aiming for lower oxygen saturation levels (as low as 70%) with no effect on death risk, and physicians were beginning to target lower oxygen levels for premature babies. The SUPPORT study was planned to compare the safety of using oxygen saturation targets toward the lower and upper ends of the range recommended by the AAP, 85-89% compared with 91-95%, ranges that had not been shown to result in differences in ROP or death.

Very premature babies have high risks of death, ROP, and a number of other health problems, whether or not they participate in research studies. The question at hand is whether it was known or anticipated that participation in the SUPPORT trial would increase these risks. If risks were known, they should have been explained to parents who gave consent for their babies to participate in the study.

Shown in the table below are the percentage of babies who had severe ROP, blindness, and death in both groups of the SUPPORT study, the babies who were eligible but not enrolled in the study, and a group of similar babies from before the SUPPORT study.

Patient group	Severe ROP(%)	Blindness (%)	Death (%)
Pre-SUPPORT (add range of years)			23.1
SUPPORT 85-89% oxygen saturation target	8.6		19.9
SUPPORT 91-95% oxygen saturation target	17.9		16.2
SUPPORT all patients			
Babies eligible but not enrolled in SUPPORT			24.1

Comment [afb1]: Should we add NDI?

Comment [WC2R1]: That is an excellent idea. It should be NDI/death as the increased survival may increase % of babies with NDI.

This table shows that the overall risks of severe ROP, blindness, and death were not increased by participation in the SUPPORT study. The babies in the lower oxygen saturation target group had lower risk of severe ROP but higher risk of death and no difference in blindness. Use of the higher oxygen saturation target resulted in 2 cases of severe ROP for each case of death prevented and 6 more survivors for each additional blind baby. This is vitally important information that was badly needed to help neonatologists decide the best target range to use for their very premature patients.

The press release of Public Citizen said that the standard care for non-participants was as follows: "The exact oxygen target level for a particular infant at any particular time would be based on the baby's individual medical needs and the wishes of the baby's parents." In fact, the target level varied among hospitals, based on the physicians' best guess from available evidence, but there was not enough information to guide an individualized approach to this aspect of care. We should add that, even now, we do not know if and how the target range should be adjusted for individual babies.

In retrospect, each participating investigator-author can see ways that our consent forms might have been written in a clearer and more informative way, but these documents were conscientiously drafted making full use of the information available at the time. If the comparative risks of the target oxygen saturation ranges used in the study had been known, there would have been no need for the study. We believe that the SUPPORT study provided valuable new evidence about the benefits and risks of using oxygen saturation targets toward the lower and upper ends of the range in common use.

We provided parents with the information we had at the time, which did not indicate increased risk resulting from participation in the study nor from being assigned to either study group.

In conclusion, the OHRP determination, the Public Citizen press release, and the New York Times story wrongly accuse the SUPPORT investigators, their institutional review boards, the NICHD, the reviewers of the SUPPORT study proposal, and the Neonatal Research Network's independent Data Safety Monitoring Committee of conducting this important study with inadequate informed consent.

Sincerely yours,

April 10, 2013

Editors
New York Times

Dear Editors:

We disagree that parents of infants in the SUPPORT study should have been informed that participation placed them at increased risk. Before the study, the standard oxygen saturation target range was 85-95%. Several studies had shown the risk of retinopathy of prematurity could be reduced by targeting saturations below 85% with no effect on mortality, and lower saturation targets were being used widely. The study was planned to compare the safety of two saturation targets within the standard range, 85-89% and 91-95%. The risks assessed were not increased by participation in the study. The infants in the lower saturation group had lower risk of ROP but higher risk of death and no difference in blindness. This information was badly needed to help decide the best target range. We provided parents with the information we had, which did not indicate increased risk from participation in the study in either study group.

Sincerely yours,

From: Bell, Edward (Pediatrics)
To: Gantz, Marie
Cc: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
Subject: RE: NRN SC Agenda and Materials
Date: Wednesday, April 10, 2013 10:51:26 PM

...and columns for NDI and NDI/death.

Thx,
Ed

From: Bell, Edward (Pediatrics)
Sent: Wednesday, April 10, 2013 8:36 PM
To: 'Gantz, Marie'
Cc: Wally Carlo; Rosemary Higgins; Abhik Das
Subject: RE: NRN SC Agenda and Materials

Can you add a column for blindness, too, since that was mentioned in the Public Citizens and other reports today.

From: Bell, Edward (Pediatrics)
Sent: Wednesday, April 10, 2013 8:26 PM
To: 'Gantz, Marie'
Cc: Wally Carlo; Rosemary Higgins; Abhik Das
Subject: RE: NRN SC Agenda and Materials

Marie,
Can you provide the data for the 4 empty cells in this table.
Thanks,
Ed

Patient group	Severe ROP(%)	Blindness	Death (%)
Pre-SUPPORT (years)			23.1
SUPPORT 85-89% oxygen saturation target	8.6		19.9
SUPPORT 91-95% oxygen saturation target	17.9		16.2
SUPPORT all patients			
Babies eligible but not enrolled in SUPPORT			24.1

From: Bell, Edward (Pediatrics)
Sent: Wednesday, April 10, 2013 8:13 PM
To: 'Gantz, Marie'
Cc: Wally Carlo; Rosemary Higgins; Abhik Das
Subject: RE: NRN SC Agenda and Materials

Marie,
Can you give us similar information for severe ROP. What was the incidence in each oxygen targeting group, in the babies who were eligible but not enrolled, and the same historical cohort for which you gave us the mortality figures?
Thanks,
Ed

From: Gantz, Marie [mailto:mgantz@rti.org]

Sent: Wednesday, April 10, 2013 1:25 PM

To: Wally Carlo, M.D.; Cunningham, Meg; Prem Fort, M.D.; Valerie Y-L Chock; Gloria_Pryhuber@URMC.Rochester.edu; Erika Fernandez; alexis.davis@stanford.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward (Pediatrics); Bill Truog; bpoindex@iu.edu; Carl D'Angio; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; wacarlo@uab.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Aasma Chaudhary; ahensman@WIHRI.org; Ann_Scorson@URMC.Rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chob.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; cldark@med.unc.edu; Conra Lacy; Dara Cucinotta; Dee Maffett; Diana Vasil; Campbell, Donia D; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.E.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen (Pediatrics); Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; Monica Collins; msacilowski@upa.chob.edu; nancy newman; Newman, Jamie; Pamela.moorehead@nationwidechildrens.org; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucd.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; shigdon@med.umich.edu; Teresa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; Namasivayam Ambalavanan; rohls@salud.unm.edu; Ronnie Guillet; Sood, Beena; Sudarshan Jadcherla; Abbey Hines; Andrea Duncan; Athina Pappas; byohr@WIHRI.org; Christopher Timan; drfrcmd@aol.com; DeMauro, Sara M; dmarshal@med.unc.edu; Donna Garey; emcgowan@tuftsmedicalcenter.org; Gary Meyers; Hallam Hurt; Howard Kilbride; jadamsc@emory.edu; Isabell Purdy; Katie Gustafason; Keith Yeates; Kelley Yost; Kimberly.Yolton@cchmc.org; Lowe, Jean; LuAnn Papile; Marsha Gerdes; Martha Carlson; Martha Fuller; Mike Steffen; Myriam Peralta, M.D.; Patrick.M.Jones@uth.tmc.edu; richard.ehrenkranz@yale.edu; Ricki F Goldstein; Roy.Hayne@UTSouthwestern.edu; soraya.abbasi@uphs.upenn.edu; srhintz@stanford.edu; Susan Gunn; Colaizy, Tarah T; Yvonne Vaucher; afurey@tuftsmedicalcenter.org; Andrea Halbrook; BRODSKYN@email.chop.edu; bss5@cwru.edu; Corri DeDomenico; Eastman, Diane; elaine.romano@yale.edu; Elizabeth Paulsen; ewoldt@med.wayne.edu; Joan Merzbach; Karen Murray; karen.osborne@hsc.utah.edu; Kathy Johnson; Margaret.Poundstone@uth.tmc.edu; Teresa.Gratton@uc.edu; Victoria Watson; Vivien Phillips
Cc: wwilli4@emory.edu; monica@bocaner.net; dale_phelps@URMC.Rochester.edu; Wrage, Lisa Ann; McDonald, Scott A.; Tan, Sylvia; Becky Brazeel; Brenda Vecchio; Garcia, Deborah; gonza025@mc.duke.edu; Heidi Kleinbart; jwaidne@emory.edu; Kristie Smiley; lmoore@med.wayne.edu; Nancy.M.Smith@uth.tmc.edu; Theresa Banker; Penelope Bradley
Subject: RE: NRN SC Agenda and Materials

A correction to Wally's correction: the death rate in the historical comparison group was 23.1% (not 23.3%).

Also, (since it came up in discussion) as reported in NEJM, there were 11 cases of bilateral blindness at 18-22 months: 5 in the low target group and 6 in the high target group.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5100

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Wednesday, April 10, 2013 1:47 PM

To: Cunningham, Meg; Prem Fort, M.D.; Valerie Y-L Chock; Gloria_Pryhuber@URMC.Rochester.edu; Erika Fernandez; alexis.davis@stanford.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; Das, Abhik; Gantz, Marie; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Wally Carlo (wacarlo@uab.edu); Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Aasma

Chaudhary; ahensman@wihri.org; Ann_Scorson@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chob.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; clclark@med.unc.edu; Conra Lacy; Dara Cucinotta; Dee Maffett; Diana Vasil; Donia Campbell; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.E.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen; Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; Monica Collins; msacilowski@upa.chob.edu; nancy newman; Newman, Jamie; Pamela.moorehead@nationwidechildrens.org; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucla.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; shigdon@med.umich.edu; Teressa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; Namasivayam Ambalavanan; rohls@salud.unm.edu; Ronnie Guillet; Sood, Beena; Sudarshan Jadchela; Abbey Hines; Andrea Duncan; Athina Pappas; byohr@wihri.org; Christopher Timan; drfcmid@aol.com; DeMauro, Sara M; dmarshal@med.unc.edu; Donna Garey; emcgowan@tuftsmedicalcenter.org; Gary Meyers; Hallam Hurt; Howard Kilbride; iadamsc@emory.edu; Isabell Purdy; Katie Gustafason; Keith Yeates; Kelley Yost; Kimberly.Yolton@cchmc.org; Lowe, Jean; LuAnn Papile; Marsha Gerdes; Martha Carlson; Martha Fuller; Mike Steffen; Myriam Peralta, M.D.; Patrick.M.Jones@uth.tmc.edu; richard.ehrenkranz@yale.edu; Ricki F Goldstein; Roy.Heyne@utsouthwestern.edu; soraya.abbasi@uphs.upenn.edu; rhintz@stanford.edu; Susan Gunn; Tarah Colaizy; Yvonne Vaucher; afurey@tuftsmedicalcenter.org; Andrea Halbrook; BRODSKYN@email.chop.edu; bss5@cwru.edu; Corri DeDomenico; diane-eastman@uiowa.edu; elaine.romano@yale.edu; Elizabeth Paulsen; ewoldt@med.wayne.edu; Joan Merzbach; Karen Murray; karen.osborne@hsc.utah.edu; Kathy Johnson; Margaret.Poundstone@uth.tmc.edu; Teresa.Gratton@uc.edu; Victoria Watson; Vivien Phillips
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Subject: RE: NRN SC Agenda and Materials

Enclosed the OHRP letter to UAB as well as Appendices 1 and 2 quoted in the letter from us to UAB and our original letter to UAB.

Table 3 in the letter from me (drafted by the NRNSC) has great talking points and one correction that Marie just gave me.

Wally

From: Cunningham, Meg [<mailto:mcunningham@rti.org>]

Sent: Tuesday, April 09, 2013 1:13 PM

To: Prem Fort, M.D.; Valerie Y-L Chock; Gloria.Pryhuber@URMC.Rochester.edu; Erika Fernandez; alexis.davis@stanford.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; bpointex@iu.edu; Carl D'Angio; Das, Abhik; Gantz, Marie; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; Aasma Chaudhary; ahensman@wihri.org; Ann_Scorson@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chob.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; clclark@med.unc.edu; Conra Lacy; Dara Cucinotta; Dee Maffett; Diana Vasil; Donia Campbell; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.E.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen; Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; Monica Collins; msacilowski@upa.chob.edu; nancy newman; Newman, Jamie; Pamela.moorehead@nationwidechildrens.org; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucla.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; shigdon@med.umich.edu; Teressa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; Namasivayam Ambalavanan; rohls@salud.unm.edu; Ronnie Guillet; Sood, Beena; Sudarshan Jadchela; Abbey Hines; Andrea Duncan; Athina Pappas; byohr@wihri.org; Christopher Timan;

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Cc: vwill4@emory.edu; monica@bocaner.net; dale_phelps@umc.rochester.edu; Wrage, Lisa Ann; McDonald, Scott A.; Tan, Sylvia; Becky Brazeel; Brenda Vecchio; Garcia, Deborah; gonza025@mc.duke.edu; Heidi Kleinbart; jwaidne@emory.edu; Kristie Smiley; lmoore@med.wayne.edu; Nancy.M.Smith@uth.tmc.edu; Theresa Banker; Penelope Bradley

Subject: NRN SC Agenda and Materials

Hi All,

Attached you will find a revised (and hopefully final this time!) agenda for this week's meeting. All handouts and concepts are now posted on the private gateway of the website following these links:

[Administration](#) > [Minutes](#) > [Steering Committee](#) > [2013](#) > [April](#) > [Handouts](#)

Safe travels and see you soon!

Meg

*Meg Cunningham, CCRP
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095
www.rti.org*

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From: Bell, Edward (Pediatrics)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Iowa SUPPORT consent form
Date: Wednesday, April 10, 2013 9:53:00 PM

Not much about oxygen saturation targets. We thought, and still do, that there were no known risks associated with using targets within the usual clinically used range.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 10, 2013 8:45 PM
To: Bell, Edward (Pediatrics)
Subject: Iowa SUPPORT consent form

FYI

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
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301-435-7909
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From: Bell, Edward (Pediatrics)
To: Wally Carlo; Michele Walsh; Pablo Sanchez; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Updates
Date: Wednesday, April 10, 2013 7:27:42 PM

Both Public Citizen and NY Times have corrected their misstatements about blindness and now correctly refer to the percentages as babies with severe ROP (previously termed "blindness" in the PC press release and Times article). Wally, note also the clarification that this happened at UAB, not the University of Alabama. Tuscaloosa is distancing themselves.

Notice: This UI Health Care e-mail (including attachments) is covered by the Electronic Communications Privacy Act, 18 U.S.C. 2510-2521, is confidential and may be legally privileged. If you are not the intended recipient, you are hereby notified that any retention, dissemination, distribution, or copying of this communication is strictly prohibited. Please reply to the sender that you have received the message in error, then delete it. Thank you.

Blansfield, Earl (NIH/NICHD) [E]

From: Maddox, Yvonne (NIH/NIMHD) [E]
Sent: Wednesday, April 10, 2013 6:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: Support Bullet points

Don't know the significance of what sanjay Gupta's presence would mean.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 06:33 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: Support Bullet points

We should also correct misinformation like (b)(5) quoted in one of the articles.

Also, Dr. Barbara Stoll has asked if dr. Sanjay Gupta from CNN (also an Emory faculty member) could be invited to talk to the NRN steering committee tomorrow- not sure how to answer this- I told her I would get guidance.

Thanks for the help

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

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 06:26 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support Bullet points

These are good, I have a few edits, will make on my computer when I get home. Thanks

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 05:51 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Bullet points

Hi Yvonne. Please see attached. Mona, Rose and I worked out some bullet points, for use if we get requests from the media.

Thanks.
Bob

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 6:46 PM
To: Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: Re: Support Bullet points

No
Barbara Stoll is the chair of pediatrics at Emory where Gupta has an appointment
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 06:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Support Bullet points

Is Gupta around "naturally" -- so that it would be considered part of the ongoing activities -- is there something special that you want him to address

Mona
Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 6:34 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: Support Bullet points

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Thanks for the help

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 06:26 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support Bullet points

These are good, I have a few edits, will make on my computer when I get home. Thanks

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 05:51 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Bullet points

Hi Yvonne. Please see attached. Mona, Rose and I worked out some bullet points, for use if we get requests from the media.

Thanks.

Bob

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Subject: Question
Date: Wednesday, April 10, 2013 6:08:34 PM

Bob

Should we or someone let NEJM know or is this not necessary (3 papers from the study thus far have been published in NEJM)

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 5:54 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: Support Bullet points

Let me know if I can share - many of our investigators have been contacted
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 05:51 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Bullet points

Hi Yvonne. Please see attached. Mona, Rose and I worked out some bullet points, for use if we get requests from the media.

Thanks.
Bob

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov)
To: [Bock, Robert \(NIH/NICHD\) \[E\]](mailto:Bock.Robert@nih.gov); [Rowe, Mona \(NIH/NICHD\) \[E\]](mailto:Rowe.Mona@nih.gov)
Subject: RE: Bullet Points for OD press
Date: Wednesday, April 10, 2013 5:32:00 PM

Yes – I used a different track change so you could see

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Bock, Robert \(NIH/NICHD\) \[E\]](mailto:Bock.Robert@nih.gov)
Sent: Wednesday, April 10, 2013 5:33 PM
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov); [Rowe, Mona \(NIH/NICHD\) \[E\]](mailto:Rowe.Mona@nih.gov)
Subject: RE: Bullet Points for OD press

You're ok with the other changes?

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov)
Sent: Wednesday, April 10, 2013 5:31 PM
To: [Rowe, Mona \(NIH/NICHD\) \[E\]](mailto:Rowe.Mona@nih.gov); [Bock, Robert \(NIH/NICHD\) \[E\]](mailto:Bock.Robert@nih.gov)
Subject: RE: Bullet Points for OD press

I went back to the UAB consent form to get the language right

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higginsr@mail.nih.gov

From: [Rowe, Mona \(NIH/NICHD\) \[E\]](mailto:Rowe.Mona@nih.gov)
Sent: Wednesday, April 10, 2013 5:15 PM
To: [Bock, Robert \(NIH/NICHD\) \[E\]](mailto:Bock.Robert@nih.gov); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov)

Subject: RE: Bullet Points for OD press

What do you folks think?

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
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31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 4:41 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: Bullet Points for OD press

Please see attached, for your review.

Renate asked me to draft them for the response to Sabrina, who is really pressing her for a response.

Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 3:07 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject:

<http://washpost.bloomberg.com/Story?docId=1376-ML0DZO6IJVW01-4CPEQJNAV9BLHF37LDEHPPE0AQ>

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Rowe, Mona \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#)
Subject: RE: Bullet Points for OD press
Date: Wednesday, April 10, 2013 5:31:00 PM
Attachments: [Support Background mr.docx](#)

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What do you folks think?

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Mona Jaffe Rowe, M.C.P.
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Subject:

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Page 0074 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0075 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Bullet Points for OD press
Date: Wednesday, April 10, 2013 5:20:00 PM

DO you want consent language from the UAB approved consent form??

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Sent: Wednesday, April 10, 2013 5:15 PM
To: Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Bullet Points for OD press

What do you folks think?

Mona

Mona Jaffe Rowe, M.C.P.
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Sent: Wednesday, April 10, 2013 4:41 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
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Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 5:15 PM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Support Bullet points

I do have some comments will share in a few minutes

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
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National Institutes of Health, DHHS
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Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 4:59 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Support Bullet points

Hi Bob:

Thanks for this but it doesn't explain our investigator's role. Sabrina thinks we are a study site. Is that coming?

Thanks,
Renate

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 4:56 PM
To: Myles, Renate (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Support Bullet points

Hi Renate. Please see attached. Mona will weigh in if she's able to.

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 4:29 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: urgent NIH question from Sabrina NYT on deadline

How's it going? Sabrina is pressing.

From: stavernise@gmail.com [mailto:stavernise@gmail.com] **On Behalf Of** Sabrina Tavernise
Sent: Wednesday, April 10, 2013 4:20 PM
To: Myles, Renate (NIH/OD) [E]
Subject: Re: urgent NIH question from Sabrina NYT on deadline

hi you. how's it going? update -- they were interested in this for P1, though i'm arguing against that but it may have prominent play. Any chance you could get someone before 6pm? Seems Guttmacher's group was pretty central in teh study

On Wed, Apr 10, 2013 at 3:21 PM, Myles, Renate (NIH/OD) [E] <mylesr@od.nih.gov> wrote:

Hi Sabrina:

Let me check for you. Be back in touch ASAP.

Renate

From: stavernise@gmail.com [mailto:stavernise@gmail.com] **On Behalf Of** Sabrina Tavernise
Sent: Wednesday, April 10, 2013 3:18 PM
To: Myles, Renate (NIH/OD) [E]
Subject: urgent NIH question from Sabrina NYT on deadline

Renate -- is there anyone who can help me with this?? I'm writing for tomrorrow. Sorry so late. I'm writing about the Office for Human Research PRotections letter of March 7 about the consent forms for the SUPPORT study of oxygen levels on premature babies that was published in 2010 in NEJM. The letter -- pasted below -- contends that the study failed to inform parents of the risk of participating - -namely that infants in high oxygen group would be at greater danger of blindness and low oxygen group greater risk of death. NIH also was one of the participating sites in teh study (it's named in the CC line of the letter). Is there anyone who could talk to me about it?

Here's the letter. Dr. Guttmacher is named in the CC line.

http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf

Sincerely,

From: [Finer, Neil](#)
To: [Wally Carlo, M.D.](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: SUPPORT Trial and media
Date: Wednesday, April 10, 2013 5:10:38 PM

In my discussions with the reported I essentially repeated the content of your letter

We went into detail about the Chow and Tin studies and I explained to him that pulse oximetry was NOT available in the 50s and that there were NO studies using pulse oximetry that reported increased death using the ranges in SUPPORT - in fact the opposite- more survival with the lower range - even lower than SUPPORT I reiterated that the range we used was within the recommended practice guidelines

He finally said - then SUPPORT was the first to show this -

I rest my case and my weary brain

Be well Wally and keep up the fight - they will have to kill me if they expect me to cave in on this

Neil

On 4/10/13 2:03 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

>Thanks for the update, Neil.

>

>The UAB vice president for research who got the OHRP letter is

>communicating with the media.

>

>I am including my letter to UAB done a few weeks ago and today's UAB

>response so you can use it when planning to talk with the media.

>

>Wally

>

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

>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]

>Sent: Wednesday, April 10, 2013 3:46 PM

>To: Duara, Shahnaz; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.

>Subject: Re: SUPPORT Trial and media

>Importance: High

>

>Hi Guys

>I spoke to a reporter from the Washington Post and gave him the full

>account of our approach and the rationale for not including death as a

>known risk in the consent.

>I think he got it but one never knows

>I am fully supportive of the study and our results and the IRB decisions

>and the consent.

>Be well

>Neil

>

>From: <Duara>, Shahnaz <SDuara@med.miami.edu<<mailto:SDuara@med.miami.edu>>>

>Date: Wednesday, April 10, 2013 1:22 PM

>To: Rosemary Higgins

><higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>>, Wally Carlo

><wcarlo@peds.uab.edu<<mailto:wcarlo@peds.uab.edu>>>

>Cc: Neil Finer <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>

>Subject: SUPPORT Trial and media

>

>Hi Rose and Wally,

>Sorry about the ongoing brouhaha with the consent forms and HHS. In view
>of the NYT article today

><http://www.nytimes.com/2013/04/11/health/parents-of-preemies-werent-told-o>

>f-risks-in-study.html?hp, is there anything the NRN is putting together,

>PR wise, for sites so that they can respond to local media questions in a

>cohesive and non-contradictory manner? The Miami Herald has already

>called and I have been fielding calls from my Chair all afternoon.

>Thanks

>Shahnaz

>

From: Bell, Edward (Pediatrics)
To: Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Wally Carlo
Subject: FW: Headline on Google News re: SUPPORT
Date: Wednesday, April 10, 2013 5:07:26 PM

From: Brumbaugh, Jane E
Sent: Wednesday, April 10, 2013 4:06 PM
To: Bell, Edward (Pediatrics)
Subject: Headline on Google News re: SUPPORT

<https://news.google.com/nwshp?hl=en&tab=wn>

HHS Charged with Bungling Preemie Study

Luckily at bottom of page where the Health section is

--

Jane E. Brumbaugh, M.D.
Associate, Department of Pediatrics
University of Iowa Children's Hospital
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Iowa City, IA 52242
Phone (319) 384-6231
Fax (319) 356-4685
Email jane-brumbaugh@uiowa.edu

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Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 5:04 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Support Bullet points
Attachments: Support Background Statement2.docx

I capitalized a few words but otherwise, this looks good. We just need to add what NICHD's role was beyond funding and make it clear NICHD was not a study site.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 4:56 PM
To: Myles, Renate (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Support Bullet points

Hi Renate. Please see attached. Mona will weigh in if she's able to.

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 4:29 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: urgent NIH question from Sabrina NYT on deadline

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Sent: Wednesday, April 10, 2013 4:20 PM
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On Wed, Apr 10, 2013 at 3:21 PM, Myles, Renate (NIH/OD) [E] <mylesr@od.nih.gov> wrote:

Hi Sabrina:

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Sent: Wednesday, April 10, 2013 3:18 PM
To: Myles, Renate (NIH/OD) [E]
Subject: urgent NIH question from Sabrina NYT on deadline

Renate -- is there anyone who can help me with this?? I'm writing for tomrorrow. Sorry so late. I'm writing about the Office for Human Research PRotections letter of March 7 about the consent forms for the SUPPORT study of oxygen levels on premature babies that was published in 2010 in NEJM. The letter -- pasted below -- contends that the study failed to inform parents of the risk of participating - -namely that infants in high oxygen group would be at greater danger of blindness and low oxygen group greater risk of death. NIH also was one of the participating sites in teh study (it's named in the CC line of the letter). Is there anyone who could talk to me about it?

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http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf

Sincerely,

--

Sabrina Tavernise

Health Reporter
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sabrinat@nytimes.com
[+1-202-630-4885](tel:+1-202-630-4885)

--

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Page 0085 of 2000

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(b)(5)

of the Freedom of Information and Privacy Act

From: [Stevens, Timothy](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Newman, Jamie <newman@rti.org>](#)
[\(newman@rti.org\)](#)
Subject: Breathing Outcomes - PAS platform presentation
Date: Wednesday, April 10, 2013 4:58:05 PM
Attachments: [Breathing Outcomes PAS 2013 NICHD-2.pptx](#)

Hi Rose, Stephanie and Jamie,

Attached is my draft presentation for PAS. I have a 10 minute platform presentation with 5 minutes for questions. I gave a practice talk today to some of our group. The talk was just less than 10 minutes.

Thanks

Tim

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, June 05, 2014 5:53 PM
To: Blansfield, Earl (NIH/NICHD) [E]
Subject: FW: Support Background Statement
Attachments: FW: sentence

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 4:52 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: Support Background Statement

One minor point = the NYTimes has asked about one of our other papers – see the attached email – this compared the enrolled versus non-enrolled. When adjustments were made for usual factors for death (i.e. no antenatal steroids, etc), the adjusted analysis was NOT significant (even though there are lower absolute #'s of deaths in the enrolled subjects

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From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 4:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support Background Statement

No, I don't think so. This is very factual, and we're under a time crunch. I'll go see if Mona is reading it.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 4:46 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Support Background Statement

On minor edit – do you need Marian to clear this??

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: ["Wally Carlo \(wacarlo@uab.edu\)"](#)
Date: Wednesday, April 10, 2013 4:04:00 PM
Attachments: [120300 Pediatrics Rich et al Enrollment in SUPPORT may not be representative.pdf](#)

PEDIATRICS®

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Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative

Wade Rich, Neil N. Finer, Marie G. Gantz, Nancy S. Newman, Angelita M. Hensman,
Ellen C. Hale, Kathy J. Auten, Kurt Schibler, Roger G. Faix, Abbot R. Lupton,
Bradley A. Yoder, Abhik Das, Seetha Shankaran and for the SUPPORT and Generic
Database Subcommittees of the Eunice Kennedy Shriver National Institute of Child
Health and Human Development Neonatal Research Network
Pediatrics 2012;129;480; originally published online February 27, 2012;
DOI: 10.1542/peds.2011-2121

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/129/3/480.full.html>

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American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative



WHAT'S KNOWN ON THIS SUBJECT: The demographics of trials that use antenatal consent may not be representative of the populations that they are intended to study.



WHAT THIS STUDY ADDS: This study analyzes the difference in clinical outcomes between the enrolled and eligible but not enrolled populations of a trial that required antenatal consent.

BACKGROUND AND OBJECTIVE: The Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) antenatal consent study demonstrated that mothers of infants enrolled in the SUPPORT trial had significantly different demographics and exposure to antenatal steroids compared with mothers of eligible, but not enrolled infants. The objective of this analysis was to compare the outcomes of bronchopulmonary dysplasia, severe retinopathy of prematurity, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL), death, and death/severe IVH/PVL for infants enrolled in SUPPORT in comparison with eligible, but not enrolled infants.

METHODS: Perinatal characteristics and neonatal outcomes were compared for enrolled and eligible but not enrolled infants in bivariate analyses. Models were created to test the effect of enrollment in SUPPORT on outcomes, controlling for perinatal characteristics.

RESULTS: There were 1316 infants enrolled in SUPPORT; 3053 infants were eligible, but not enrolled. In unadjusted analyses, enrolled infants had significantly lower rates of death before discharge, severe IVH/PVL, death/severe IVH/PVL (all < 0.001), and bronchopulmonary dysplasia ($P = .003$) in comparison with eligible, but not enrolled infants. The rate of severe retinopathy of prematurity was not significantly different. After adjustment for perinatal factors, enrollment in the trial was not a significant predictor of any of the tested clinical outcomes.

CONCLUSIONS: The results of this analysis demonstrate significant outcome differences between enrolled and eligible but not enrolled infants in a trial using antenatal consent, which were likely due to enrollment bias resulting from the antenatal consent process. Additional research and regulatory review need to be conducted to ensure that large moderate-risk trials that require antenatal consent can be conducted in such a way as to ensure the generalizability of results. *Pediatrics* 2012;129:480–484

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KEY WORDS

antenatal steroids, clinical research/trials, informed consent, neonatal

ABBREVIATIONS

ANS—antenatal steroids
BPD—bronchopulmonary dysplasia
GA—gestational age
GDB—Generic Database
IVH—intraventricular hemorrhage
NRN—Neonatal Research Network
PVL—periventricular leukomalacia
ROP—retinopathy of prematurity
SUPPORT—Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial

This trial has been registered at www.clinicaltrials.gov (identifier NCT 00233324).

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COMPANION PAPER: A companion to this article can be found on page 576 and online at www.pediatrics.org/cgi/doi/10.1542/peds.2011-3455.

The Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely low birth weight infants was a randomized, 2×2 factorial designed multicenter trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) (identifier NCT 00233324).^{1,2} The trial prospectively compared continuous positive airway pressure and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< hour) intratracheal administration of surfactant followed by conventional mechanical ventilation. Infants were also randomly assigned to a prospective comparison of a lower oxygen saturation target range (85%–89%) with a higher, more conventional target range (91%–95%) until 36 weeks' postmenstrual age or the infant was no longer requiring ventilatory support or oxygen, by using purpose-altered oximeters. Eligible infants were those born at NRN centers at 24 0/7 to 27 6/7 weeks' gestational age (GA), without known major congenital malformations, and with full resuscitation intended. Antenatal consent was required for enrollment.

A prospective cohort study of the antenatal consenting practices of SUPPORT research personnel was conducted during the last half of the trial, and the results were published.³ As part of the ongoing NRN Generic Database (GDB) observational study, data were collected routinely for inborn infants at NRN centers, including most of those who met the GA eligibility criteria for SUPPORT. These data were used to identify eligible, nonenrolled infants. In this previous analysis, comparisons were made between enrolled versus nonenrolled eligible infants as well as between infants whose mothers were approached versus not approached. Comparing all GDB infants who were

eligible for SUPPORT but whose mothers were not approached with those whose mothers were approached for consent revealed that mothers in the latter group were significantly more likely to be older, to have a high school degree, private medical insurance, and at least 1 prenatal care visit. Infants of these mothers were more likely to be non-Hispanic white. Failure to be treated with antenatal steroids (ANS) was >4 times more prevalent among infants who were eligible, but not enrolled in SUPPORT in comparison with those who were enrolled.

In view of these results, we felt that it was essential to determine if the outcomes of infants enrolled in SUPPORT differed in substantial ways from infants enrolled in the GDB during the same period who were SUPPORT eligible but were not enrolled.

Based on the differences in prenatal care and antenatal steroid use between the populations that we had found previously, we postulated that the infants enrolled in SUPPORT would have lower rates of bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), mortality, and death or intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) in comparison with infants of the same GAs who were entered into the NRN GDB during the period of SUPPORT recruitment (February 2005 through February 2009) but not enrolled in the trial. Previous trials have compared contemporaneous controls to study subjects to determine if being in the trial affected outcomes, and have found that enrolled subjects did better overall than their contemporaneous comparison groups.^{4,5} Because this trial had no placebo group, we created statistical models that controlled for demographic characteristics and receipt of ANS to test for this trial effect.

METHODS

This analysis compared 1316 infants enrolled in SUPPORT with 3053 infants

born at NRN centers that met the eligibility criteria for the SUPPORT trial but were not enrolled. Perinatal characteristics, delivery room interventions, and neonatal outcomes were compared for enrolled and nonenrolled infants in bivariate analyses by using *t* tests and χ^2 tests.

Data for SUPPORT infants were obtained from trial documents and the GDB, and nonenrolled infant data were collected from the GDB only. Because not all of the data collected for the trial subjects were available for nonenrolled infants, severe ROP was defined as retinal detachment or documented surgery during initial hospitalization (up to 120 days of life) for survivors to discharge or transfer. BPD was compared by using the conventional definition of oxygen at 36 weeks' postmenstrual age only, and does not include the NRN physiologic definition of BPD. Severe IVH, PVL, and necrotizing enterocolitis outcomes were based on GDB data.

Logistic regression models were created to test the "trial effect" of enrollment in SUPPORT on outcomes, controlling for GA, birth weight, gender, race, center, and antenatal steroid exposure.

RESULTS

Bivariate analyses of demographic characteristics demonstrated small, but statistically significant differences in GA, birth weight, and race between enrolled and nonenrolled infant groups (Table 1). Receipt of ANS and treatment with prenatal antibiotics were significantly higher for enrolled infants. Infants in the nonenrolled group were significantly more likely to have an Apgar score of <3 at both 1 and 5 minutes, and delivery room interventions, including intubation, compressions, and epinephrine were significantly more frequent in the nonenrolled group (Table 2). In unadjusted analysis of outcomes, infants enrolled in SUPPORT had significantly lower rates of BPD, death

TABLE 1 Demographic Information for Randomly Assigned Versus Nonenrolled Infants

Variable	Enrolled (N = 1316)	Nonenrolled (N = 3053)	Unadjusted P
GA (wk) (mean \pm SD)	26.2 \pm 1.1	26.0 \pm 1.2	<.001
Birth weight (g) (mean \pm SD)	830.1 \pm 193.2	812.5 \pm 191.8	.006
Male	54.1%	52.6%	.373
White, non-Hispanic	39.6%	36.1%	.030
Prenatal antibiotics	78.1%	65.4%	<.001
ANS (any)	96.2%	84.4%	<.001
ANS (full course)	71.7%	49.4%	<.001

before discharge, severe IVH/PVL, and death/severe IVH/PVL in comparison with infants eligible but not enrolled. Rates of severe ROP and necrotizing enterocolitis were not significantly different (Table 3).

In the logistic regression models used to test whether there was a trial effect related to enrollment in SUPPORT, we found that enrollment in the SUPPORT trial itself was not a significant predictor of BPD, severe ROP, death, severe IVH/PVL, or death/severe IVH/PVL when we controlled for GA, birth weight, gender, race, center, and antenatal steroid exposure.

DISCUSSION

When providing the enrollment tables for their trials, authors generally start with an enumeration of eligible subjects, and then describe how many refused, had missing data, etc. This group of eligible subjects is better described as "identified eligible subjects"—in other words, those whom the investigator identified as eligible at the time they would normally be approached for consent. In the SUPPORT study, there were additional mothers who were missed by

the investigators because of time of day, rapidity of admission, duration of stay, etc. Because of the nature of the GDB of the NRN, which identifies and tracks all infants fitting broad GA criteria, we were able to look not just at the subjects enrolled in SUPPORT, but also those who were not enrolled or, in some cases, were not even identified as eligible by the research team. This allowed us to make a unique comparison of all infants who were born in NRN centers who met the SUPPORT study criteria, both those who were enrolled and those who were not.

The increased level of prenatal care received by the mothers of infants enrolled in SUPPORT, including receipt of ANS, and the increased frequency of delivery room interventions and poor Apgar scores among nonenrolled infants indicate that SUPPORT infants were less disadvantaged than the overall eligible population. Unadjusted comparisons of outcomes between the 2 groups confirmed that nonenrolled infants had greater incidences of poor neonatal outcomes, including BPD, death, severe IVH/PVL, and death/severe IVH/PVL. The fact that the differences in

outcomes between the groups were not significant after controlling for infant characteristics at birth indicates that the birth characteristics, rather than enrollment in the trial itself, were likely responsible for the improved outcomes of enrolled infants.

Our findings suggest that using antenatal consent to conduct a trial such as SUPPORT under the constraints of pre-intervention informed consent creates a situation where population bias is a significant issue. We agree with the concerns expressed by Schmidt et al⁴ that this circumstance can create a threat to the external validity of the trial. Title 45 of the Code of Federal Regulations allows institutional review boards to waive some or all elements of consent.⁵ Our previous observations, combined with the further analysis of this trial, suggest that allowing for the deferral of consent until after birth for trials comparing routinely used interventions can help to ensure that we include the sickest and most at-risk populations, and thus contribute to a more generalizable study population.

What remains unclear is how to deal with trials of greater than minimal risk that require antenatal consent. Current standards for waiver of consent would be the same as those used for "emergency" trials, such as the use of a blood substitute in a prehospital environment. These requirements include high risk balanced with a life-threatening situation, a direct benefit, public disclosure, and the existence of an independent data safety board. Most near-birth trials would not meet the standard of a life-threatening situation, and neonatal trials with prespecified direct benefit are extremely uncommon. In a review of clinical research in critically ill patients, Truog et al concluded that informed consent is required for research interventions that, if they were clinical interventions, would not require specific consent.

TABLE 2 Delivery Room Status and Interventions

Variable	Enrolled (N = 1316), %	Nonenrolled (N = 3053), %	Unadjusted P
Apgar \leq 3 at 1 min	24.4	31.9	<.001
Apgar \leq 3 at 5 min	4.4	8.4	<.001
Intubated in DR	63.6	75.8	<.001
Surfactant in DR or NICU	82.5	86.5	<.001
Chest compressions in DR	5.9	9.7	<.001
Epinephrine in DR	3.1	6.0	<.001

DR, delivery room

TABLE 3 Neonatal Outcomes

Outcome	SUPPORT Enrolled (N = 1316)	Nonenrolled (N = 3053)	Unadjusted P
Death	18.0%	24.1%	<.001
BPD (oxygen at 36 wk)	42.2	47.7	.003
BPD or death by 36 wk	51.4	59.1	<.001
ROP (surgery or retinal detachment)	10.4	12.4	.101
NEC (medical or surgical)	11.3	12.7	.214
IVH grade 3–4	13.0	17.6	<.001
PVL	3.8%	5.1%	.068
IVH 3–4 or PVL	15.1%	19.8%	<.001
Death or IVH 3–4 or PVL	27.4%	35.6%	<.001

NEC, necrotizing enterocolitis.

They suggest that the requirement for consent in a clinical trial be based on 5 criteria: (1) whether all of the treatments in the trial could be offered outside the trial, (2) whether there is minimal additional risk compared with the alternative clinical treatment, (3) whether there is equipoise, (4) whether a reasonable person would have a preference between the 2 treatments, and (5) that the subject be informed that the previous 4 criteria are the basis for determining the need for specific rather than general consent in the institution involved.⁷ Based on these characteristics, one could make the argument that the SUPPORT trial could have been carried out under waiver. Luce countered this argument with the statement that informed consent in critically ill subjects is necessary to promote respect for patients and their right of self-determination, and because investigator self-regulation is inadequate.⁸

In trials that compare currently used interventions and afford minimal risk, it is suggested that a waiver of consent and a postnatal written consent to use the infant's information be sought. This stipulation allows parents to decide whether they want their infant's information included in the study. This type of delayed consent has been successfully applied in non-US clinical trials requiring near-birth interventions. However, more complex trials requiring antenatal consent are still at risk for the

lack of generalizability seen in our results. Additional dialogue with regulatory agencies needs to be conducted to determine the best method of balancing the safety and security of subjects with the need for the evidence that can be properly obtained from large trials that are generalizable to the intended population or population at risk.

CONCLUSIONS

The results of this analysis demonstrate significant outcome differences between enrolled and nonenrolled infants in the eligible population of a trial using antenatal consent; these differences were likely due to enrollment bias resulting from the antenatal consent process. A waiver or delay of parental consent should be considered to promote the generalizability of minimal-risk trials of interventions in the delivery room or shortly after birth. Additional research and regulatory review need to be carried out to ensure that large moderate-risk trials that currently require antenatal consent can be conducted in such a way as to ensure the generalizability of results.

ACKNOWLEDGMENTS

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed, and analyzed the data for this study. On behalf of the NRN, Drs Abhik Das

(DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

The following investigators, in addition to those listed as authors, participated in this study: NRN Steering Committee Chairs: Alan H. Jobe, MD, PhD, University of Cincinnati (2003–2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006–2011). Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904): William Oh, MD; Dan Gingras, RRT; Susan Barnett, RRT; Sarah Lillie, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN. Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80): Michele C. Walsh, MD, MS; Avroy A. Fanaroff, MD; Bonnie S. Siner, RN. Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084): Vivek Narendran, MD, MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN, CCRC; Marcia Worley Mersmann, RN, CCRC; Holly L. Mincey, RN, BSN; Jody Hessling, RN. Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30): C. Michael Cotten, MD, MHS; Ronald N. Goldberg, MD; Kimberly A. Fisher, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN, CRA. Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, UL1 RR25008, M01 RR39): Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD; Ann M. Blackwelder, RNC, BS, MS. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development: Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA. Indiana University, University Hospital, Methodist

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Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative

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Blansfield, Earl (NIH/NICHD) [E]

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Wednesday, April 10, 2013 3:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: sentence
Attachments: 120300_Pediatrics_Rich et al_Enrollment in SUPPORT may not be representative.pdf

FYI

From: James Bakken [mailto:jimb@uab.edu]
Sent: Wednesday, April 10, 2013 2:42 PM
To: Wally Carlo, M.D.; Richard B Marchase
Cc: Dale G Turnbough
Subject: FW: sentence

The New York Times is asking if we dispute the conclusion in the attached Pediatrics journal article [see question(s) below]. Are we familiar with this?

Jim Bakken
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From: Sabrina Tavernise [mailto:stavernise@gmail.com]
Sent: Wednesday, April 10, 2013 2:30 PM
To: James Bakken
Subject: Re: sentence

Jim -- on this "concurrent" group -- any other data you have on them besides gestational age and weight and born in same hospitals? There was a Pediatrics piece that addressed the differences between the two groups essentially saying that the "concurrent" group was sicker and therefore not a fair comparison (see attachment). Would you guys (Dr. Marchase) dispute that conclusion? Sabrina

On Wed, Apr 10, 2013 at 1:35 PM, James Bakken <jimb@uab.edu> wrote:

The "concurrent group" is the babies of similar gestational age and weight born in the same hospitals at 23 sites around the country during the same time of the SUPPORT study. They either chose not to participate or were not asked. The historical group data were from 2002 to 2004, just prior to the SUPPORT study, at the same 23 sites. Mortality rates of study participants in both lower- and higher-oxygen groups were lower than the mortality rates of a historic reference group, according to the Neonatal Research Network, as well as a concurrent group of non-study participants at the participating study sites during the duration of the study. Mortality rates in the study participants were 16.2-19.9 percent, compared to 21.1 percent in the historical reference group (3,800 infants) and 24.1 in the concurrent group (3,053 infants). In short, study participants had more favorable mortality rates no matter which arm they were assigned to.

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From: Sabrina Tavernise [<mailto:stavernise@gmail.com>]

Sent: Wednesday, April 10, 2013 11:55 AM

To: James Bakken

Subject: Re: sentence

hm. dn't really understand this. what is "concurrent group" -- are they babies born in same hospitals at 23 sites around teh country? what is "historical group" exactly -- same? born in same hospitals and were of same gestational ages?

On Wed, Apr 10, 2013 at 12:53 PM, James Bakken <jimb@uab.edu> wrote:

Finally, answers:

The SUPPORT study groups included about 600 participants each.

Historical group (infants from 2002-2004 just before SUPPORT started): 3,800

Concurrent group: 3,053

Please let me know if you have questions.

Many thanks,

Jim Bakken

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From: Sabrina Tavernise [<mailto:stavernise@gmail.com>]
Sent: Wednesday, April 10, 2013 11:00 AM
To: James Bakken
Subject: Re: sentence

mine is not wrong then. let's get the exact details of what that group is before i make a change. story should be posted very soon on web

On Wed, Apr 10, 2013 at 11:53 AM, James Bakken <jimb@uab.edu> wrote:

I talked with Dr. Marchase. He suggests the following is more accurate:

Those infants, not a control group in the study but larger in number and roughly comparable in gestation and weight to those in the study group, had a 24 percent mortality rate, compared to a 20 percent mortality rate for the infants in the low-oxygen group.

Jim Bakken

University of Alabama at Birmingham Media Relations

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From: Sabrina Tavernise [<mailto:stavernise@gmail.com>]
Sent: Wednesday, April 10, 2013 10:39 AM
To: James Bakken
Subject: sentence

Those infants were not a control group in the study, but were roughly similar in number and in age to those in the study group, had a 24 percent mortality rate, compared to a 20 percent mortality rate for the infants in the low-oxygen group.

--

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: PLEASE READ
Date: Wednesday, April 10, 2013 2:28:00 PM
Attachments: FW_SUPPORT Trial - UAB response.msg

http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf

Alabama sent the attached response to OHRP following the March 7 letter

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Gail, Dorothy (NIH/NHLBI) [E]
Sent: Wednesday, April 10, 2013 2:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PLEASE READ

Hi Rose – sorry you are going through this. Do you know if OHRP has closed this case, or is it still on-going? Jim Kiley asked us.

From: Kiley, James (NIH/NHLBI) [E]
Sent: Wednesday, April 10, 2013 12:53 PM
To: Gail, Dorothy (NIH/NHLBI) [E]; Moore, Tim (NIH/NHLBI) [E]
Cc: Weinmann, Gail (NIH/NHLBI) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: PLEASE READ

Has ohrp closed this case or is it still ongoing?

From: Gail, Dorothy (NIH/NHLBI) [E]
Sent: Wednesday, April 10, 2013 12:46 PM
To: Moore, Tim (NIH/NHLBI) [E]
Cc: Weinmann, Gail (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]
Subject: FW: PLEASE READ

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:13 PM

To: Gail, Dorothy (NIH/NHLBI) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: PLEASE READ

Here is how UAB responded to OHRP

Rosemary D. Higgins, MD
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From: Gail, Dorothy (NIH/NHLBI) [E]
Sent: Wednesday, April 10, 2013 12:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: PLEASE READ

Just read this.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 11:50 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: PLEASE READ
Importance: High

Please confirm receipt of this.
I am at the NRN SC meeting over in Silver Spring

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]

Sent: Wednesday, April 10, 2013 11:02 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: PLEASE READ
Importance: High

I am at the NRN Steering Committee meeting and we have just discovered this press release just issued--

<http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3859>

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Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, June 05, 2014 5:54 PM
To: Blansfield, Earl (NIH/NICHD) [E]
Subject: FW: Letter to UAB IRB 3 20 13
Attachments: Letter to UAB IRB 3 20 13.doc

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 2:12 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Letter to UAB IRB 3 20 13

Bob

This is the letter that Wally sent to his IRB – helpful for factual knowledge

UAB MEDICINE

NEONATOLOGY



**Children's
of Alabama**

March 20, 2013

Dr. Richard B. Marchase
Vice President for Research and Economic Development
Administration Building
marchase@uab.edu

Dear Dr. Marchase:

We are in receipt of the letter from OHRP dated February 8, 2013 outlining concerns and questions about the informed consent process employed in the SUPPORT Trial. 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 consider the following report and analysis and 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.

We suggest that UAB adopt a similarly collegial approach to OHRP in response to their letter. At the same time, we suggest that UAB's response may be strengthened by the clarifications to the history of the extant literature at the time of the study design, which we set forth below. Second, we will explain that at every continuing review, we as investigators provided the UAB IRB with appropriate safety reports, none of which indicated that amendments to the ICF risk section should be made to include the risk of death. Third, we will explain that to have included the risk of death in the ICF would have inappropriately combined the risks of research with the risks of everyday life for the high-risk infants whose parents were invited to give permission for them to participate in this study. Our understanding is that it is best practice when writing informed consent materials to clearly differentiate between research and non-research risks, and to exclude non-research risks for the sake of clarity and comprehensibility.

Historical Background to the SUPPORT Trial

We would like to offer an alternative view of the state of the science prior to the start of the SUPPORT Trial. . The summary on page 4 of the review of the literature states that, "In short, the research and data analyses that had occurred prior to the SUPPORT Trial demonstrated that the use of higher versus lower levels of oxygen could significantly affect the likelihood of a preterm infant developing ROP and other aspects of morbidity and mortality."

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Original data from the 1950s trials

The evidence of increased mortality with restriction of oxygen was based on observational studies. The trials comparing a practice that restricted oxygen supplementation to $\leq 50\%$ inspired oxygen concentration regardless of the condition of the preterm infants did not report an increase in mortality. The unrestricted oxygen policy provided oxygen routinely for 2 to 7 weeks at over 50% concentration. The meta-analysis of these 5 trials (1950 to 1970) showed that oxygen restriction decreased the incidence and severity of retinopathy without an effect on mortality (Askie LM, Henderson-Smart DJ, Ko H. *Cochrane Database Syst Rev.* 2009. Jan 21;1: CD001077). These trials included few extremely preterm infants whereas the SUPPORT trial enrolled only extremely preterm infants. Restriction of oxygen using an arbitrary cut-off of inspired oxygen concentration has not been a standard clinical practice in US NICUs for many decades, and this was not a practice tested in the SUPPORT trial. Furthermore, oxygen monitoring in the 1950s was done by monitoring the infant's skin color whereas continuous oxygen saturation monitoring was used in SUPPORT. In addition, most NICU practices have changed substantially since the 1950s. Notice that the references used in the "Background" in the OHRP letter are for 1956 (ref. 4), 1973 (ref. 5), and 1984 (ref. 6). Reference 8 published in 2006 states, "marked variability in opinion exists with respect to oxygen targets" but does not include references to support the statement or new data.

Standard of Care at the Time of SUPPORT

The American Academy of Pediatrics and American College of Obstetrics and Gynecology Guidelines for Perinatal Care is the official publication that sets standards of perinatal care in the US. The Guidelines for Perinatal Care 6th Edition (2007) states "The optimal range for oxygen saturation and PaO₂ that balances tissue metabolism, growth and development, and toxicity has not been elucidated fully for preterm infants receiving supplemental oxygen. Oxygen saturation values between 85-95% and PaO₂ values between 50 mm Hg and 80 mm Hg are examples of ranges pragmatically determined by some clinicians to guide oxygen therapy in preterm infants. Additional research to determine the "optimal" oxygenation ranges for oxygen saturation and PaO₂ is needed" (Appendix 1). The prior edition of the Guidelines for Perinatal Care (2002) has the same PaO₂ range but oxygen saturation ranges are not given (Appendix 2). Thus, both SUPPORT protocol oxygen saturation target ranges (85-89% and 91-95%) were within the standard of care in the US.

Evidence Available Prior to SUPPORT to Determine that Reasonably Expected Risk and Benefits did not Include Increased Mortality

The best prior evidence for the design of the SUPPORT Trial included the following cohort studies:

The study by Tin *et al.* (Tin W, Milligan DW, Pennefather P, Hey E. *Arch Dis Child Fetal Neonatal Ed.* 2001;84:F106-10) was the most rigorous study that tested targets of oxygen saturation less than 95% before SUPPORT was performed. The Tin study was a multicenter population-based prospective cohort study of infants <28 weeks (just like SUPPORT). The Tin study was the only one with follow-up assessments to at least 10 months of age.

The policy for oxygen saturation targets and alarm limits varied among the centers. ROP was decreased in the 70-90% saturation target patients **without a difference in survival (51.6% survival in the 70-90% O₂ saturation target group vs. 51.7% in 84-95% group, Table 1).**

Table 1.

Saturation Alarm Targets	N	Survival	Survival with ROP	Survival with Cerebral Palsy
70-90%	126	51.6%	6.2%	15.4%
84-95%	319	51.7%	15.8%	15.5%
88-98%	123	52.8%	27.7%	16.9%

It should be noted that impaired neurodevelopmental outcome was not higher with oxygen saturation targets as low as 70-90%. Furthermore, not a single case of blindness was reported in infants at targets up to 95% despite the difference in ROP.

The Chow *et al.* study (Chow LC, Wright KW, Sola A, CSMC Oxygen Administration Study Group. *Pediatrics*. 2003;111:339-45) was a single center prospective cohort study to assess the impact of implementation of an oxygen monitoring and administration policy for very low birth weight infants. Outcomes for very low birth weight infants with a lower saturation target (83-93%) were compared to outcomes of very low birth weight infant during a previous period when the oxygen saturation target was 90-98%. With the lower oxygen saturation target, severe ROP decreased from 12.5% to 2.5% and the need for ROP laser treatment decreased from 4.5% to 0%. Over the years of the study, there was a trend **for increased survival following implementation of the restrictive oxygen policy** (contrary to what we found in SUPPORT). Survival improved from 48 to 75% in the infants 500-749 g and from 74 to 81% in the infants 750-999 g from 1997 to 2001. The policy was changed in the middle of 1998 (Table 2).

Table 2.

Birth Weight (g)	1997		1998		1999		2000		2001		Total	
	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival
500-749	14	48	15	40	18	73	15	87	12	75	74	58
750-999	25	74	27	78	18	78	21	82	17	81	108	83
1000-1249	24	88	20	100	26	96	28	100	21	94	119	95
1250-1500	29	97	27	100	26	100	28	100	36	97	146	99
Total	92	81	89	83	88	85	92	93	86	90	447	86

The American Academy of Pediatrics Guidelines for Perinatal Care recommended targets oxygen saturation for preterm infants although they acknowledge that the optimal range had not been elucidated (Guidelines for Perinatal Care, 6th Edition (2007, Attachment 1). Their recommendation specified oxygen saturation target of 85-95% and PaO₂ values between 50 and 80 mm Hg as “pragmatically determined by some clinicians to guide oxygen therapy in preterm infants”. The prior edition of those Guidelines (2002, Attachment 2) provides the same PaO₂ ranges but did not specify an oxygen saturation target. Thus, the SUPPORT Trial treatments were in compliance with the Guidelines for Perinatal Care.

Disclosure of Risks in the SUPPORT Consent Form

The best available studies, those with the highest level of evidence, when SUPPORT was designed and conducted suggested that lower oxygen saturation targets would lead to a decrease in ROP and decreased BPD. Furthermore, there was not even suggestive evidence from relevant prior literature that would suggest an increase in death, blindness, or other serious morbidity with either set of oxygen saturation targets used in SUPPORT.

Based on these and other studies, many clinicians started to recommend lower oxygen saturation targets and developed educational programs promoting the same. The most prominent program was developed by Dr. Jay Goldsmith from Ochsner Clinic (not published in the peer-reviewed literature). In this program Dr. Goldsmith and colleagues recommended oxygen saturation targets of 85 to 93%. The benefits stated were decreased ROP, decreased days on a ventilator and on oxygen, and decreased hospitalization duration. Risk for adverse effects or increased mortality was not included in the materials.

Four other multicenter trials were designed after the SUPPORT Trial was conceived. These trials were led by investigators based in the United Kingdom, Australia, New Zealand, and Canada. These protocols were also designed without the expectation of increased mortality in the lower oxygen saturation group.

The SUPPORT consent template, the UAB consent forms, and those of other clinical centers were appropriately written based on the relevant knowledge available at the time. Furthermore, throughout the trial, survival was better than the historical reference group used prospectively to monitor the trial by the independent Neonatal Research Network (NRN), DSMC, and the NRN Steering Committee. Rates of morbidities and mortality compared to historic controls were reviewed during each quarterly NRN Steering Committee meeting and found to be lower than the historical reference group. Concurrent infants not enrolled in the SUPPORT Trials had a mortality rate of 24.1% compared to infants in the higher saturation group (16.2%) and infants in the lower oxygen saturation group (19.9%) although these differences were not statistically significant in adjusted regression analyses (Table 3).

Table 3.

	Mortality Rates
Historic reference group	21.1%
SUPPORT 85-89% target group	19.9%
SUPPORT 91-95% target group	16.2%
Concurrent eligible not enrolled in SUPPORT	24.1%

With the effort to more precisely control oxygen saturation and prevent the wide swings in oxygen saturation with levels substantially below 85 or above 95 that often occur in extremely premature infants in usual clinical practice, it is possible that participation in the trial reduced the true likelihood of death in both groups below the expected levels had the infants not been in the trial.

Death was included in the primary outcomes of the SUPPORT Trial because it is a competing outcome of retinopathy of prematurity and bronchopulmonary dysplasia not because an increase in mortality was expected in either case. Inclusion of death as part of the primary outcome measures is done in almost all large randomized controlled trials in the NICHD Neonatal Research Network and other major neonatal research groups when research involves extremely preterm infants.

Ongoing Safety Review and IRB Continuing Review

We have explained above that at the time of initial IRB review, the known risks did not indicate that it was appropriate to include mortality in the risks section of the informed consent form. Of course, known risks can change over the course of the study – hence the importance of at least annual IRB review, a sound data and safety monitoring plan, site monitoring, etc. We provided safety information to the UAB IRB at continuing review and adhered to reportable event requirements. At no time did changes in the literature or safety reviews in this study indicate that the risks section of the informed consent form should be amended to include mortality as a risk of study procedures. Indeed, the difference in mortality became apparent after enrollment had been completed.

We ask that the UAB IRB collaborate with us in reviewing their records of our continuing review submissions and minutes of the convened meetings at which continuing reviews were discussed, in order to identify any deficiencies in the IRB's practices or our own that may have contributed to missing a newly identified risk. If we can execute such due diligence, we can report to OHRP that we have done so. If we identify weaknesses, we should fashion a corrective and preventive action plan as investigators and the institution (for the IRB) to do better going forward, and report these issues to the OHRP.

Research-related Risks and Not Research-related Risks

It is our understanding that the DHHS regulations require that the informed consent include a description of all research-related risks – not non-research risks that may be common to the target population. In this case, the risk of death is high for these vulnerable infants because of

their prematurity. To have included the risk of death in the informed consent form would have blurred the important distinction between research-related risks and underlying risks of daily life for these babies.

Summary

In summary, the existing published data that were pertinent when the SUPPORT Trial was designed and conducted did not portend an increase in mortality or blindness in either treatment group. Other morbidities had not been reported in the published studies. The best available evidence indicated no discernible increased probability of death or other harms as a result of participating in this trial comparing two methods of care widely used both within and outside the NICHD Neonatal Research Network. The SUPPORT Trial consent form was thus appropriately written for this comparative effectiveness trial based on the relevant knowledge available at the time. Further, continuing review of risks over the course of the study did not indicate the need for amendment to include mortality. Finally, to include mortality would have blurred the important distinction between the high risks of daily life for these premature infants and the risks of participation, and to create such confusion would have inappropriately created obstacles to comprehension for the parents considering whether to grant permission for their children.

Thanks for your consideration of our analysis.

Respectfully submitted,

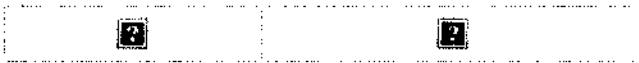


Waldemar A. Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries

CC: Jonathan E. Miller
jonathanm@uab.edu

From: Ronald Goldberg, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NYTimes.com: U.S. Says Study of Babies Failed to Disclose Risks
Date: Wednesday, April 10, 2013 1:41:23 PM

From: goldb008 <emailthis@ms3.lga2.nytimes.com>
Reply-To: Ronald Goldberg <ronald.goldberg@dm.duke.edu>
Date: Wednesday, April 10, 2013 1:30 PM
To: Ronald Goldberg <ronald.goldberg@dm.duke.edu>
Subject: NYTimes.com: U.S. Says Study of Babies Failed to Disclose Risks



This page was sent to you by: goldb008@mc.duke.edu

LATEST NEWS | April 10, 2013

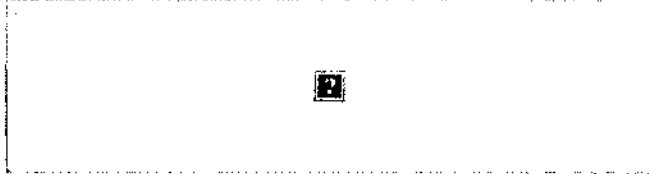
U.S. Says Study of Babies Failed to Disclose Risks

BY SABRINA TAVERNISE

Parents involved in a large study on premature babies were not warned about increased risks of blindness or death, a federal office has said.

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From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN SC Agenda and Materials
Date: Wednesday, April 10, 2013 1:27:52 PM

I got off the phone- the line was still open.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 1:20 PM
To: Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: FW: NRN SC Agenda and Materials

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, April 10, 2013 1:18 PM
To: Cunningham, Meg; Prem Fort, M.D.; Valerie Y-L Chock; Gloria_Pryhuber@URMC.Rochester.edu; Erika Fernandez; alexis.davis@stanford.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; Das, Abhik; Gantz, Marie; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@safud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Aasma Chaudhary; ahensman@wihri.org; Ann_Scorsone@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chob.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; clark@med.unc.edu; Conra Lacy; Dara Cucinotta; Dee Maffett; Diana Vasil; Donia Campbell; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.E.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen; Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; Monica Collins; msacilowski@upa.chob.edu; nancy newman; Newman, Jamie; Pamela.moorehead@nationwidechildrens.org; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucla.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; shigdon@med.umich.edu; Teresa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; Namasivayam Ambalavanan; rohls@salud.unm.edu; Ronnie Guillet; Sood, Beena; Sudarshan Jadcherla; Abbey Hines; Andrea Duncan; Athina Pappas; bvohr@wihri.org; Christopher Timan; drfjcmd@aol.com; DeMauro, Sara M; dmarshal@med.unc.edu; Donna Garey; emcgowan@tuftsmedicalcenter.org; Gary Meyers; Hallam Hurt; Howard Kilbride; iadamsc@emory.edu.; Isabell Purdy; Katie Gustafason; Keith Yeates; Kelley Yost;

Kimberly.Yolton@cchmc.org; Lowe, Jean; LuAnn Papile; Marsha Gerdes; Martha Carlson; Martha Fuller; Mike Steffen; Myriam Peralta, M.D.; Patrick.M.Jones@uth.tmc.edu; richard.ehrenkranz@yale.edu; Ricki F Goldstein; Roy.Heyne@utsouthwestern.edu; soraya.abbasi@uphs.upenn.edu; srhintz@stanford.edu; Susan Gunn; Tarah Colaizy; Yvonne Vaucher; afurey@tuftsmedicalcenter.org; Andrea Halbrook; BRODSKYN@email.chop.edu; bss5@cwru.edu; Corri DeDomenico; diane-eastman@uiowa.edu; elaine.romano@yale.edu; Elizabeth Paulsen; ewoldt@med.wayne.edu; Joan Merzbach; Karen Murray; karen.osborne@hsc.utah.edu; Kathy Johnson; Margaret.Poundstone@uth.tmc.edu; Teresa.Gratton@uc.edu; Victoria Watson; Vivien Phillips
Cc: vwilli4@emory.edu; monica@bocaner.net; dale_phelps@urmc.rochester.edu; Wrage, Lisa Ann; McDonald, Scott A.; Tan, Sylvia; Becky Brazeel; Brenda Vecchio; Garcia, Deborah; gonza025@mc.duke.edu; Heidi Kleinbart; jwaidne@emory.edu; Kristie Smiley; Imoore@med.wayne.edu; Nancy.M.Smith@uth.tmc.edu; Theresa Banker; Penelope Bradley
Subject: RE: NRN SC Agenda and Materials

This is the UAB response to multiple media outlets calls.

From: Cunningham, Meg [mailto:mcunningham@rti.org]

Sent: Tuesday, April 09, 2013 1:13 PM

To: Prem Fort, M.D.; Valerie Y-L Chock; Gloria.Pryhuber@URMC.Rochester.edu; Erika Fernandez; alexis.davis@stanford.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; bpindex@iu.edu; Carl D'Angio; Das, Abhik; Gantz, Marie; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; yanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; Aasma Chaudhary; ahensman@wihri.org; Ann_Scorione@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chop.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; clclark@med.unc.edu; Conra Lacy; Dara Cucinotta; Dee Maffett; Diana Vasil; Donia Campbell; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.F.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen; Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; Monica Collins; msacilowski@upa.chop.edu; nancy newman; Newman, Jamie; Pamela.moorehead@nationwidechildrens.org; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucla.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; shigdon@med.umich.edu; Teressa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; Greg Sokol; Hareh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; Namasivayam Ambalavanan; rohls@salud.unm.edu; Ronnie Guillet; Sood, Beena; Sudarshan Jadcherla; Abbey Hines; Andrea Duncan; Athina Pappas; bvoht@wihri.org; Christopher Timan; drfjcmd@aol.com; DeMauro, Sara M; dmarshal@med.unc.edu; Donna Garey; emcgowan@tuftsmedicalcenter.org; Gary Meyers; Hallam Hurt; Howard Kilbride; jadamsc@emory.edu; Isabell Purdy; Katie Gustafson; Keith Yeates; Kelley Yost; Kimberly.Yolton@cchmc.org; Lowe, Jean; LuAnn Papile; Marsha Gerdes; Martha Carlson; Martha Fuller; Mike Steffen; Myriam Peralta, M.D.; Patrick.M.Jones@uth.tmc.edu; richard.ehrenkranz@yale.edu; Ricki F Goldstein; Roy.Heyne@utsouthwestern.edu; soraya.abbasi@uphs.upenn.edu; srhintz@stanford.edu; Susan Gunn; Tarah Colaizy; Yvonne Vaucher; afurey@tuftsmedicalcenter.org; Andrea Halbrook; BRODSKYN@email.chop.edu; bss5@cwru.edu; Corri DeDomenico; diane-eastman@uiowa.edu; elaine.romano@yale.edu; Elizabeth Paulsen; ewoldt@med.wayne.edu; Joan Merzbach; Karen Murray; karen.osborne@hsc.utah.edu; Kathy Johnson; Margaret.Poundstone@uth.tmc.edu; Teresa.Gratton@uc.edu; Victoria Watson; Vivien Phillips
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Subject: NRN SC Agenda and Materials

Hi All,

Attached you will find a revised (and hopefully final this time!) agenda for this week's meeting. All handouts and concepts are now posted on the private gateway of the website following these links:

[Administration](#) > [Minutes](#) > [Steering Committee](#) > [2013](#) > [April](#) > [Handouts](#)

Safe travels and see you soon!

Meg

*Meg Cunningham, CCRP
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095
www.rti.org*

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN SC Agenda and Materials
Date: Wednesday, April 10, 2013 1:21:37 PM

Thx.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 1:20 PM
To: Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: FW: NRN SC Agenda and Materials

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, April 10, 2013 1:18 PM
To: Cunningham, Meg; Prem Fort, M.D.; Valerie Y-L Chock; Gloria_Pryhuber@URMC.Rochester.edu; Erika Fernandez; alexis.davis@stanford.edu; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; Das, Abhik; Gantz, Marie; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Aasma Chaudhary; ahensman@wihri.org; Ann_Scorson@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chob.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; clark@med.unc.edu; Conra Lacy; Dara Cucinotta; Dee Maffett; Diana Vasil; Donia Campbell; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.E.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen; Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; Monica Collins; msacilowski@upa.chob.edu; nancy newman; Newman, Jamie; Pamela.moorehead@nationwidechildrens.org; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucla.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; shigdon@med.umich.edu; Teressa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; Namasivayam Ambalavanan; rohls@salud.unm.edu; Ronnie Guillet; Sood, Beena; Sudarshan Jadcherla; Abbey Hines; Andrea Duncan; Athina Pappas; bvohr@wihri.org; Christopher Timan; drfjcmd@aol.com; DeMauro, Sara M; dmarshal@med.unc.edu; Donna Garey; emcgowan@tuftsmedicalcenter.org; Gary Meyers; Hallam Hurt; Howard Kilbride; iadamsc@emory.edu.; Isabell Purdy; Katie Gustafson; Keith Yeates; Kelley Yost;

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Subject: RE: NRN SC Agenda and Materials

This is the UAB response to multiple media outlets calls.

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Safe travels and see you soon!

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*Meg Cunningham, CCRP
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post
Date: Wednesday, April 10, 2013 1:16:00 PM

From the NY Times

http://www.nytimes.com/2013/04/11/health/parents-of-preemies-werent-told-of-risks-in-study.html?_r=0

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Let's have a five minute discussion, Bob and Mona.

Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892
Phone: 301-496-1848
Fax: 301-402-1104
E-mail: maddoxy@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:01 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: PLEASE READ FW: query from the Washington Post
Importance: High

Bob

Do you have any guidance on how to handle???

Rose

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higginsr@mail.nih.gov

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, April 10, 2013 11:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: query from the Washington Post

Is this something you should handle?

Wally

From: Brown, David M [<mailto:David.Brown@washpost.com>]
Sent: Wednesday, April 10, 2013 10:50 AM
To: Wally Carlo, M.D.
Subject: query from the Washington Post

Dear Dr. Carlo

I am a science reporter at the Washington Post (also a physician) who is doing a story for tomorrow's paper on the OHRP letter of March 7 saying that the informed consent for the oxygen part of the SUPPORT trial was inadequate. I would like to get your comment on the letter and also ask a few questions about how neonatologists chose which O2 saturation levels in the "standard of care range" (85-95%) range before the SUPPORT study, and whether care has changed as a result of it.

I have to do this story in the next few hours so if you are willing and able to talk then the earlier the better.

Thanks and best
David Brown

David Brown National Staff The Washington Post

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browndm@washpost.com

(202) 334-5049

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post
Date: Wednesday, April 10, 2013 1:01:09 PM

For NRN

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:58 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re: PLEASE READ FW: query from the Washington Post

Yvonne said their site human subjects person as they already talked to NY times
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Rose,

I think

(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:14 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Ok

Will call your office now

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31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892
Phone: 301-496-1848
Fax: 301-402-1104
E-mail: maddoxy@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:01 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: PLEASE READ FW: query from the Washington Post
Importance: High

Bob
Do you have any guidance on how to handle???

Rose

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Wally

From: Brown, David M [<mailto:David.Brown@washpost.com>]
Sent: Wednesday, April 10, 2013 10:50 AM

To: Wally Carlo, M.D.

Subject: query from the Washington Post

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Thanks and best

David Brown

David Brown National Staff The Washington Post

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From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post
Date: Wednesday, April 10, 2013 1:00:56 PM

Am on the phone now.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:58 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re: PLEASE READ FW: query from the Washington Post

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Sent: Wednesday, April 10, 2013 12:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
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Rose,

I think (b)(5)

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Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, April 10, 2013 11:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: query from the Washington Post

Is this something you should handle?

Wally

From: Brown, David M [<mailto:David.Brown@washpost.com>]
Sent: Wednesday, April 10, 2013 10:50 AM

To: Wally Carlo, M.D.

Subject: query from the Washington Post

Dear Dr. Carlo

I am a science reporter at the Washington Post (also a physician) who is doing a story for tomorrow's paper on the OHRP letter of March 7 saying that the informed consent for the oxygen part of the SUPPORT trial was inadequate. I would like to get your comment on the letter and also ask a few questions about how neonatologists chose which O2 saturation levels in the "standard of care range" (85-95%) range before the SUPPORT study, and whether care has changed as a result of it.

I have to do this story in the next few hours so if you are willing and able to talk then the earlier the better.

Thanks and best

David Brown

David Brown National Staff The Washington Post

browndm@washpost.com

(202) 334-5049

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post
Date: Wednesday, April 10, 2013 12:59:09 PM

Does that person know the answer to all the questions that the reporter posed?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:58 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re: PLEASE READ FW: query from the Washington Post

Yvonne said their site human subjects person as they already talked to NY times
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Rose,

I think (b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:14 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Ok

Will call your office now

Rosemary D. Higgins, MD
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From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Let's have a five minute discussion, Bob and Mona.

Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892
Phone: 301-496-1848
Fax: 301-402-1104
E-mail: maddoxy@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:01 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: PLEASE READ FW: query from the Washington Post
Importance: High

Bob
Do you have any guidance on how to handle???
Rose

Rosemary D. Higgins, MD
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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, April 10, 2013 11:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: query from the Washington Post

Is this something you should handle?

Wally

From: Brown, David M [<mailto:David.Brown@washpost.com>]
Sent: Wednesday, April 10, 2013 10:50 AM

To: Wally Carlo, M.D.

Subject: query from the Washington Post

Dear Dr. Carlo

I am a science reporter at the Washington Post (also a physician) who is doing a story for tomorrow's paper on the OHRP letter of March 7 saying that the informed consent for the oxygen part of the SUPPORT trial was inadequate. I would like to get your comment on the letter and also ask a few questions about how neonatologists chose which O2 saturation levels in the "standard of care range" (85-95%) range before the SUPPORT study, and whether care has changed as a result of it.

I have to do this story in the next few hours so if you are willing and able to talk then the earlier the better.

Thanks and best

David Brown

David Brown National Staff The Washington Post

browndm@washpost.com

(202) 334-5049

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 12:34 PM
To: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: Fw: Public Citizen letter to Sebelius today: <http://www.citizen.org/documents/2111.pdf>

Hi all:

Alerting you to this letter. I've spoken to Diane Gianelli from OASH who is the press point for OHRP. The letter is criticizing OHRP for not penalizing NIH and Univ. of Ala. sufficiently. OHRP has received calls from NYT, Bloomberg, WaPo. We have not received calls but have agreed with Diane that we'll refer calls to them. Mona has alerted the NICHD program officer to refer press calls to the NICHD press office. We'll let you know if anything changes.

Thanks,
Renate

Renate Myles
Senior Press Officer
National Institutes of Health
Tel: 301-435-3638

From: Gianelli, Diane M (OASH)
Sent: Wednesday, April 10, 2013 11:59 AM
To: Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Myles, Renate (NIH/OD) [E]; Migliaccio, Kate (HHS/OASH)
Subject: Public Citizen letter to Sebelius today: <http://www.citizen.org/documents/2111.pdf>

Diane M. Gianelli
Office of Communications
Office of the Assistant Secretary for Health
U.S. Dept. of Health and Human Services
202-690-7169
Diane.Gianelli@hhs.gov

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Ott, Sandra \(NIH/NICHD\) \[E\]](#)
Subject: Fw: PLEASE READ FW: query from the Washington Post
Date: Wednesday, April 10, 2013 12:22:48 PM

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

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: Re: PLEASE READ FW: query from the Washington Post

Be back in 5 min

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:13 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Ok
Will call your office now

Rosemary D. Higgins, MD
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From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ FW: query from the Washington Post

Let's have a five minute discussion, Bob and Mona.

Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

National Institutes of Health
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892
Phone: 301-496-1848
Fax: 301-402-1104
E-mail: maddoxy@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 12:01 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: PLEASE READ FW: query from the Washington Post
Importance: High

Bob
Do you have any guidance on how to handle???

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, April 10, 2013 11:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: query from the Washington Post

Is this something you should handle?

Wally

From: Brown, David M [<mailto:David.Brown@washpost.com>]
Sent: Wednesday, April 10, 2013 10:50 AM
To: Wally Carlo, M.D.
Subject: query from the Washington Post

Dear Dr. Carlo

I am a science reporter at the Washington Post (also a physician) who is doing a story for tomorrow's paper on the OHRP letter of March 7 saying that the informed consent for the oxygen

part of the SUPPORT trial was inadequate. I would like to get your comment on the letter and also ask a few questions about how neonatologists chose which O2 saturation levels in the "standard of care range" (85-95%) range before the SUPPORT study, and whether care has changed as a result of it.

I have to do this story in the next few hours so if you are willing and able to talk then the earlier the better.

Thanks and best
David Brown

David Brown National Staff The Washington Post

browndm@washpost.com (202) 334-5049

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 12:17 PM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Fine, Amanda (NIH/OD) [E]
Subject: Fw: Public Citizen letter to Sebelius today: <http://www.citizen.org/documents/2111.pdf>

Mona can you call me on 703 (b)(6)

Renate Myles
Senior Press Officer
National Institutes of Health
Tel: 301-435-3638

From: Gianelli, Diane M (OASH)
Sent: Wednesday, April 10, 2013 11:59 AM
To: Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Myles, Renate (NIH/OD) [E]; Migliaccio, Kate (HHS/OASH)
Subject: Public Citizen letter to Sebelius today: <http://www.citizen.org/documents/2111.pdf>

Diane M. Gianelli
Office of Communications
Office of the Assistant Secretary for Health
U.S. Dept. of Health and Human Services
202-690-7169
Diane.Gianelli@hhs.gov

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Subject: Re: PLEASE READ
Date: Wednesday, April 10, 2013 12:09:44 PM

Also sent over to nhlbi
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Sent: Wednesday, April 10, 2013 12:07 PM
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: PLEASE READ

ok

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Sent: Wednesday, April 10, 2013 12:02 PM
To: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Subject: RE: PLEASE READ

Already talked to her – she is talking to Alan-she thinks (b)(5)

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higginsr@mail.nih.gov

From: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Sent: Wednesday, April 10, 2013 11:57 AM
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: PLEASE READ

Rose,

I am sorry about this. I see that you sent the very abbreviated letter from UAB to Yvonne- does she know about this?

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Sent: Wednesday, April 10, 2013 11:02 AM
To: [Bock, Robert \(NIH/NICHD\) \[E\]](#); [Rowe, Mona \(NIH/NICHD\) \[E\]](#)
Cc: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Subject: PLEASE READ
Importance: High

I am at the NRN Steering Committee meeting and we have just discovered this press release just issued--

<http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3859>

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, June 05, 2014 5:56 PM
To: Blansfield, Earl (NIH/NICHD) [E]
Subject: FW: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 12:07 PM
To: Myles, Renate (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Fine, Amanda (NIH/OD) [E]; Machalek, Alisa Zapp (NIH/NIGMS) [E]
Subject: RE: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

And David Brown from the Post just called. Maybe OHRP will take all calls. I have to step out but will give Diane a quick call.

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 11:59 AM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Fine, Amanda (NIH/OD) [E]; Machalek, Alisa Zapp (NIH/NIGMS) [E]
Subject: RE: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

Yes, they may so I would (b)(5) Diane just let me know that they also got a call from Bloomberg. Anything you can share on what our response was would be helpful.

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 11:52 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Fine, Amanda (NIH/OD) [E]; Machalek, Alisa Zapp (NIH/NIGMS) [E]
Subject: RE: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

Hi Renate-- Do you think that there is any chance they will try calling our program person directly?

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowcm@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, April 10, 2013 11:26 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Fine, Amanda (NIH/OD) [E]
Subject: FW: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study
Importance: High

Hi Bob and Mona:

Sabrina Tavernise of the NYT has reached out to OHRP about the SUPPORT Study. Bob: if my memory serves me correctly, you (b)(5) Do you have our response? I'm not finding it in the database or a clearance request on it. I'd like to share our response with Diane. See what they had cleared back in Feb. for potential media inquiries below. We should be prepared for a call from Sabrina.

Thanks,
Renate

From: Gianelli, Diane M (OASH)
Sent: Wednesday, April 10, 2013 11:05 AM
To: Myles, Renate (NIH/OD) [E]
Subject: FW: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

I found this...

From: Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]
Sent: Tuesday, February 26, 2013 10:40 AM
To: Gianelli, Diane M (OASH)
Subject: RE: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

Sorry; on an HHS call at the moment. Actually, you can send them to me and Amanda Fine and we'll coordinate with the relevant ICs.

Thanks,
Renate

From: Gianelli, Diane M (OASH)
Sent: Tuesday, February 26, 2013 10:37 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

Sure. If this is the funding source, to whom should we refer press calls? NICHD? Or NHLBI?

Disclosures: SUPPORT was funded by the National Institutes of Health and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute.

From: Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]
Sent: Tuesday, February 26, 2013 10:35 AM
To: Gianelli, Diane M (OASH)
Subject: RE: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

Thanks, Diane.

From: Gianelli, Diane M (OASH)
Sent: Tuesday, February 26, 2013 10:34 AM
To: Myles, Renate (NIH/OD) [E]
Subject: FW: Heads-Up: Possible media interest in OHRP determination letter regarding SUPPORT Study

Renate – just wanted you to know we'll be sending this through ASPA today. (Not for blanket coverage, just an advance notice, in case we get calls.) The determination letter is already posted. I believe it's an NICHD-funded study (Ann Bradley is checking). If we get any calls about the study, we'll send to NICHD and U-Alabama. Can you please give me a press contact for NICHD?

Thanks, Diane

Reporters: TBD
Publications: TBD
Topic: OHRP determination letter regarding *The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) Study*
Type of interview: TBD
Deadline: TBD
Spokesperson: Jerry A, Menikoff, MD, JD, director, Office for Human Research Protections

Name of office head or surrogate who reviewed/approved content: Dr. Menikoff and OGC's Laura Odwazny approved proposed content that follows.

Additional information: Please see http://www.hhs.gov/ohrp/detrm_lettrs/YR13/feb13a.pdf

Expected place of publication: TBD

Expected date of publication/airing: TBD

Expected prominence: TBD

Background: OHRP recently posted a "determination letter," to http://www.hhs.gov/ohrp/detrm_lettrs/YR13/feb13a.pdf, citing findings against a large, NICHD-funded, multi-site (22 locations) study headed by the University of Alabama at Birmingham. The study, which took place between 2004-2009, attempted to learn the appropriate oxygen levels to give to low birth weight infants to protect against blindness, neurological problems and death. OHRP found that the study violated regulatory requirements for informed consent, stemming from its failure to describe the reasonably foreseeable risks of blindness, neurological damage and death.

Any (cleared) conversations with reporters will focus on an elaboration of OHRP's determination letter, the current regulations and OHRP's oversight procedures. Jerry Menikoff is also prepared to discuss whether and, if so, how current regulations might be improved (i.e., through improved clarity and specificity of informed consent) to ensure that prospective subjects can accurately gauge risks, benefits, and alternatives associated with research participation. OHRP would refer inquiries concerning actual ramifications of the SUPPORT study to NIH (NICHD?) or the University of Alabama-Birmingham.

Key messages/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.

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) How might current processes for obtaining informed consent be improved?

Current regulations might be revised to provide greater specificity about how consent forms should be written and what information they should contain. The goal would be consent forms that are shorter, more readily understood, and less confusing but that contain all the key information, and that could serve as useful aids to decision-making.

4) What is the status of the July 2011 ANPRM envisioned to enhance human research protections and improved efficiencies of the review and oversight processes.

HHS has received public comments and is at present considering next steps.

5) 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.

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.

Additional information: NIH/NICHD subject matter experts have received emailed copies of the determination letter last week.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: PLEASE READ
Date: Wednesday, April 10, 2013 11:49:00 AM
Importance: High

Please confirm receipt of this.

I am at the NRN SC meeting over in Silver Spring

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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Sent: Wednesday, April 10, 2013 11:02 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: PLEASE READ
Importance: High

I am at the NRN Steering Committee meeting and we have just discovered this press release just issued--

<http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3859>

Rosemary D. Higgins, MD
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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Maddox, Yvonne \(NIH/NICHD\) \[E\]](#); [Ott, Sandra \(NIH/NICHD\) \[E\]](#)
Cc: [Willinger, Marian \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#); [Rowe, Mona \(NIH/NICHD\) \[E\]](#)
Subject: AAP 2007 guidelines regarding oxygen
Date: Wednesday, April 10, 2013 11:24:00 AM
Attachments: [Appendix 1 2007 Perinatal Guidelines 6th Ed.pdf](#)

Hi

Here is the chapter from the AAP's guidelines for perinatal care published in 2007 (During the SUPPORT Study) which list target oxygen saturations from 85-95%.

Rose

guidelines for
**PERINATAL
CARE**

Sixth Edition

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN™

The American College
of Obstetricians
and Gynecologists



WOMEN'S HEALTH CARE PHYSICIANS

Guidelines for Perinatal Care was developed through the cooperative efforts of the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn and the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice. The guidelines should not be viewed as a body of rigid rules. They are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or the type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

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Hydration

There is no evidence that excess fluid administered to the neonate decreases the serum bilirubin concentration. Some neonates who are admitted to the hospital with high bilirubin concentrations also may be mildly dehydrated and may need supplemental fluid intake to correct dehydration. In the absence of dehydration, routine supplementation (with dextrose-water) of neonates receiving phototherapy is not indicated. However, in sick, VLBW neonates receiving phototherapy, excess evaporative water loss is known to occur and frequently necessitates increased fluid intake, environmental humidity, or both for replacement or prevention of ongoing losses.

Phototherapy

Phototherapy is effective in reducing serum bilirubin concentrations in neonates with nonhemolytic jaundice. Phototherapy is less effective in neonates with ABO and CDE (Rh) group hemolytic disease, reducing, but not eliminating, the need for exchange transfusions in these neonates. Exchange transfusion is the treatment of choice when the bilirubin concentration appears to pose an imminent threat to the health of the neonate.

There is no standardized method for delivering phototherapy. However, detailed recommendations on phototherapy can be found in the hyperbilirubinemia practice parameters from the AAP. Commonly used phototherapy units contain daylight, cool white, blue, or "special blue" fluorescent tubes. Other units use tungsten-halogen lamps in different configurations, either freestanding or as part of a radiant-warming device. Fiber optic systems have been developed that deliver high-intensity light via a fiber optic blanket.

The efficacy of phototherapy is influenced by the energy output (irradiance) in the blue spectrum (measured in microwatt per centimeter squared), the spectrum of light source, and the surface area of the neonate exposed to the light source. The irradiance of a unit should be monitored and bulbs changed as needed to maintain maximum energy output. It is acceptable to interrupt phototherapy during feeding or brief parental visits. Intensive phototherapy can be achieved by use of blue lights, decreasing the distance of the source from the neonate and increasing the surface area exposed to the lights. The neonate's temperature should be monitored frequently while phototherapy is being applied.

Although phototherapy has many biologic effects, it has no known lasting toxic effects in the human neonate. Because experiments in animals have doc-

umented retinal damage from phototherapy, the neonate's eyes should be covered with opaque patches during exposure to phototherapy light. Known potential complications from improper monitoring of eye-patch placement include exposure to high-energy light, malposition and obstruction of the nares, inadequate securing of the patch that allows lid opening and resultant corneal abrasion, and conjunctivitis from use without intermittent removal to assess the condition of the covered tissues.

The determination of a neonate's suitability for early discharge requires heightened awareness of the normal course of physiologic hyperbilirubinemia. Recent data suggest that there is some predictability to the progressive increase in serum bilirubin concentrations from nonpathologic sources. It is suggested that for neonates who are otherwise candidates for early discharge, a pre-discharge serum bilirubin determination can be helpful in predicting risk for a subsequent increase to more concerning concentrations. A neonate with early onset jaundice (within the first 24 hours) should have hemolysis excluded as a cause before being considered for early discharge. After the newborn is discharged from the birthing hospital, the mother and child should receive a seamless continuation of care as outlined in the AAP guideline.

Some neonates with uncomplicated nonhemolytic jaundice may be treated with phototherapy at home. Guidelines should be developed by each institution to define criteria for neonates who are eligible for home phototherapy. Home care requires appropriate follow-up and supervision by a health care professional with access to serum bilirubin determinations as clinically indicated. With proper instruction of the parents or guardians, phototherapy can be provided by using a freestanding device or a fiber optic blanket. If serum bilirubin concentrations do not decrease in response to conventional phototherapy, admission to the hospital may be indicated for more intensive phototherapy or exchange transfusion and for evaluation of the underlying cause (Fig. 8-1 and Fig. 8-2).

Clinical Considerations in the Use of Oxygen

The hazards associated with nonindicated administration of supplemental oxygen to preterm neonates have been recognized for many years. Studies conducted in the 1950s indicated that prolonged oxygen therapy without clinical indication was associated with increased rates of retinopathy of prematurity, formerly called retrolental fibroplasia. The ensuing blanket restriction of ambient oxygen therapy resulted in a marked decrease in retinopathy of prematurity at the cost of an increase in morbidity and mortality. Current practice includes

the prudent use of supplemental oxygen as needed, based on an objective determination of oxygen requirements.

When supplemental oxygen therapy is considered, the potential risks, in terms of both hypoxia and hyperoxia, should be weighed. Clinical judgment of physical signs alone as a guide to the amount of supplemental oxygen needed is acceptable for short periods, emergencies, or abrupt clinical changes. However, ongoing use of supplemental oxygen should be guided by an objective assessment of patient oxygenation.

Administration and Monitoring

In an emergency, high concentrations of supplemental oxygen may be administered by a face mask, nasal prongs, or endotracheal tube. When a neonate requires oxygen therapy beyond the emergency period, the oxygen should be warmed and humidified and the concentration or flow should be monitored and regulated. Supplemental oxygen can be delivered via endotracheal tube, oxygen hood, nasal prongs, or incubator. Oxygen analyzers should be calibrated in accordance with manufacturers' recommendations. Orders for oxygen therapy should include desired ambient concentration, flow, or both. The concentration or flow rate of oxygen should be checked routinely. Alternatively, orders should be written to adjust fraction of inspired oxygen (FI_{O_2}) or flow within a stated range to maintain oxygen saturation within specific limits. There should be an institutional guideline for ordering, delivering, and documenting oxygen therapy and monitoring.

An important development in the care of neonates who require oxygen therapy is the ability to monitor oxygenation continuously with noninvasive techniques. The pulse oximeter measures oxyhemoglobin saturation and the transcutaneous oxygen analyzer provides an indirect measurement of Pa_{O_2} . Because neither technique measures Pa_{O_2} directly, they should be used as adjuncts to, rather than substitutes for, arterial blood gas sampling, especially in neonates with moderate to severe respiratory distress.

Periodic or continuous measurement of Pa_{O_2} in samples from an umbilical or peripheral artery catheter is the most reliable method of assessing the effectiveness of oxygen therapy. If an indwelling arterial catheter is not in place, peripheral artery puncture can be used, but this is painful and repeated sampling from these sites is not always possible. Oxygenation is not accurately estimated in arterialized capillary samples. However, arterialized capillary sampling provides fairly reliable estimates of arterial pH and Pa_{CO_2} . The combined use of continuous, transcutaneous oxygen saturation monitoring and intermittent

percutaneous arterial or arterialized blood gases to guide oxygen therapy is an attractive pragmatic strategy when invasive arterial catheters are not in place.

In neonates whose condition is unstable, noninvasive measurements should be correlated with Pa_{O_2} as often as every 8–24 hours. More frequent analyses of arterial blood gas may be indicated for the assessment of pH and Pa_{CO_2} . In neonates whose condition is stable, correlation with arterial blood gas samples may be performed when clinically indicated.

The use of either pulse oximetry or transcutaneous oxygen measurement may shorten the time required to determine optimum inspired oxygen concentration and ventilator settings in the acute care setting. Both measurements are particularly useful in monitoring oxygen therapy in neonates who are recovering from respiratory distress or who require long-term supplemental oxygen. Pulse oximetry is particularly advantageous for long-term monitoring of oxygen therapy because transcutaneous oxygen measurements underestimate oxygenation in older neonates with bronchopulmonary dysplasia (BPD) and may cause burns. Pulse oximetry also is widely available.

In consideration of the current, but incomplete, understanding of the effects of oxygen administration, the following recommendations are offered:

- Supplemental oxygen should be used for specific indications, such as cyanosis, low Pa_{O_2} , or low oxygen saturation.
- The continuous use of supplemental oxygen, other than for resuscitation, should be monitored by assessments of Pa_{O_2} , oxygen saturation, or both.
- Oxygenation monitoring should be available whenever oxygen is continuously administered to newborns.
- For neonates who require oxygen therapy for acute care, measurements of blood pH and Pa_{CO_2} should accompany measurements of Pa_{O_2} . In addition, a record of blood gas measurements, noninvasive measurements of oxygenation, details of the oxygen delivery system (eg, ventilator, continuous positive airway pressure, nasal cannula, hood, mask, settings), and ambient oxygen concentrations (FI_{O_2} , liter of flow per minute, or both) should be maintained.
- The optimal range for oxygen saturation and Pa_{O_2} that balances tissue metabolism, growth and development, and toxicity has not been elucidated fully for preterm infants receiving supplemental oxygen. Oxygen saturation values between 85–95% and Pa_{O_2} values between 50 mm Hg and 80 mm Hg are examples of ranges pragmatically determined by some

clinicians to guide oxygen therapy in preterm infants. Additional research to determine the "optimal" oxygenation ranges for oxygen saturation and PaO_2 is needed. Of note, even with careful monitoring, oxygen saturation and PaO_2 may fluctuate outside specified ranges, particularly in neonates with cardiopulmonary disease.

- Regular and periodic (every 1–4 hours) measurement and recording of the concentration of oxygen delivered to the neonate receiving supplemental oxygen is recommended.
- Except for an emergency situation, air–oxygen mixtures should be warmed and humidified before being administered to newborns.

Retinopathy of Prematurity

A myriad of factors, including but not limited to hyperoxia, may contribute to the pathogenesis of retinopathy of prematurity. Prematurity, low birth weight, twin gestation, severity of illness, prolonged ventilatory support (especially when accompanied by episodes of hypoxia and hypercapnia) and clinical conditions, including acidosis, shock, sepsis, apnea, anemia, chronic lung disease, intraventricular hemorrhage, patent ductus arteriosus, and vitamin E deficiency, also have been associated with retinopathy of prematurity.

To date, a safe level of PaO_2 in relation to retinopathy of prematurity has not been established. Retinopathy of prematurity has occurred in preterm neonates who have never received supplemental oxygen therapy and in neonates with cyanotic, congenital heart disease in whom PaO_2 levels never exceeded 50 mm Hg. Conversely, retinopathy of prematurity has not developed in some preterm neonates after prolonged periods of hyperoxemia. Data have demonstrated no additional progression of active prethreshold retinopathy of prematurity when supplemental oxygen was administered at pulse oximetry saturations between 96% and 99%. Further, continuous, close monitoring of transcutaneous oxygen tension has not resulted in a decrease in the incidence of retinopathy of prematurity when compared with intermittent transcutaneous monitoring. However, recent data in extremely low birth weight infants between 23 weeks and 29 weeks of gestation suggest that oxygen saturation in the lowest range (70–90%) compared with highest range (88–98%) was associated with significantly less threshold retinopathy of prematurity. A one-year follow-up showed similar neurodevelopmental outcome. Randomized, controlled-trial studies will need to be done before this lower range of oxygenation can be recommended.

On the basis of published data, the following statements regarding retinopathy of prematurity and oxygen use are warranted:

- Retinopathy of prematurity is not preventable in some neonates, especially extremely premature neonates.
- Many factors other than hyperoxia contribute to the pathogenesis of retinopathy of prematurity.
- Transient hyperoxemia alone cannot be considered sufficient to cause retinopathy of prematurity.
- Strict adherence to existing guidelines for supplemental oxygen therapy will not completely prevent complications or side effects.
- An ophthalmologist with experience in retinopathy of prematurity and indirect ophthalmoscopy should examine the retinas of all preterm neonates born at 30 weeks of gestation or less or weighing less than 1,500 g at birth, as well as selected infants between 1,500–2,000 g birth weight with an unstable clinical course who are thought to be at risk by their attending pediatrician or neonatologist. The examination should be performed at 4–6 weeks of chronologic age or at 31–33 weeks postmenstrual age (gestational age at birth plus chronologic age), as determined by the neonate's attending pediatrician or neonatologist. The use of a digital, wide-field camera system to photograph retinas of neonates at high risk is being evaluated and may prove valuable to facilitate analysis by experienced off-site ophthalmologists.

Table 8–1 represents a suggested schedule for timing of initial eye examinations based on postmenstrual age and chronologic (postnatal) age to detect retinopathy of prematurity before it becomes severe enough to result in retinal detachment and to allow for earlier intervention, while minimizing the number of examinations, which potentially are traumatic to the baby.

The timing of follow-up examinations is best determined from the findings of the first examination, using the International Classification of Retinopathy of Prematurity. Treatment generally should be accomplished, when possible, within 72 hours of diagnosed treatable disease so as to minimize the risk of retinal detachment. The retinal findings requiring strong consideration of ablative treatment recently have been revised as follows:

- Zone I retinopathy of prematurity: any stage with plus disease
- Zone I retinopathy of prematurity: stage 3, no plus disease
- Zone II: stage 2 or 3 with plus disease

From: Willinger, Marian (NIH/NICHD) [E]
To: Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Williams, Sabrina (NIH/NIAID) [C]
Subject: RE: Today
Date: Wednesday, April 10, 2013 8:21:53 AM

Thanks!

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

From: Raju, Tonse (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 8:03 AM
To: Willinger, Marian (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]
Subject: Re: Today

Sorry to hear this. (b)(6) Marian.
Tonse

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

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Wednesday, April 10, 2013 07:51 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]
Subject: Today

Hi all,

(b)(6) I will be checking email and also dialing into the NRN SC at 1:00.

Maurice- this means I will not be on the sleep call.
Marian

From: Gantz, Marie
To: jmd3@case.edu
Cc: Zaterka-Baxter, Kristin; juliann.difiore@case.edu; mcw3@case.edu; Richard.Martin@UHhospitals.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: FW: acquiring SpO2 data from the Network
Date: Monday, April 08, 2013 1:54:39 PM

Julie,

I would be happy to send you the information when we send the data (I am working on writing it up for you now). If you happen to be using SAS software, I could also send you some programming code.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-537-5110

From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Monday, April 08, 2013 1:52 PM
To: Gantz, Marie
Cc: Zaterka-Baxter, Kristin; juliann.difiore@case.edu; mcw3@case.edu; Richard.Martin@UHhospitals.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: Re: FW: acquiring SpO2 data from the Network

Marie,

If you can send send me the algorithm I can do the smoothing here. That would also be helpful for me to understand how the initial remapping and conversion back with the smoothing algorithm may or may not affect other potential models such as sample entropy and wavelet analysis (which we have not included in the current proposal because of the mapping issues).

Take Care,

Julie

On 4/8/2013 12:42 PM, Gantz, Marie wrote:

Hi Julie,

I notice that the proposal states "The SUPPORT trial algorithm used by Masimo to blind the oximeters to the low and high targets does not allow for one to one mapping back to the original SpO2 values in the SpO2 range of 85-95%. The analysis proposed above is restricted to SpO2 values <80% which are not affected by the re-mapping limitations," but it also says "We will calculate actual daily mean/medians of baseline oxygen saturation over the SUPPORT monitoring period, with baseline oxygen saturation defined as the mean oxygen saturation minus periods of intermittent

hypoxia." To accomplish the latter, you will need to use oximeter data with SpO2 values >80% and will need to account for the remapping limitations. If, as before, you are requesting the oximeter data in binary format, the conversion from display to actual SpO2 values will have to be done at Case. I have recently redone the smoothing of the oximeter data using quadratic and cubic smoothing, and I can provide a document that describes the process that was used.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

From: Juliann Di Fiore [<mailto:jmd3@case.edu>]
Sent: Monday, April 08, 2013 10:42 AM
To: Zaterka-Baxter, Kristin
Cc: juliann.difiore@case.edu; mcw3@case.edu; Richard.Martin@UHHospitals.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Subject: Re: FW: acquiring SpO2 data from the Network

Attached is the updated IH and mortality proposal. We will forward the signed DUA shortly.

Thanks,

Julie

On 4/6/2013 10:01 AM, Zaterka-Baxter, Kristin wrote:

Hi all,

Please find attached the original proposal from 2005, the original DUA and an update DUA form partially completed. Please review the draft language and amend where needed, have your institutional officials review and sign if approved and send back to me for RTI signatures and release of data.

Thanks and please let me know if you have any questions,
Kris

From: Juliann Di Fiore [<mailto:jmd3@case.edu>]
Sent: Wednesday, March 27, 2013 9:58 AM
To: Das, Abhik
Cc: Walsh, Michele; Richard Martin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: acquiring SpO2 data from the Network

That is correct.

Julie

On 3/27/2013 9:23 AM, Das, Abhik wrote:

So, just so that I understand, you are talking about releasing the data to Case so that you can do the analyses in-house?

Thanks

Abhik

From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]

Sent: Wednesday, March 27, 2013 9:16 AM

To: jmd3@case.edu; Richard Martin; Das, Abhik

Subject: RE: acquiring SpO2 data from the Network

Hi Abhik: We are waiting to hear about the R03 funding- but want to go ahead with the saturation analysis using local funds if R03 is not funded. I think the next step is a data use agreement since SUPPORT subcom already agreed. Can you send us in the right direction for this?
Michele

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

From: Juliann Di Fiore [<mailto:jmd3@case.edu>]

Sent: Tue 3/26/2013 4:59 PM

To: Walsh, Michele; Richard Martin

Subject: acquiring SpO2 data from the Network

Michele,

I spoke with Richard about stats funding for the IH and mortality project. He has a means of covering those costs if the RO3 does not go through. :(

I would like to move forward and request the SpO2 data from the network but I don't remember how to proceed. Do you, as the Cleveland PI for the network, have to contact them for a new Data Use Agreement or do Richard/I take care of that? If it is the latter, who do I contact?

Julie

--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
Division of Neonatology, room 3100

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Cleveland, OH 44106
(216) 368-1245

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Research Engineer

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Page 0157 of 2000

Withheld pursuant to exemption
of the Freedom of Information and Privacy Act

From: Zaterka-Baxter, Kristin
To: juliann.difiore@case.edu; mcw3@case.edu; Richard.Martin@UHhospitals.org
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD); Adas@rti.org; [Gantz, Marie](mailto:Gantz,Marie)
Subject: FW: acquiring SpO2 data from the Network
Date: Saturday, April 06, 2013 10:01:39 AM
Attachments: [DUA Update request RTI releases2013.doc](#)
[Episodic Desaturations - Version 5.doc](#)
[DUA Martin DeFiori Walsh.pdf](#)

Hi all,

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Sent: Wednesday, March 27, 2013 9:58 AM
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Cc: Walsh, Michele; Richard Martin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: acquiring SpO2 data from the Network

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(216) 368-1245

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by law.

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Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
Division of Neonatology, room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 368-1245

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Federal and Ohio law protect patient medical information, including psychiatric disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

DATA USE AGREEMENT
RTI INTERNATIONAL
Release of Data by RTI

Information that is obtained or used for research is confidential and must be used only for statistical reporting or research purposes. Therefore, it is necessary to insure, to the extent possible, that any use of such data be limited to research by legitimate researchers, and in accordance with applicable laws and this Data Release Agreement (Agreement). Before research data ("Data") can be released, the Provider of the Data and the Recipient of the Data must agree to several provisions.

This Agreement to share data is between the following parties:

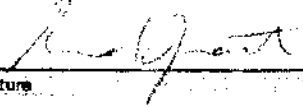
Provider of the Data (Releasing Institution): RTI International

and

Recipient of the Data (Institution Receiving Data): Case Western Reserve University

A. RECIPIENT, PROVIDER AND DATA INFORMATION

1. Information about the Researcher who is requesting the Data (Recipient Researcher):

 8/5/10
Signature Date
Richard J. Martin, MD
Name of Researcher at Recipient Institution (printed or typed)
Case Western Reserve University
Institution/Organization
Rainbow Babies & Children's Hospital, 11100 Euclid Ave. Cleveland, OH
44106-6010
Address
Phone: (216) 844-3387 Fax: (216) 844-3380
Telephone No. FAX No.
rxm6@case.edu
E-mail address

2. Information about the research project from which the Data are requested:

RTI Project Title for which Data will be released: <u>The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants</u>
RTI Project Number: 0208838.013.170.001
RTI IRB Number of Project: 11286
RTI Contact Person for the Project: <u>Kris Zaterka-Baxter</u>
Contact Person RTI e-mail address: <u>kzaterka@rti.org</u>
Contact Person RTI telephone no. <u>919-485-7750 (ext. 7750)</u>

3. Types of Data being requested and the study population from which the Data were collected.

Data Requested: The SUPPORT data files extracted from the Masimo oximeter from the Cleveland and San Diego sites. We request that the data be corrected back to the true oxygen saturation values. Data should be in the original binary format that is compatible with Textrac software to convert from binary to ascii. Files should be identified by the original filenames ([patientID][download#.dat]). In addition, a list of group assignment (group 1 or 2) for each patient is requested.
--

4. Are any direct identifiers (e.g., name, address, telephone numbers, Social Security numbers, medical record numbers) or sensitive indirect identifiers (e.g., date of birth, zip code, State, etc.) included in the Data being requested?

Direct Identifiers	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Indirect Identifiers	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>

If Yes, list the direct identifiers that are included in the Data:
If Yes, list the indirect identifiers that are included in the Data: We are not requesting indirect identifiers but we will have the ability to identify the site (Cleveland or San Diego) by the filename.

5. Proposed use and analysis plans for the Data.

Proposed Uses and Analysis:

Statistical analysis will include linear regression to assess the univariate relationship between continuous variables, such as the relationship between the number of desaturation episodes and mental or motor scores. When examining the relationship between baseline SaO₂ and number of desaturation episodes, we will have multiple measures per infant, consisting of the baseline SaO₂ and the co-variant number of desaturation episodes. Because multiple pairs of measures on the same infant are correlated, we will use generalized estimating equations [GEE] to analyze periodic desaturation episodes by the baseline SaO₂ over a corresponding time.

6. Safeguards (administrative, technical, physical) that will be used by the Recipient to protect the confidentiality of the Data.

Safeguards to protect the confidentiality of the data:

There will be no identifiers included in the data files. In addition, data will be kept in a locked office on an encrypted drive. Only investigators directly involved with this study will have access to the data.

7. List of Individuals, Groups, or Classes of Persons who will have access to or use the requested Data at the Recipient Institution, including the principal Researcher (named in Item 1). NOTE: Data may not be shared with researchers outside the Recipient Institution via this DUA. Researchers at other Institutions must establish their own DUA with RTI to access these data .

Identity of persons with Data access:

Richard J. Martin, MD
Juliana DiFiore, B.S.E.E
Michele Walsh, MD
Chris Wilson PhD
Ryan Foglyano

Case Western Reserve University
Rainbow Babies & Children's Hospital
11100 Euclid Ave.
Cleveland, OH 44106-6010

8. Time period for which Data are being requested.

Requested date of Data release to you: July 25, 2010

Estimated date of Data return or destruction: July 25, 2014
Per our normal IRB guidelines we anticipate keeping data for 3 years after publication

B. TERMS AND CONDITIONS

By receiving the Data described above from the Provider (RTI), the Recipient agrees to the following:

1. Recipient certifies that the statements made in this Agreement (above) regarding the planned use of the Data are complete and accurate.
2. Recipient will not use the Data for purposes other than described in this Agreement and as approved by the Recipient's IRB.
3. Recipient will establish and maintain the appropriate administrative, technical, and physical safeguards to protect the confidentiality of the data and to prevent unauthorized use or access to the Data. ~~[INCLUDE THIS TEXT IF CIPSEA APPLIES, OTHERWISE DELETE: These data were collected under and their confidentiality is protected by the Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA). Violations of the confidentiality of these data as stated in CIPSEA are subject to criminal felony penalties of imprisonment for not more than five years, fines of not more than \$250,000, or both. The Researcher identified in A.1 above and all persons with access to the Data as specified in box A.7 above are required to complete CIPSEA Training and submit a signed confidentiality agreement provided by the Provider before the Data are released to the Recipient. Subsequent to release of the Data, Recipient is responsible for ensuring that any person not specified in box A.7 above who requires access to the Data will complete the CIPSEA Training and submit a signed confidentiality statement to Provider prior to being given access to the Data.]~~
4. Recipient will not disclose Data nor permit others to use the Data except as described in this Agreement. Within the recipient's institution or organization, access to the Data shall be limited to the minimum number of individuals necessary to achieve the purpose stated in the Agreement.
5. No findings or information derived from the Data may be released if such findings contain any combination of data elements that might allow for identification or the deduction of a study participant's identity.
6. In the event the Recipient discovers or is able to deduce the identity of a specific participant, Recipient agrees not to reveal the participant's identifying information nor any associated information in the Data to non-authorized persons nor attempt to contact these individuals.
7. Recipient agrees to subject any findings or manuscripts proposed for public release (e.g., abstracts, presentations, publications) to a stringent review to assure that data confidentiality is maintained and that individual study participants cannot be identified.
8. Recipient will report immediately to the Provider any use or disclosure of the Data other than as permitted by this Agreement, and will take all reasonable steps to mitigate the effects of


such improper use or disclosure, cooperating with all reasonable requests by the Provider towards that end.

9. Recipient agrees that in the event that the Provider determines or has a reasonable belief that Recipient has violated any terms of this Agreement, the Provider may terminate this Agreement and require that the Recipient return the Data and all derivative files. Provider may also seek injunctive relief against Recipient to prevent any disclosure of Data by Recipient to other than the Provider. Recipient understands that as a result of this determination or reasonable belief that a violation of this agreement has occurred, Provider may also refuse to release further data to Recipient. In addition, Provider will report any misuse or improper disclosure of Data as required by applicable laws.
10. Upon completion of the research or the date of Data return specified in box A.8 above whichever comes first, Recipient agrees to destroy the Data and all derivative data sets or where directed by the Provider to return the Data to the Provider per their instruction. Recipient will be required to certify such destruction or return by signing and returning to the person specified by the Provider on this form (i.e., the RTI Project Contact listed in box A.2 above) a Certificate of Data Return or Destruction provided by Provider.
11. If the Researcher leaves the employ of the Recipient, Recipient will notify the Provider in writing at least 14 days before the Researcher leaves. Researcher is not permitted to take the Data or any derivative data sets with them. Return or destruction of the Data and all derivative data sets as specified in item B.10 above is required by the Researcher's departure date. If continued use of the Data is needed by the institution, then Recipient must specify this in their notification of Researcher leaving and request a revised Data Use Agreement with a new Researcher. Provider will notify Recipient if the request is accepted and specify procedures to revise the Data Use Agreement. If the Researcher would like to continue the use of the data then a new Data Use Agreement will have to be put in place with the Researcher's new institution.
12. If Recipient requires use of the Data or any derivative data sets beyond the date specified in box A.8 above as the Date Data to be returned or destroyed, then Recipient must request a revision to this date in writing at least 30 days before the return or destroy date and specify the reasons for needing the revision.
13. Either party may terminate this Agreement upon thirty days written notice. Upon termination of this Agreement, Recipient will return or destroy, at the Provider's instruction, all copies of Data or portions thereof in its possession that were received from the Provider or created (or had others create) using Data received from the Provider.
14. This Agreement shall be construed in accordance with the laws of the State of North Carolina, and in a manner that supports compliance by Recipient and Provider with all applicable requirements of HIPAA (Health Insurance Portability and Accountability Act), and the Privacy Act of 1974.
15. The Terms and Conditions of this Agreement are for the sole benefit of Recipient and Provider and do not create any third party beneficiary rights.

C. Signatures and Clearance for PROVIDER Institution (RTI): RTI Researcher, RTI ORP Clearance and RTI ORC Signature

The signatures below indicate that RTI agrees to release the Data to the Recipient under the above stated provisions.

1. Signature of RTI Researcher Responsible for this Data Release

 _____ 9/15/10
Signature Date

Abhik Das, PhD
Name of RTI Researcher Releasing Data (printed or typed)

RTI International
Institution/Organization

301-770-8214 **adas@rti.org**
Telephone No. E-mail Address.

2. Clearance by RTI's Office of Research Protection (ORP)

[Affix ORP stamp here]

**RTI International
Office of Research Protection**

SEP 15 2010

Approved on Date Above

3. Signature of Official from RTI's Office of Research Contracts

On behalf of RTI, the undersigned individual hereby attests that he or she is authorized to legally bind RTI to the terms of this Agreement and agrees to all the terms specified herein

William Castonguay
Signature

09/15/2010
Date

William Castonguay, Sr. Manager, Contracting Officer

Name of Official from Office of Research Contracts (printed or typed)

RTI International

Institution/Organization

919-541-8835

Telephone No.

wcastonguay@rti.org

E-mail Address

D. Signature of Official from RECIPIENT Institution

On behalf of the Researcher requesting the Data and the Recipient Institution, the undersigned individual hereby attests that he or she is authorized to legally bind the Recipient Institution to the terms of this Agreement and agrees to all the terms specified herein.

Robert H. Miller
Signature

Date

Robert H. Miller, Vice Dean for Research, School of Medicine

Name of Official from Recipient Institution (printed or typed)

Case Western Reserve University

Institution/Organization

(216) 368-6269

Telephone No.

robert.miller@case.edu

E-mail Address

DATA USE AGREEMENT-- DATA UPDATE REQUEST

RTI INTERNATIONAL

RTI is Provider Institution (Releasing Data)

1. Recipient Institution:			
Case Western Reserve University			
2. Requestor Name and Signature			
<hr/> Name of Researcher requesting update from Recipient Institution (printed or typed)			
<hr/> Signature of Requesting Researcher Date			
3. Project Title: The SURfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial)			
4. DUA Number(s) (if applicable):	5. Contract/Grant No (if applicable): 2U10HD036790-16		
6. RTI Project Number (RTI Researchers provide for Recipient Researcher): 0208838.016.011	7. RTI IRB Number (RTI Researchers provide for Recipient Researcher): 12312_18		
8. The following additional data files/variables are being requested under this current DUA The SUPPORT trial data files extracted from the Masimo ® oximeter from <i>the 15 additional participating NRN centers</i> (original DUA requested these data specifically from CWRU and UCSD). We request the data be corrected back to the oxygen saturation values. Data should be in the original binary format that is compatible with Textrac software to convert from binary to ascll. Files should be identified by the original file name ([patientID](download#).dat). IN addition, a list of group assignments (Group 1 or 2) fro each patient is requested.			
PARTICIPATING CENTERS <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <td style="padding: 5px; vertical-align: top;"> Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital University of Texas-Dallas (4) Wayne State University (5) Children's Hospital of Michigan Emory University (9) Grady Memorial Hospital University of Cincinnati (11) University of Cincinnati Hospital Indiana University (12) Yale University (13) The Children's Hospital at Yale – New Haven Brown University (14) </td> <td style="padding: 5px; vertical-align: top;"> Women and Infant's Hospital Stanford University (15) Stanford University Med Center University of Alabama (16) University of Alabama at Birmingham University of Texas- Houston (18) Duke University (19) University of California-San Diego (22) Tufts NEMC (23) University of Iowa (24) University of Utah (25) University of New Mexico (26) </td> </tr> </table>		Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital University of Texas-Dallas (4) Wayne State University (5) Children's Hospital of Michigan Emory University (9) Grady Memorial Hospital University of Cincinnati (11) University of Cincinnati Hospital Indiana University (12) Yale University (13) The Children's Hospital at Yale – New Haven Brown University (14)	Women and Infant's Hospital Stanford University (15) Stanford University Med Center University of Alabama (16) University of Alabama at Birmingham University of Texas- Houston (18) Duke University (19) University of California-San Diego (22) Tufts NEMC (23) University of Iowa (24) University of Utah (25) University of New Mexico (26)
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital University of Texas-Dallas (4) Wayne State University (5) Children's Hospital of Michigan Emory University (9) Grady Memorial Hospital University of Cincinnati (11) University of Cincinnati Hospital Indiana University (12) Yale University (13) The Children's Hospital at Yale – New Haven Brown University (14)	Women and Infant's Hospital Stanford University (15) Stanford University Med Center University of Alabama (16) University of Alabama at Birmingham University of Texas- Houston (18) Duke University (19) University of California-San Diego (22) Tufts NEMC (23) University of Iowa (24) University of Utah (25) University of New Mexico (26)		
9. Current Retention Date/Expiration Date: _____ July 25, 2014 _____			

10. Signature of Official from RECIPIENT Institution

On behalf of the Researcher requesting the Updated Data and the Recipient Institution, the undersigned individual hereby attests that he or she is authorized to legally bind the Recipient Institution to the terms of the existing agreement and agrees to all the terms specified therein.

Signature

Date

Name of Official from Recipient Institution (printed or typed)

Telephone No.

E-mail Address

(Requestor and Authorized Signatory at Recipient Institution should complete and sign this section of this form and send to RTI Research Staff Responsible for this releasing updated data under this existing DUA)

11. To be completed by RTI Researcher Responsible for this Updated Data Release

Abhik Das, PhD

Name of RTI Researcher Responsible for this Updated Data Release

The Signature below indicates that the RTI Researcher responsible for this data release agrees to the update of this Data Use Agreement with the above named Researcher at the Recipient Institution

Signature of RTI Researcher releasing updated data for this existing Data Use Agreement
Date

(RTI Researcher Responsible for updated data release should complete this section—*but not sign* and e-mail the document for review and clearance to the RTI Office of Research Protection for human data DUAs and to Regulatory and Quality Assurance for non-human DUAs.)

12. To be completed by RTI Office of Research Protection (ORP) or Regulatory and Quality Assurance (RQA)

Stamp below to indicate ORP or RQA Review and Clearance for DUA Extension:

13. Signature of Official from RTI's Office of Contracts or Supply Chain Management

On behalf of RTI, the undersigned individual hereby attests that he or she is authorized to legally bind RTI to the terms of the existing Agreement including the requested update and agrees to all the terms specified therein.

Signature

Date

Name of Official from Office of Contracts or Supply Chain Management (printed or typed)

Telephone No.

E-mail Address.

The RTI Researcher sends a fully-executed copy to records@rti.org.

INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS
ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY:

A Proposed Secondary Study

Richard J. Martin, M.D., Juliann M. DiFiore, B.S.E.E., Michele C. Walsh, M.D.
[Case Western Reserve University School of Medicine, Cleveland, OH]

Neil Finer, M.D., Wade Rich, R.C.P.T.
[University of California, San Diego, CA]

ABSTRACT:

Episodes of oxygen desaturation, typically a consequence of apnea or hypoventilation, are almost universal in very low birth weight infants. Neither their incidence, nor potential adverse effects on later neurodevelopmental outcome or respiratory patterns are known. The NICHD Neonatal Research Network, of which we are a participant, is about to embark on a multicenter trial in which preterm infants of 24-28 weeks' gestation will be randomized to two levels of baseline oxygen saturation. The effect of baseline oxygen saturation on neurodevelopment at 18 months comprises one of several outcome measures in this trial. However, preliminary data suggest that the frequency of episodic desaturation increases at lower baseline oxygen, and that intermittent hypoxemic episodes may have long lasting effects on neural plasticity, manifest as altered respiratory control. As the specially designed software for the pulse oximeters in this trial will not detect brief episodes of desaturation, we are proposing an ancillary study to quantify desaturation episodes during the first month of life and relate them to potential consequences. This ancillary study is being proposed in Cleveland, and another NICHD Network site, and coordinated closely with the Data Coordinating Center. The proposed study will provide a unique opportunity to characterize the incidence of, risk factors for, and significance of, intermittent hypoxemic episodes in preterm infants, an issue of great importance for the well-being of this population.

A. SPECIFIC AIMS:

We seek to perform a prospective trial at two clinical sites [Cleveland, Univ. CA @ San Diego] involved in the SUPPORT Trial to identify the incidence and consequences of intermittent hypoxemic episodes in preterm infants of 24-28 weeks' gestation. Three sub-aims are proposed:

1. To characterize and compare the incidence and magnitude of episodic desaturation episodes in infants enrolled to the different arms [high vs low baseline oxygen saturation] of the SUPPORT Trial.
2. To correlate the incidence and magnitude of such desaturation episodes over the first month of life with neurodevelopmental outcome at 18-22 months.
3. To correlate the incidence and magnitude of episodic desaturation episodes over the first month with the incidence of subsequent desaturation episodes at 18-22 months as a measure of sleep disordered breathing in early infancy.

B. HYPOTHESES TO BE TESTED:

1. Frequency of episodic desaturation in the neonatal period is increased at lower baseline oxygen saturation.
2. Higher incidence of episodic desaturation in neonates is associated with greater neurodevelopmental handicap at 18-22 months.
3. Higher incidence of episodic desaturation in neonates is associated with greater sleep disordered breathing [manifest by persistent episodes of desaturation] at 18-22 months.

C. RATIONALE:

The SUPPORT Trial will randomize infants to two ranges of SpO₂ in order to test the hypothesis that use of a lower SpO₂ range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity [ROP] and/or the need for surgical intervention. However, the potential risk of a lower SpO₂ range in increasing the incidence of episodic desaturation is unknown. In addition, although the SUPPORT Trial is documenting the total time spent below various levels of SaO₂, prior studies in animal models have suggested that the neural effects of intermittent or episodic hypoxia may differ greatly than those of sustained hypoxia [see below: *Consequences of Episodic Desaturation on Respiratory Control*]. **Therefore, this study represents a unique opportunity to acquire additional data to characterize the safety and consequences of episodic desaturation in a large cohort of preterm infants.**

D. BACKGROUND:

1. Incidence and causes of episodic desaturation:

Desaturation episodes are ubiquitous in preterm infants, both ventilated and spontaneously breathing. Nonetheless, the precise incidence of these events is not well documented. They are thought to be a consequence of immature respiratory control and aggravated by underlying lung disease [typically bronchopulmonary dysplasia (BPD)]. During assisted ventilation these episodes are secondary to hypoventilation or ineffective ventilation. They may be aggravated by loss of functional residual capacity [FRC] associated with recruitment of abdominal muscles during expiration [Bolivar '95]. This, in turn, may decrease the effectiveness of spontaneous ventilatory efforts [Dimaguila '97], especially in ventilated infants with BPD [Durand '92] and during alert states rather than active or quiet sleep states [Lehtonen '03].

During the transition from assisted ventilation through continuous positive airway pressure [CPAP] to spontaneous breathing, there are minimal data on the incidence of such events. We speculate that the incidence of episodic desaturation [e.g., a fall in SaO₂ of 10%] would be greater at lower baseline SaO₂. Although this is not clearly documented in neonates, it is known that supplemental oxygen decreases apnea and periodic breathing. In addition, the slight improvement in SaO₂ associated with prone positioning does decrease intermittent hypoxemia [McEvoy '97].

2. Consequences of Episodic Desaturation on Neurodevelopmental Outcome:

There are limited clinical data on the potential consequences of episodic desaturation in

preterm infants [Martin & Fanaroff '98]. Taylor ['98] observed that, in addition to severe cerebral ultrasound abnormality and BPD, a history of apnea of prematurity was predictive of later impairment of neurodevelopmental outcome. Data from the CHIME Study demonstrate that cardiorespiratory events in the home are associated with a five-point lower mental development index at 12 months [Hunt '04]. These studies have all focused on apnea rather than the accompanying hypoxemic events. The only study to address the latter issue is the observation that mean oximetry desaturation during documented apnea has been shown to predict motor scores at outcome [Cheung '99]. There is also the consistent observation that presence of BPD contributes to a poorer neurodevelopmental outcome in virtually all available trials [Hack '00]. It is possible that the higher incidence of desaturation episodes in these infants with BPD [Durand '92] contributes to the adverse effect of BPD on neurodevelopmental outcome.

3. Consequences of Episodic Desaturation on Respiratory Control:

There is great emerging interest in the field of respiratory neurobiology on the long term consequences of intermittent or episodic hypoxia. **Available data indicate the biologic consequences of intermittent hypoxia may differ greatly to those of sustained hypoxia.** Several groups working independently have provided evidence in immature and mature rats that intermittent, but not sustained, hypoxia provides long-lasting changes in neural plasticity. This is manifest primarily as long-term facilitation of carotid body sensory activity, and it has been proposed that such intermittent hypoxia-induced respiratory plasticity may create selective vulnerability to hypoxia during development [Peng '03, Gozal '03, Mitchell '01]. In the developing rat brain, age at time of exposure to intermittent hypoxia [as well as duration of exposures] affect cortical and hippocampal vulnerability as measured by apoptosis [Gozal '01]. Ancillary imaging studies [e.g., MRI] focused on the brain stem may provide a novel correlation with frequency of episodic desaturation.

During the transition of neonates to childhood, there are very limited data on either the incidence or consequence of episodic desaturation. Healthy two-year olds do exhibit some desaturation episodes [Poets '93] and a history of preterm birth increases the odds of sleep disordered breathing in 8 to 11 year olds [Rosen '03]. Finally, preterm infants with persistent apnea of prematurity appear to exhibit enhanced hypoxic ventilatory responses, suggesting that a history of prior desaturation episodes may influence respiratory control mechanisms and stability in this population [Nock '04]. Therefore, it is proposed [Hypothesis #3] that a measure of the incidence of episodic desaturation be obtained as a measure of respiratory instability at 18-24 months follow-up of this cohort.

E. METHODOLOGIC ISSUES :

1. Oximetry Sampling:

The infants will be monitored over a period of four to eight weeks, regardless of the need for supplemental oxygen and/or ventilator support. At this time they will have achieved a postconceptional age of 32 weeks. Oximetry data will be acquired utilizing ProFox[®] software as a means of downloading data from the Masimo[®] and for further analysis. We propose that desaturation be defined as a fall in SaO₂ >10% from baseline. Other data

[much of which is being collected for the SUPPORT Trial] includes mean lowest saturation during desaturation episodes, mean SaO₂ during entire monitoring period, time <90%, <85%, <80%, <70%, and total number of desaturation episodes.

Episodes of desaturation can occur rapidly and may last for a short duration, therefore, a relatively short averaging time [Farre '98] sample rate are needed for accurate detection. We are currently generating preliminary data to establish an adequate sample rate and averaging time. This will probably result in some adjustment of these parameters as currently proposed in the SUPPORT Trial.

This proposal will require that the infants enrolled in the collaborating centers for this secondary will acquire the oximetry data at 1 sample every 2 seconds as opposed to 1 sample every 10 seconds. This will require a weekly download as opposed to a monthly download. The data will be forwarded to RTI and the data converted to 1 sample every 10 seconds for the main SUPPORT data base. We will work closely with the Research Triangle Institute [RTI] in resolving these details.

2. Sample Size:

Based on prior data [Cheung '99] using a sample of 63 infants, birthweight 750-999 grams, the correlation between mean desaturation secondary to apnea and Bayley Mental Score was estimated to be 0.25. A sample of 123 infants is needed to provide 80% power to detect a correlation of this magnitude [$\alpha = .05$, 2-sided test]. Using previously recorded data from 12 hour overnight cardiorespiratory monitoring studies in 13 preterm infants, the correlation between baseline SaO₂ and the number of desaturations was estimated to be 0.23. A sample of 140 infants is needed to provide 80% power to detect an effect of this magnitude [$\alpha = .05$, 2-sided test]. To account for loss to follow-up, we will inflate the sample by 20% to 168. Confirmation of this sample size will utilize data collected during the pilot phase in Cleveland.

3. Statistical Analysis:

Statistical analysis will include linear regression to assess the univariate relationship between continuous variables, such as the relationship between the number of desaturation episodes and mental or motor scores. When examining the relationship between baseline SaO₂ and number of desaturation episodes, we will have multiple measures per infant, consisting of the baseline SaO₂ and the co-variant number of desaturation episodes. Because multiple pairs of measures on the same infant are correlated, we will use generalized estimating equations [GEE] to analyze periodic desaturation episodes by the baseline SaO₂ over a corresponding time.

F. DISCUSSION OF ANTICIPATED RESULTS:

We anticipate that the low baseline oxygen saturation group will have both an increase in number of desaturation episodes and a greater decrease in oxygen saturation during such episodes when compared to the high baseline group. We speculate that this will be associated with lower mean neurodevelopmental outcome scores at 18-22 months in the low baseline group when compared to the high baseline group.

If there is no difference in the number or severity of desaturation episodes between the low and high baseline oxygen saturation groups we will conclude that keeping the infants in the low baseline oxygen saturation range does not put them at greater risk for episodic desaturation. Even with this finding there will still be variability in the number and severity of desaturation episodes within each group. Therefore, after combining the infants into one group, we anticipate a wide range of desaturation episodes within this group and an association between these episodes and outcome.

We also anticipate an association between the incidence of desaturation episodes in early postnatal life and sleep disordered breathing at 18-22 months. This hypothesis will be tested by comparing low and high oxygen groups if they differ in episodic desaturation, or by pooling the data as above if the two groups do not differ in incidence of desaturation episodes.

A challenge is to attempt to determine whether an association between incidence or severity of episodic desaturation and outcome reflects a causal relationship. Our study design is such that we are targeting one group to have a lower baseline oxygen and [based on preliminary data (Laptook '04)] more episodic desaturation. The two randomized groups by design should be comparable in all other perinatal and neonatal parameters. Therefore, a putative association between outcome and either baseline oxygen or episodic desaturation would suggest a causal relationship. As the SUPPORT Trial will examine the association between baseline saturation and outcome, we believe that additional quantification of the potentially confounding effects of episodic desaturation is essential in order to clarify the mechanism underlying a causal association between baseline oxygen and neurodevelopmental [or respiratory] outcome.

G. BUDGET:

No allocation of funds beyond \$10,000 is being requested at this time by the study sites.

REFERENCES:

1. Cheung P-Y, Barrington KJ, Finer NN, Robertson MT: Early childhood neurodevelopment in very low birth weight infants with pre-discharge apnea. *Pediatr Pulmonol* 27:14-20, 1999.
2. Nock ML, DiFiore JM, Arko MK, Martin RJ: Relationship of the ventilatory response to hypoxia with neonatal apnea in preterm infants. *J Pediatr* 144:291-295, 2004.
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From: Luc Brion
To: Das, Abhik; Wrage, Lisa Ann
Cc: Jackie LeVan; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Presentation | LeVan, Changes in Therapy
Date: Monday, April 01, 2013 1:17:20 PM

Lisa;
Could you please run adjusted analyses of the secondary outcomes taking into account baseline variables that reached significance.
Please let me know if you wish to discuss this further.
Thanks
Luc

From: Das, Abhik [adas@rti.org]
Sent: Monday, April 01, 2013 9:00 AM
To: Luc Brion
Cc: Wrage, Lisa Ann; Jackie LeVan; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Well, I think we may be criticized for reporting unadjusted analyses for the secondary outcomes when there are clearly some changes in the risk factors over time.

Thanks

Abhik

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, March 29, 2013 11:46 PM
To: Das, Abhik
Cc: Wrage, Lisa Ann; Jackie LeVan; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Abhik:
Here is a revised version with adjusted RR only for primary outcomes.
I attach the latest version of the protocol.
Are you suggesting we should change the protocol to only include adjusted RR for all variables?
Luc

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From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Friday, March 29, 2013 11:58 AM
To: Luc Brion
Cc: Wrage, Lisa Ann
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Interesting findings. I think you need to list out the variables that are adjusted for. I would also report adjusted p values for the secondary outcomes. Since we seem to be running into some secular trends (more ANS, more maternal diabetes and HT), it is crucial that we report what we adjusted for and present only adjusted results.

Thanks

Abhik

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, March 27, 2013 9:16 PM
To: Wrage, Lisa Ann; (b)(6)@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; Lisa Ann " <wrage@rti.org>, " Wally.Carlo@ndb-mr3.cc.emory.edu; M.D." <WCarlo@peds.uab.edu>, "; Barbara Stoll; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Lisa;

Thanks for the email.

Here is the revised poster, taking into account the new NICHD logo's , Barbara and Lisa's suggestions.

Luc

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Wednesday, March 27, 2013 9:16 AM
To: Luc Brion; (b)(6)@gmail.com
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Luc, I notice in the Background section you have: 30% O₂ oxygen.

Lisa

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, March 27, 2013 10:12 AM
To: (b)(6)@gmail.com; Wrage, Lisa Ann; archerst@mail.nih.gov
Subject: FW: PAS Presentation | LeVan, Changes in Therapy

Thanks
Luc

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Wednesday, March 27, 2013 8:00 AM
To: Luc Brion
Subject: PAS Presentation | LeVan, Changes in Therapy

Hi Luc,

Here is the poster with the new logo in it.

Stephanie

UT Southwestern Medical Center
The future of medicine, today.

From: [Luc Brion](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Jackie LeVan](#)
Subject: RE: First draft of Jackie LeVan's poster for PAS-- bjs comments
Date: Friday, March 29, 2013 8:26:22 PM

Maybe a few centers changed their policy re oxygen saturation goals or maybe some physicians changed their approach after publication of SUPPORT.

We can't find out with available data; would you suggest we should do a survey of the NRN centers involved in SUPPORT?

Luc

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From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, March 29, 2013 9:46 AM
To: Luc Brion
Subject: RE: First draft of Jackie LeVan's poster for PAS-- bjs comments

Luc

This is very nice – can you give an explanation for the decline in ROP??

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-5575
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From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Tuesday, March 26, 2013 8:28 PM
To: Barbara Stoll; Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; " <(b)(6)>@gmail.com>," Wrage@ndb-mr3.cc.emory.edu; Lisa Ann " <wrage@rti.org>," Wally.Carlo@ndb-mr3.cc.emory.edu; M.D." <WCarlo@peds.uab.edu>,"
Subject: RE: First draft of Jackie LeVan's poster for PAS-- bjs comments

Barbara;

Thanks a lot for your comments.

I entered them all into this revised version.

For GA I was unclear if you wanted a change or not; I changed the description closer to the way it is in the SUPPORT NEJM paper.

Stephanie:

Could you please enter the new logos into this poster?

Thanks

Luc

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From: Barbara Stoll [<mailto:Barbara.Stoll@oz.ped.emory.edu>]

Sent: Tuesday, March 26, 2013 2:05 PM

To: Luc Brion

Cc: Higgins, Rosemary (NIH/NICHD) [E]; " (b)(6) @gmail.com", "Wrage@ndb-mr3.cc.emory.edu; Lisa Ann " <wrage@rti.org>, "Wally.Carlo@ndb-mr3.cc.emory.edu; M.D." <WCarlo@peds.uab.edu>, "

Subject: First draft of Jackie LeVan's poster for PAS-- bjs comments

Wonderful poster and project

Increase in maternal DM and hypertension is curious-- but should not influence primary outcome.

Below-- some wordsmithing to the Conclusions (in caps):

- Infants 240/7 to 276/7 weeks GA born AT NETWORK CENTERS after release of the results of the SUPPORT had significantly decreased percentages of DR intubation, BPD or death, and ROP or death compared to SIMILAR infants born before the initiation of the SUPPORT at the 11 NRN centers participating in the trial.
- After adjustment for baseline variables, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.
- Percentages of INFANTS WITH BPD, death at 36 weeks, severe ROP, death before discharge, and death or mechanical ventilation at day of life 7, as well as ventilator days, significantly decreased in the post-SUPPORT group.
- These findings SUGGEST THAT THE RESULTS OF THE SUPPORT TRIAL INFLUENCED BOTH CLINICAL PRACTICE AND PATIENT OUTCOMES AT NRN STUDY SITES. MORE BROADLY, OUR FINDINGS support the POTENTIAL impact that the results of a randomized controlled trial MAY have on clinical practice management and patient outcomes.

THANKS

BJS

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From: Finer, Neil
To: Luc Brion; Wrage, Lisa Ann; (b)(6)@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; Lisa Ann " <wrage@rti.org>, " Wally.Carlo@ndb-mr3.cc.emory.edu; Barbara Stoll; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Presentation | LeVan, Changes in Therapy
Date: Thursday, March 28, 2013 11:17:10 AM

Hi Luc
This looks good and so did a similar manuscript!!
Be well
Neil

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, March 27, 2013 6:16 PM
To: Wrage, Lisa Ann; (b)(6)@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; Lisa Ann " <wrage@rti.org>, " Wally.Carlo@ndb-mr3.cc.emory.edu; Finer, Neil; Barbara Stoll; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Lisa;
Thanks for the email.

Here is the revised poster, taking into account the new NICHD logo's , Barbara and Lisa's suggestions.
Luc

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, March 27, 2013 9:16 AM
To: Luc Brion; (b)(6)@gmail.com
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Luc, I notice in the Background section you have: 30% O₂oxygen.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, March 27, 2013 10:12 AM
To: (b)(6)@gmail.com; Wrage, Lisa Ann; archerst@mail.nih.gov
Subject: FW: PAS Presentation | LeVan, Changes in Therapy

Thanks
Luc

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Wednesday, March 27, 2013 8:00 AM
To: Luc Brion
Subject: PAS Presentation | LeVan, Changes in Therapy

Hi Luc,

Here is the poster with the new logo in it.

Stephanie

UT Southwestern Medical Center
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From: Luc Brion
To: Wrage, Lisa Ann; (b)(6)@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; Lisa Ann " <wrage@rti.org>," Wally Carlo@ndb-mr3.cc.emory.edu; M.D." <WCarlo@peds.uab.edu>,"; Barbara Stoll; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Presentation | LeVan, Changes in Therapy
Date: Thursday, March 28, 2013 5:48:51 AM
Attachments: LeVan, Changes in Therapy, 2013-03-27 rev.pptx

Lisa;

Thanks for the email.

Here is the revised poster, taking into account the new NICHD logo's , Barbara and Lisa's suggestions.

Luc

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, March 27, 2013 9:16 AM
To: Luc Brion; doctorlevan@gmail.com
Subject: RE: PAS Presentation | LeVan, Changes in Therapy

Luc, I notice in the Background section you have: 30% O₂ oxygen.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, March 27, 2013 10:12 AM
To: (b)(6)@gmail.com; Wrage, Lisa Ann; archerst@mail.nih.gov
Subject: FW: PAS Presentation | LeVan, Changes in Therapy

Thanks
Luc

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Wednesday, March 27, 2013 8:00 AM
To: Luc Brion
Subject: PAS Presentation | LeVan, Changes in Therapy

Hi Luc,

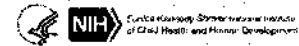
Here is the poster with the new logo in it.

Stephanie

UT Southwestern Medical Center
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NICHD
NEONATAL RESEARCH NETWORK



CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO; Luc P Brion, MD; Lisa A Wrage, MPH; for the NICHD Neonatal Research Network

In the NICHD Neonatal Research Network (NRN) SUPPORT Trial preterm neonates 24 weeks 0 days to 27 weeks 7 days gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) and subsequent limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85-89% or 91-95%.

The interventions did not affect the primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks, with an attempt at withdrawal of supplemental O₂ in those who were receiving < 30% O₂), and death or severe retinopathy of prematurity (ROP). However, randomization to low O₂ saturation targets increased deaths and decreased severe ROP.

We hypothesized that the risk for DR intubation would decrease after dissemination of the results, and that BPD/death and severe ROP/death would not be affected.

- To compare DR intubation, BPD/death at 36 weeks, and severe ROP/death by discharge in time periods before SUPPORT and after its publication
- To determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal intubation in the DR in preterm inborn infants

• Retrospective cohort study using the prospective NRN generic database.

• Inclusion criteria: infants 24 weeks 0 days to 27 weeks 6 days GA born before (1/03-12/04) and after SUPPORT (1/10-12/12) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-12.

• Exclusion criteria: infants with syndromes/major malformations and those receiving comfort care.

• Primary outcome variables: DR intubation, composite of death or BPD at 36 weeks (oxygen requirement at 36 weeks of postmenstrual age), and composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital.

• Total study population of 3,849 infants (1,617 infants in the pre-SUPPORT group and 2,232 in the post-SUPPORT group).

• Baseline characteristics: more antenatal steroid use, maternal hypertension, and maternal diabetes in the Post-SUPPORT group (p value <0.0001).

• Primary outcomes: significantly decreased frequency of DR intubation, death or BPD, and death or ROP in the post-SUPPORT group.

• After adjustment for baseline variables and other variables of interest, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.

• Secondary outcomes: significantly decreased frequencies of BPD, death at 36 weeks, severe ROP, death before discharge, and ventilator days.

• Centers with pre-SUPPORT percent DR intubations > 80% had a significant decrease in the percentage of DR intubations post-SUPPORT (90.2% to 75.1%, p<0.001), while centers with pre-SUPPORT percent DR intubations < 80% did not have a significant decrease (56.6% to 54.3%, p=0.46).

Table 1. Maternal and Neonatal Characteristics

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	P-Value
Birth Weight (g)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Males	858 (53.1)	1126 (50.5)	0.11
Antenatal Steroids	1338/1616 (82.8)	1994/2225 (89.6)	<0.0001
Maternal Hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal Diabetes	42 (2.6)	120/2231 (5.4)	<0.0001

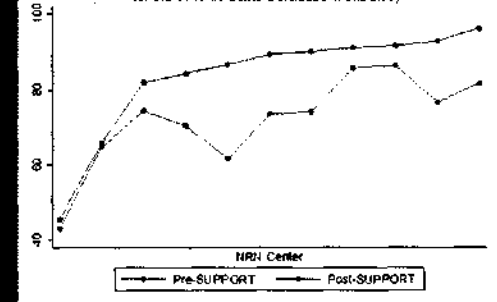
Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	P-Value	Adjusted RR 95% CI	Adjusted P-value
Intubated in DR	1313 (81.2)	1539 (69)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60)	1199/2213 (54.2)	0.0003	1.02 (0.97-1.1)	0.44
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.82 (0.74-0.9)	<0.0001
Death by discharge	358/1614 (22)	393/2196 (17.9)	0.0010	0.85 (0.74-0.95)	0.034

Table 3. Secondary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1943	P-Value
BPD*	664/1311 (50.7)	855/1869 (45.8)	0.0064
Death at 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009
Days on Ventilator (survivors)**	22.3 (24.4)	17.8 (21.3)	<0.0001
Death or Mechanical Ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001

% Delivery Room intubations by Pre/Post SUPPORT Epoch for the 11 NRN Centers included in this study



• Infants 24 weeks 0 days to 27 weeks 6 days GA born at Network Centers after release of the results of the SUPPORT had significantly decreased percentages of DR intubation, BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT at the 11 NRN centers participating in the trial.

• After adjustment for baseline variables, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.

• Percentages of infants with BPD, death at 36 weeks, severe ROP, death before discharge, and death or mechanical ventilation at day of life 7, as well as ventilator days, significantly decreased in the post-SUPPORT group.

• These findings suggest that the results of the SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites.

• More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. Any real or apparent conflicts of interest related to the content of this poster have been resolved. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug.
Acknowledgements: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University; Children's Mercy Hospital/University of Missouri; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Nationwide Children's Hospital/Ohio State University; RPI International; Stanford University; University of Alabama at Birmingham; University of California - Los Angeles; University of New Mexico; University of New Mexico; University of Pennsylvania; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University.

From: Das, Abhik
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Trial - UAB response
Date: Wednesday, March 27, 2013 9:32:27 AM

Wally and Rose:

I am somewhat embarrassed to let you know that I have just been told by RTI's senior legal/risk management folks that, unbeknownst to me or anyone else at RTI working on the NRN, they had a call with the Director of the OHRP Compliance Office, presenting their concerns that RTI was listed on the determination letter that was directed to Dr. Marchase at UAB. It seems that a few days after this call, OHRP re-issued the letter without RTI's name and a copy of the revised letter with a cover letter was sent overnight to RTI explaining that OHRP was re-issuing the letter and why—Dr. Marchase should also have received that notification and revised letter by overnight delivery. Regular mail versions of the re-issued letter have been and are still being delivered to those who were cc'd on the original version. The new re-issued letter is posted on the OHRP website and is a matter of public record now. Clearly, our risk management people were more concerned about protecting RTI than the broader issues concerning the NRN. I again want to emphasize that the RTI risk management and legal team took this action without consulting me or anyone on the project side.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, March 25, 2013 1:21 PM
To: Das, Abhik
Subject: RE: SUPPORT Trial - UAB response

Sure.

Wally

-----Original message-----

From: "Das, Abhik" <adas@rti.org>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Mon, Mar 25, 2013 16:44:54 GMT+00:00
Subject: RE: SUPPORT Trial - UAB response

Great. Is it ok to share this with the RTI officials addressed in the OHRP letter?

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Monday, March 25, 2013 12:38 PM
To: higginsr@mail.nih.gov; Das, Abhik
Subject: FW: SUPPORT Trial - UAB response

Here is the UAB letter.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
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Cell: 205 (b)(6)

From: Jonathan E Miller [<mailto:jonathanm@uab.edu>]
Sent: Friday, March 22, 2013 4:20 PM
To: Wally Carlo, M.D.
Cc: Richard B Marchase; Laretta Gerrity; Ferdinand Urthaler
Subject: FW: SUPPORT Trial - UAB response

Dr. Carlo,
Please see attached for UAB's response to OHRP.

Sincerely,
Jonathan

Jonathan E. Miller, MPPA, CIP
Director, UAB IRB

From: Jonathan E Miller
Sent: Friday, March 22, 2013 4:12 PM
To: Buchanan, Lisa (HHS/OASH)
Cc: Laretta Gerrity; Richard B Marchase; Ferdinand Urthaler
Subject: SUPPORT Trial - UAB response

Ms. Buchanan,
Please find attached UAB's response to OHRP's correspondence dated February 8, 2013 (and subsequent revision dated March 7, 2013). Hard copy original documents have been sent to the address noted on the letter.

Please let me know if you have any questions or if I can be of assistance.

Sincerely,

Jonathan

Jonathan E. Miller, MPPA, CIP

Director, Office of the Institutional Review Board

University of Alabama at Birmingham

205-975-3919

jonathanm@uab.edu

From: Luc Brion
To: Barbara Stoll; Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; "(b)(6)"@gmail.com; "Wrage@ndb-mr3.cc.emory.edu; Lisa Ann " <wrage@rti.org>; "Wally Carlo@ndb-mr3.cc.emory.edu; M.D." <WCarlo@peds.uab.edu>; ""
Subject: RE: First draft of Jackie LeVan's poster for PAS-- bjs comments
Date: Wednesday, March 27, 2013 6:02:05 AM
Attachments: Jackie LeVan_PAS Poster 032613 LPB rev.pptx

Barbara;

Thanks a lot for your comments.

I entered them all into this revised version.

For GA I was unclear if you wanted a change or not; I changed the description closer to the way it is in the SUPPORT NEJM paper.

Stephanie:

Could you please enter the new logos into this poster?

Thanks

Luc

Luc P. Brion, MD

Professor of Pediatrics

Director, Fellowship Training Program in Neonatal-Perinatal
Medicine

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From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Tuesday, March 26, 2013 2:05 PM
To: Luc Brion
Cc: Higgins, Rosemary (NIH/NICHD) [E]; " (b)(6) @gmail.com", " Wrage@ndb-mr3.cc.emory.edu; Lisa Ann " <wrage@rti.org>, " Wally.Carlo@ndb-mr3.cc.emory.edu; M.D." <WCarlo@peds.uab.edu>, ""
Subject: First draft of Jackie LeVan's poster for PAS-- bjs comments

Wonderful poster and project

Increase in maternal DM and hypertension is curious-- but should not influence primary outcome.

Below-- some wordsmithing to the Conclusions (in caps):

- Infants 240/7 to 276/7 weeks GA born AT NETWORK CENTERS after release of the results of the SUPPORT had significantly decreased percentages of DR intubation, BPD or death, and ROP or death compared to SIMILAR infants born before the initiation of the SUPPORT at the 11 NRN centers participating in the trial.
- After adjustment for baseline variables, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.
- Percentages of INFANTS WITH BPD, death at 36 weeks, severe ROP, death before discharge, and death or mechanical ventilation at day of life 7, as well as ventilator days, significantly decreased in the post-SUPPORT group.
- These findings SUGGEST THAT THE RESULTS OF THE SUPPORT TRIAL

INFLUENCED BOTH CLINICAL PRACTICE AND PATIENT OUTCOMES AT NRN STUDY SITES. MORE BROADLY, OUR FINDINGS support the POTENTIAL impact that the results of a randomized controlled trial MAY have on clinical practice management and patient outcomes.

THANKS

BJS

UT Southwestern Medical Center
The future of medicine, today.



NICHD
NEONATAL RESEARCH NETWORK



CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO, Luc P Brion, MD, Lisa A Wrage, MPH, on behalf of the NICHD Neonatal Research Network

Background

In the NICHD Neonatal Research Network (NRN) SUPPORT Trial preterm neonates 24 weeks 0 days to 27 weeks 7 days gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) and subsequent limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85-89% or 91-95%.

The interventions did not affect the primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 26 weeks, with an attempt at withdrawal of supplemental O₂ in those who were receiving < 30% O₂ oxygen), and death or severe retinopathy of prematurity (ROP). However, randomization to low O₂ saturation targets increased deaths and decreased severe ROP.

We hypothesized that the risk for DR intubation would decrease after dissemination of the results, and that BPD/death and severe ROP/death would not be affected.

Objectives

- To compare DR intubation, BPD/death at 36 weeks, and severe ROP/death by discharge in time periods before SUPPORT and after its publication
- To determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal intubation in the DR in preterm (born) infants

Methods

- Retrospective cohort study using the prospective NRN generic database.
- Inclusion criteria: infants 24 weeks 0 days to 27 weeks 6 days GA born before (1/03-12/04) and after SUPPORT (1/10-12/12) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-12.
- Exclusion criteria: infants with syndromes/major malformations and those receiving comfort care.
- Primary outcome variables: DR intubation, composite of death or BPD at 36 weeks (oxygen requirement at 36 weeks of postmenstrual age), and composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital.

Results

- Total study population of 3,849 infants (1,617 infants in the pre-SUPPORT group and 2,232 in the post-SUPPORT group).
- Baseline characteristics: more antenatal steroid use, maternal hypertension, and maternal diabetes in the Post-SUPPORT group (p value <0.0001).
- Primary outcomes: significantly decreased frequency of DR intubation, death or BPD, and death or ROP in the post-SUPPORT group.
- After adjustment for baseline variables and other variables of interest, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.
- Secondary outcomes: significantly decreased frequencies of BPD, death at 36 weeks, severe ROP, death before discharge, and ventilator days.
- Centers with pre-SUPPORT percent DR intubations > 80% had a significant decrease in the percentage of DR intubations post-SUPPORT (90.2% to 75.1%, p<.0001), while centers with pre-SUPPORT percent DR intubations < 80% did not have a significant decrease (56.6% to 54.3%, p=0.46).

Results

Table 1. Maternal and Neonatal Characteristics

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	P-Value
Birth Weight (g)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Males	858 (53.1)	1126 (50.5)	0.11
Antenatal Steroids	1338/1616 (82.8)	1994/2225 (89.6)	<0.0001
Maternal Hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal Diabetes	42 (2.6)	120/2231 (5.4)	<0.0001

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	P-Value	Adjusted RR 95% CI	Adjusted P-Value
Intubated in DR	1313 (81.2)	1539 (69)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60)	1199/2213 (54.2)	0.0003	1.02 (0.97-1.1)	0.44
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.82 (0.74-0.9)	<0.0001
Death by discharge	358/1614 (22)	393/2196 (17.9)	0.0010	0.85 (0.74-0.99)	0.034

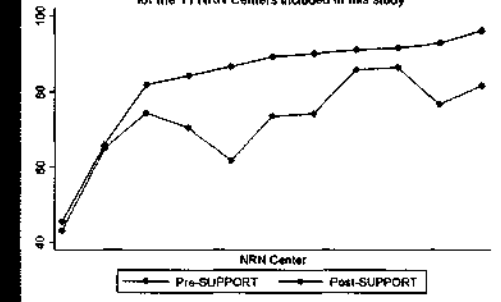
Table 3. Secondary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1943	P-Value
BPD*	664/1311 (50.7)	855/1869 (45.8)	0.0064
Death at 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009
Days on Ventilator (survivors)**	22.3 (24.4)	17.8 (21.3)	<0.0001
Death or Mechanical Ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001

* Number (%); ** Survivors to discharge or 120 days, whichever came first, max 120 days

Results

% Delivery Room Intubations by Pre/Post SUPPORT Epoch for the 11 NRN Centers included in this study



Conclusions

- Infants 24 weeks 0 days to 27 weeks 6 days GA born at Network Centers after release of the results of the SUPPORT had significantly decreased percentages of DR intubation, BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT at the 11 NRN centers participating in the trial.
- After adjustment for baseline variables, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.
- Percentages of infants with BPD, death at 36 weeks, severe ROP, death before discharge, and death or mechanical ventilation at day of life 7, as well as ventilator days, significantly decreased in the post-SUPPORT group.
- These findings suggest that the results of the SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites.
- More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. Any real or apparent conflicts of interest related to the content of this paper have been resolved. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug.
 Acknowledgments: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University; Children's Mercy Hospital/University of Missouri; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Madonwade Children's Hospital/Ohio State University; RTI International; Stanford University; University of Alabama at Birmingham; University of California - Los Angeles; University of Iowa; University of New Mexico; University of Pennsylvania; University of Rochester; University of Texas Southwestern Medical Center; University of Utah Health Science Center at Houston; Wayne State University.

From: Luc Brion
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Jackie LeVan; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PAS Abstracts | Presentation and Poster templates
Date: Wednesday, March 27, 2013 5:04:16 AM
Attachments: Jackie LeVan PAS Poster 032613 LPB rev.pptx

Correction:

This is a revised version that includes Barbara Stoll's edits.

LUC

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www.utsouthwestern.edu (<http://www.utsouthwestern.edu/>)

From: Luc Brion
Sent: Tuesday, March 26, 2013 7:30 PM
To: 'Archer, Stephanie (NIH/NICHD) [E]'
Cc: 'Jackie LeVan'; 'Wrage, Lisa Ann'
Subject: RE: PAS Abstracts | Presentation and Poster templates

Stephanie;

Here is our poster, which I had submitted to Rose yesterday.

Could you please enter the logos

Thanks

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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www.utsouthwestern.edu (<http://www.utsouthwestern.edu/>)

From: Archer, Stephanie (NIH/NICHD) [E] [<mailto:archerst@mail.nih.gov>]

Sent: Tuesday, March 26, 2013 1:04 PM

To: 'Namasivayam Ambalavanan (nambalayanan@peds.uab.edu)'; Roy Heyne; 'Lilia DeJesus'; 'Sara DeMauro'; 'Brenda Poindexter'; 'Bill Truog'; 'Ricki Goldstein'; 'Kurt Schibler'; 'Ravi Patel'; 'Hussnain Mirza'; 'Yvonne Vaucher'; 'Athina Pappas'; 'Seetha Shankaran'; 'Girija Natarajan'; 'John Dagle'; 'Erin Clark'; 'Courtney Thornburg'; 'Mike Cotten'; Luc Brion; 'Ariel Salas'; 'Tim Stevens (Timothy_Stevens@URMC.Rochester.edu)'; 'Weissman, Scott'
Cc: 'Roger Faix (roger.faix@hsc.utah.edu)'; Luc Brion; 'Meg Cunningham (mcunningham@rti.org)'; 'Betty Vohr (bvohr@wihri.org)'; 'Abbot Laptook (alaptook@wihri.org)'; 'Abhik Das (adas@rti.org)'; 'Amanda Lewis-Evans (alewis@rti.org)'; 'Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)'; 'Barbara Schmidt (barbara.schmidt@uphs.upenn.edu)'; 'Barbara Stoll (barbara_stoll@oz.ped.emory.edu)'; 'Beena Sood (bsood@med.wayne.edu)'; 'Brenda Poindexter (bpoindex@iupui.edu)'; 'Carl D'Angio (carl_dangio@umc.rochester.edu)'; 'Carolyn Petrie Huitema (petrie@rti.org)'; 'Cheri Gaudin (cagauldin@cmh.edu)'; 'David P. Carlton (dpcarl@emory.edu)'; 'David Stevenson (dstevenson@stanford.edu)'; 'Dennis Wallace (dwallace@rti.org)'; 'Edward Bell (edward-bell@uiowa.edu)'; 'Greg Sokol (gsokol@iupui.edu)'; 'Haresh Kirpalani (KIRPALANI@email.chop.edu)'; 'Jenna Gabrio (jgabrio@rti.org)'; 'Jon Tyson (Jon.E.Tyson@uth.tmc.edu)'; 'Kathleen Kennedy (Kathleen.A.Kennedy@uth.tmc.edu)'; 'Ken Poole (kpo@rti.org)'; 'Krisa P. Van Meurs (vanmeurs@stanford.edu)'; 'Kristi Watterberg (kwatterberg@salud.unm.edu)'; 'Kristie Smith (KSmith@mednet.ucla.edu)'; 'Kristin Zaterka-Baxter (kzaterka@rti.org)'; 'Kurt Schibler (kurt.schibler@cchmc.org)'; 'Leif Nelin (Leif.Nelin@nationwidechildrens.org)'; 'Luc Brion'; 'Martin Keszler (mkeszler@wihri.org)'; 'Meg Cunningham (mcunningham@rti.org)'; 'Michele C. Walsh (mcw3@cwru.edu)'; 'Mike Cotten (cotte010@mc.duke.edu)'; 'Namasivayam Ambalavanan (nambalayanan@peds.uab.edu)'; 'Pablo Sanchez'; 'Richard Polin (rap32@mail.cumc.columbia.edu)'; 'Robin Ohls (rohls@salud.unm.edu)'; 'Ron Goldberg (goldb008@mc.duke.edu)'; 'Ronnie Guillet (ronnie_guillet@umc.rochester.edu)'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Satyan Lakshminrusimha (slakshmi@buffalo.edu)'; 'Seetha Shankaran (sshankar@med.wayne.edu)'; 'Suhas Kallapur (suhas.kallapur@cchmc.org)'; 'Uday Devaskar (udevaskar@mednet.ucla.edu)'; 'Wally Carlo (wcarlo@peds.uab.edu)'; 'William Truog (wtruog@cmh.edu)'
Subject: RE: PAS Abstracts | Presentation and Poster templates

NIH has redesigned its logo (and replaced all of the IC logos). I have revised the PAS presentation and poster templates to include the new logo. The updated templates have been posted on the website at:

Presentation Templates

[Instructions for NRN Templates](#)

[NRN Poster Template](#)

[NRN Presentation Template](#)

If you have already started creating your presentations/posters, I can add the new logo after you have a final draft. Just send your file to me.

As a reminder, **All final presentations/posters need to go through NICHD Clearance. Please send electronic files of your materials to Rose and I by April 15th.**

Thank you,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
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Rockville, MD 20852

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Fax 301-496-3790
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From: Archer, Stephanie (NIH/NICHD) [E]

Sent: Wednesday, February 13, 2013 4:21 PM

To: Namasivayam Ambalavanan (nambalayanan@peds.uab.edu); 'Roy Heyne'; 'Lilia DeJesus'; 'Sara DeMauro'; 'Brenda Poindexter'; 'Bill Truog'; 'Ricki Goldstein'; 'Kurt Schibler'; 'Ravi Patel'; 'Hussnain Mirza'; 'Yvonne Vaucher'; 'Athina Pappas'; 'Seetha Shankaran'; 'Girija Natarajan'; 'John Dagle'; 'Erin Clark'; 'Courtney Thornburg'; 'Mike Cotten'; Luc Brion (luc.brion@utsouthwestern.edu); 'Ariel Salas'; 'Tim Stevens (Timothy_Stevens@URMC.Rochester.edu)'; 'Weissman, Scott'
Cc: 'Roger Faix (roger.faix@hsc.utah.edu)'; Luc Brion (luc.brion@utsouthwestern.edu); 'Meg Cunningham (mcunningham@rti.org)'; 'Betty Vohr (bvohr@wihri.org)'; 'Abbot Laptook (alaptook@wihri.org)'; 'Abhik Das (adas@rti.org)'; 'Amanda Lewis-Evans (alewis@rti.org)'; 'Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)'; 'Barbara Schmidt (barbara.schmidt@uphs.upenn.edu)'; 'Barbara Stoll (barbara_stoll@oz.ped.emory.edu)'; 'Beena Sood (bsood@med.wayne.edu)'; 'Brenda Poindexter (bpoindex@iupui.edu)'; 'Carl D'Angio (carl_dangio@umc.rochester.edu)'; 'Carolyn Petrie Huitema (petrie@rti.org)'; 'Cheri Gaudin (cagauldin@cmh.edu)'; 'David P. Carlton (dpcarl@emory.edu)'; 'David Stevenson (dstevenson@stanford.edu)'; 'Dennis Wallace (dwallace@rti.org)'; 'Edward Bell

(edward-bell@uiowa.edu); Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANI@email.chop.edu); Jenna Gabrio (jgabrio@rti.org); Jon Tyson (Jon.E.Tyson@uth.tmc.edu); Kathleen Kennedy (Kathleen.A.Kennedy@uth.tmc.edu); Ken Poole (kpoole@rti.org); Krisa P. Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kristie Smith (KSmiley@mednet.ucla.edu); Kristin Zaterka-Baxter (kzaterka@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Leif Nelin (Leif.Nelin@nationwidechildrens.org); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); Meg Cunningham (mcunningham@rti.org); Michele C. Walsh (mcw3@cwru.edu); Mike Cotten (cotte010@mc.duke.edu); Namasivayam Ambalavanan (nambalavanan@peds.uab.edu); Pablo Sanchez (Pablo.Sanchez@UTSouthwestern.edu); Richard Polin (rap32@mail.cumc.columbia.edu); Robin Ohls (rohls@salud.unm.edu); Ron Goldberg (goldb008@mc.duke.edu); Ronnie Guillet (ronnie.guillet@urmc.rochester.edu); Rose Higgins (higginsr@mail.nih.gov); Satyan Lakshminrusimha (slakshmi@buffalo.edu); Seetha Shankaran (sshankar@med.wayne.edu); Suhas Kallapur (suhas.kallapur@cchmc.org); Uday Devaskar (udevaskar@mednet.ucla.edu); Wally Carlo (wcarlo@peds.uab.edu); William Truog (wtruog@cmh.edu)

Subject: PAS Abstracts | Presentation and Poster templates

Congratulations on having your abstracts accepted for PAS!

Below is the list of accepted abstracts. Meg is pulling together the schedule for the various platform and poster sessions.

NRN PowerPoint presentation and poster templates are available on the private website: <https://neonatal.rti.org/index.cfm?fuseaction=administration.publications>

Please let me know if you have any trouble accessing or using them. If you do not have a password for the private website, please contact your center's coordinator.

All final presentations/posters need to go through NICHD Clearance. Please send electronic files of your materials to Rose and I by April 15th.

Ambalavanan N; Cotten CM; Carlo WA; Murray J; Mariani T; Page G	Analysis of Biological Pathways Associated with Bronchopulmonary Dysplasia in a Genome-wide Study
Clark, Erin; Faix RG; Varner M; Esplin MS	Early Preterm Birth: Genetic Predisposition to Adverse Neurodevelopmental Outcome
Cotten CM; Page G; DeAngelis M; Hartnett ME; and Genomics Subcommittee	Candidate Gene Study of Retinopathy of Prematurity in Extremely Low Birthweight Infants
Dagle, John M.; Colaizy TT; Bell EF; Murray JC	Genetic Variants Associated with Patent Ductus Arteriosus in Extremely Low Birthweight Infants
De Jesus I; Sood BG; Shankaran S; Das A; Bell EF; Stoll BJ; Laptook AR; Walsh MC; Hale EC; Newman N; Bara R; Higgins RD for the Neonatal Research Network	Acute Cardiorespiratory Effects of Antenatal Magnesium Sulfate in Preterm Infants <29 weeks Gestation
DeMauro SB; D'Agostino JA; Kirpalani H	Outcomes of Very Low Birth Weight Infants with Tracheostomies
Goldstein RF; Cotten CM	Apolipoprotein E, Intraventricular Hemorrhage (IVH) and Recovery in Extremely Low Birthweight (ELBW) Infants
Heyne RJ	Bayley III Motor Composite Score Threshold for Neurodevelopmental Impairment
LeVan J; Brion LP; Wrage LA; for the NICHD Neonatal Research Network	Changes in Therapy and Outcomes Associated with the SUPPORT Trial
Mirza, Hussnain; Oh W; Vohr BR; Laptook Ar; Stonestreet B; the GDB Subcommittee	Indomethacin Prophylaxis (IP) for Intraventricular Hemorrhage (IVH) in Extremely Low Birth Weight Infants: Effects of Time of Administration
Mourani, Peter; Rose, Rebecca; Cotten CM; Page G; Higgins RD; Ingram, David; Abman, Steven; Poindexter BB	Candidate Genes Associated with BPD in ELBW Infants
Natarajan G; Shankaran S; Pappas A; Bann CM; for the Extended Hypothermia Subcommittee of the Neonatal Research Network	Association between Parental perception of Functional Status (FS) and Impact on the family (IOF) in neonatal hypoxic-ischemic encephalopathy (HIE) and childhood disability
Pappas A; Carlo WA; Shankaran S	Cytokines and Outcome in Hypothermia for HIE
Patel, Ravi M.; Stoll BJ; Hale EC; and the GDB Subcommittee	Cause and Timing of Mortality in Extremely Preterm Infants from 2000 to 2011
Poindexter BB; Hintz SR; Ehrenkranz RA	Have We Caught Up? Growth and Neurodevelopmental Outcomes in ELBW Infants
Salas AA; Ambalavanan N; Das A; Carlo WA	Birth weight or gestational age: which is better as baseline indicator of risk in preterm infants?
Schibler KR; Page G; Cotten CM; for the NICHD Neonatal Research Network	Candidate Genes Associated with Necrotizing Enterocolitis in Extremely Low Birthweight Infants

Shankaran S; Luptook AR; McDonald SA; Hintz SR; Barnes P; Das A; Higgins RD	Perinatal Sentinel Events, Brain Injury Pattern and Outcome in Infants Undergoing a Trial of Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy (HIE)
Stevens T	Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial
Thornburg, Courtney; Page G; for the NICHD Neonatal Research Network	Variants in Thrombotic Factor Genes and Brain Injury in Premature Infants
Truog W; Nelin L	Inhaled Nitric Oxide Usage in Preterm Infants in the NICHD Neonatal Research Network Generic Database: Changing Use Pattern and Any Evidence of Efficacy?
Vaucher YE; Hintz SR; Rich W	Antenatal Enrollment in Clinical Trials: Is Neurodevelopmental Outcome Representative?
Weissman, Scott J.; Hansen NJ; Petrie-Huitema C; Zaterka-Baxter KM; Higgins RD; Stoll BJ; for the NICHD Neonatal Research Network	Emergence of antibiotic resistance-associated clones among Escherichia coli isolates from early-onset sepsis and meningitis in the United States, 2008-2009

Stephanie

Stephanie Wilson Archer
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
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From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; (b)(6) @gmail.com; Wrape, Lisa Ann; Wally Carlo, M.D.; "Barbara Stoll"; "infiner@ucsd.edu"
Subject: First draft of Jackie LeVan's poster for PAS
Date: Tuesday, March 26, 2013 5:16:03 AM
Attachments: Jackie LeVan PAS Poster 032513 LPB rev.pptx

Here is the first draft of Jackie LeVan's poster for PAS.

This draft includes data up to December 2012, which have just been available.

The poster was prepared by Jackie and edited by Lisa and me.

Please review and comment.

Thanks in advance,

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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NICHD
NEONATAL RESEARCH NETWORK



CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO, Luc P Brion, MD, Lisa A Wrage, MPH, on behalf of the NICHD Neonatal Research Network

Background

In the NICHD Neonatal Research Network (NRN) SUPPORT Trial preterm neonates 24-27^{6/7} weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) and subsequent limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85-89% or 91-95%.

The interventions did not affect the primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks, with an attempt at withdrawal of supplemental O₂ in those who were receiving < 30% O₂ oxygen), and death or severe retinopathy of prematurity (ROP). However, randomization to low O₂ saturation targets increased deaths and decreased severe ROP.

We hypothesized that the risk for DR intubation would decrease after dissemination of the results, and that BPD/death and severe ROP/death would not be affected.

Objectives

- To compare DR intubation, BPD/death at 36 weeks, and severe ROP/death by discharge in time periods before SUPPORT and after its publication

- To determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal intubation in the DR in preterm inborn infants

Methods

- Retrospective cohort study using the prospective NRN generic database.

- Inclusion criteria: infants 24-27 6/7 weeks GA born before (1/03-12/04) and after SUPPORT (1/10-12/12) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-12.
- Exclusion criteria: infants with syndromes/major malformations and those receiving comfort care.

- Primary outcome variables: DR intubation, composite of death or BPD at 36 weeks (oxygen requirement at 36 weeks of postmenstrual age), and composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital.

Results

- Total study population of 3,849 infants (1,617 infants in the pre-SUPPORT group and 2,232 in the post-SUPPORT group).
- Baseline characteristics: more antenatal steroid use, maternal hypertension, and maternal diabetes in the Post-SUPPORT group (p value <0.0001).
- Primary outcomes: significantly decreased frequency of DR intubation, death or BPD, and death or ROP in the post-SUPPORT group.
- After adjustment for baseline variables and other variables of interest, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.
- Secondary outcomes: significantly decreased frequencies of BPD, death at 36 weeks, severe ROP, death before discharge, and ventilator days.
- Centers with pre-SUPPORT percent DR intubations > 80% had a significant decrease in the percentage of DR intubations post-SUPPORT (80.2% to 75.1%, p<.0001), while centers with pre-SUPPORT percent DR intubations < 80% did not have a significant decrease (56.6% to 54.3%, p=0.46).

Results

Table 1. Maternal and Neonatal Characteristics

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	P Value
Birth Weight (g)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Males	858 (53.1)	1126 (50.5)	0.11
Antenatal Steroids	1338/1616 (82.8)	1994/2225 (89.6)	<0.0001
Maternal Hypertension	322 (19.9)	630/2230 (27.4)	<0.0001
Maternal Diabetes	42 (2.6)	120/2231 (5.4)	<0.0001

Table 2. Primary Outcomes

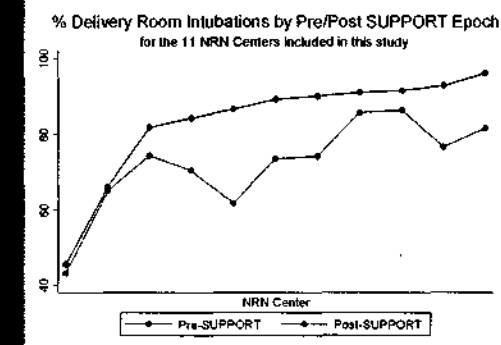
Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value	Adjusted RR 95% CI	Adjusted P-Value
Intubated in DR	1313 (81.2)	1539 (69)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60)	1189/2213 (54.2)	0.0003	1.02 (0.97-1.1)	0.44
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.82 (0.74-0.9)	<0.0001
Death by discharge	358/1614 (22)	393/2196 (17.9)	0.0010	0.85 (0.74-0.99)	0.034

Table 3. Secondary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1943	P-Value
BPD*	664/1311 (50.7)	855/1869 (45.8)	0.0064
Death at 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009
Days on Ventilator (survivors)**	22.3 (24.4)	17.8 (21.3)	<0.0001
Death or Mechanical Ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001

* Number (%); ** Survivors to discharge or 120 days, whichever came first, max 120 days

Results



Conclusions

- Infants 24^{6/7} to 27^{6/7} weeks GA born after release of the results of the SUPPORT had significantly decreased percentages of DR intubation, BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT at the 11 NRN centers participating in the trial.

- After adjustment for baseline variables, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.

- Percentages of BPD, death at 36 weeks, severe ROP, death before discharge, and death or mechanical ventilation at day of life 7, as well as ventilator days, significantly decreased in the post-SUPPORT group.

- These findings support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. Any real or apparent conflicts of interest related to the content of this poster have been resolved. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug.
Acknowledgments: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University; Children's Mercy Hospital/University of Missouri; Cleveland Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Nationwide Children's Hospital/Ohio State University; RTI International; Stanford University; University of Alabama at Birmingham; University of California - Los Angeles; University of Iowa; University of New Mexico; University of Pennsylvania; University of Rochester; University of Texas Southwestern Medical Center; University of Utah Health Science Center at Hogle; Wayne State University.

Blansfield, Earl (NIH/NICHD) [E]

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Monday, March 25, 2013 12:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: FW: SUPPORT Trial - UAB response
Attachments: 3271_001.pdf

Here is the UAB letter.

Wally

Wally Carlo, M.D.
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From: Jonathan E Miller [<mailto:jonathanm@uab.edu>]
Sent: Friday, March 22, 2013 4:20 PM
To: Wally Carlo, M.D.
Cc: Richard B Marchase; Laretta Gerrity; Ferdinand Urthaler
Subject: FW: SUPPORT Trial - UAB response

Dr. Carlo,
Please see attached for UAB's response to OHRP.

Sincerely,
Jonathan

Jonathan E. Miller, MPPA, CIP
Director, UAB IRB

From: Jonathan E Miller
Sent: Friday, March 22, 2013 4:12 PM
To: Buchanan, Lisa (HHS/OASH)
Cc: Laretta Gerrity; Richard B Marchase; Ferdinand Urthaler
Subject: SUPPORT Trial - UAB response

Ms. Buchanan,
Please find attached UAB's response to OHRP's correspondence dated February 8, 2013 (and subsequent revision dated March 7, 2013). Hard copy original documents have been sent to the address noted on the letter.

Please let me know if you have any questions or if I can be of assistance.

Sincerely,

Jonathan

Jonathan E. Miller, MPPA, CIP

Director, Office of the Institutional Review Board

University of Alabama at Birmingham

205-975-3919

jonathanm@uab.edu



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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Page 2 of 2

Lisa R. Buchanan – OHRP

March 22, 2013

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,



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

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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, breastfeeding 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 Betasan, Enapror, and Ditserin. 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 waiver 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: _____

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

<input type="checkbox"/> HSP	<input type="checkbox"/> Sponsor Protocol (date) _____	
<input type="checkbox"/> PORF or CTCR	<input type="checkbox"/> Titles Match - <input type="checkbox"/> Grant/Sponsor Protocol <input type="checkbox"/> HSP <input type="checkbox"/> ICF	
<input type="checkbox"/> 1572	<input type="checkbox"/> IB, Package Insert, or Device Manual _____	
<input type="checkbox"/> Waiver of IC	<input type="checkbox"/> Waiver of Auth & IC <input type="checkbox"/> Waiver of IC Documentation	
<input type="checkbox"/> Consent/Assent Form(s) # _____	<input type="checkbox"/> Sponsor Sample CF <input type="checkbox"/> 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	

<input type="checkbox"/> Pharmacy Release	<input type="checkbox"/> TKC, notif attached - Y N
<input type="checkbox"/> Radiation Safety Approval	<input type="checkbox"/> UH, notif attached - Y N
<input type="checkbox"/> Infection Control Approval	<input type="checkbox"/> UAB Highlands, notif attached - Y N
<input type="checkbox"/> Pathology Release	<input type="checkbox"/> TCHA, notif attached - Y N
<input type="checkbox"/> IBC Approval	<input type="checkbox"/> EFH, notif attached - Y N
<input type="checkbox"/> CIRB Conflict Identified	<input type="checkbox"/> CRU, notification attached - Y N
<input type="checkbox"/> Include CIRB Language	<input type="checkbox"/> Other UAB sites _____
<input type="checkbox"/> FERPA Applies	<input type="checkbox"/> Non UAB sites _____
<input type="checkbox"/> PPRA Applies	

Engaged in Research: Y N If yes, IRB approvals Y N

<input type="checkbox"/> Children - CRL# _____	<input type="checkbox"/> Pregnant Women & Fetuses	<input type="checkbox"/> Nonviable or UV Neonates	<input type="checkbox"/> Decisionally Impaired
<input type="checkbox"/> Prisoners - Cat# _____	<input type="checkbox"/> Student/Employees	<input type="checkbox"/> Non-English Speakers	
<input type="checkbox"/> Recruitment Materials _____		<input type="checkbox"/> Partial Waiver of Authorization	
<input type="checkbox"/> SAE Log submitted. Date/numbers _____		<input type="checkbox"/> Screening Script/Questionnaire	
<input type="checkbox"/> 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.

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: OHRP Determination Letters for NICHD NRN SUPPORT trial
Date: Friday, March 22, 2013 9:44:03 AM

Is Wally planning to share that letter with the NRN? If so, can it be shared with the DSMC?

Thanks

Abhik

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 22, 2013 9:43 AM
To: Das, Abhik
Subject: RE: FW: OHRP Determination Letters for NICHD NRN SUPPORT trial

The current plan for Alabama to respond to the letter as requested by OHRP

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, March 22, 2013 9:41 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: FW: OHRP Determination Letters for NICHD NRN SUPPORT trial

What do you think I should tell her?

Thanks

Abhik

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

From: Christine A. Gleason [mailto:cgleason@u.washington.edu]
Sent: Friday, March 22, 2013 2:56 AM
To: Das, Abhik
Subject: Re: FW: OHRP Determination Letters for NICHD NRN SUPPORT trial

I don't have any comments about this issue. But, have there been any updates on it since our conference call?

On Wed, 20 Mar 2013, Das, Abhik wrote:

>

> Hello All:

>
>
>

> Please let me know if you have any comments about this issue or want to discuss any further.

>
>
>

> Thanks

>
>
>

> Abhik

>
>
>

> From: Das, Abhik

> Sent: Wednesday, February 27, 2013 9:46 AM

> To: Christine A. Gleason (cgleason@u.washington.edu); Marian Willinger

> (willingm@mail.nih.gov); Marilee C. Allen, MD; Menachem Miodovnik;

> Michael O'Shea; Robert Boyle (RJB6J@hscmail.mcc.virginia.edu); Steven

> Weiner (Weiner@Biostat.bsc.gwu.edu); Traci Clemons

> (telemons@emmes.com)

> Cc: Zaterka-Baxter, Kristin; Cunningham, Meg; Wallace, Dennis;

> Higgins, Rosemary (NIH/NICHD) [E]

> Subject: FW: OHRP Determination Letters

>
>
>

> Hello members of the Neonatal Research Network DSMC:

>
>
>

> Sorry for the last minute email. Pursuant to some complaint that the

> federal Office of Human Research Protection (OHRP) received, they have

> recently issued a determination letter related to the SUPPORT trial conducted by the network (see link below).

While a response is being formulated by the investigators, we wanted to let you know that this is going on, and if you like, we can discuss at the end of the call today if there is time.

>
>
>

> http://www.hhs.gov/ohrp/detrm_letters/YR13/feb13a.pdf

>
>
>

> Thanks a lot

>
>
>

> Abhik

>
>
>

>
>

> Abhik Das, Ph.D.

> Senior Research Statistician

>

- > RTI International
- > 6110 Executive Blvd., Suite 902
- > Rockville, MD 20852-3903
- > e-mail: adas@rti.org
- > Phone: 301-770-8214
- > Fax: 301-230-4646

- >
- >
- >
- >
- >

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Poindexter, Brenda B"
Cc: "waldemer carlo"
Subject: RE: DHSS letter re. research protections violations (IUSM subcontract)
Date: Wednesday, March 20, 2013 4:58:00 PM

I do not have a copy

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Poindexter, Brenda B [mailto:bpoindex@iu.edu]
Sent: Wednesday, March 20, 2013 9:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: waldemer carlo
Subject: FW: DHSS letter re. research protections violations (IUSM subcontract)

Rose,

I just received this from our IRB. Thankfully I am on the Executive Committee. I thought this sounded like a very reasonable approach. Do we have a copy of the response letter to OHRP from UAB? It would be nice if I could also share that with the Executive Committee. I'm copying Wally so that he is in the loop as well.

Brenda

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

From: Axe, Shawn L
Sent: Wednesday, March 20, 2013 8:46 AM
To: Poindexter, Brenda B
Subject: RE: DHSS letter re. research protections violations (IUSM subcontract)

Hi Dr. Poindexter,

I consulted with the Compliance Office and they agreed that no formal response to this letter is indicated. However, they suggested the IRB Executive Committee be apprised of the letter and circumstances. Would you be willing to present the information at the next meeting of the Executive Committee? It's scheduled for April 10 at 7:30 am.
Thank you,
Shawn

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

From: Poindexter, Brenda B
Sent: Tuesday, February 19, 2013 8:28 AM
To: Axe, Shawn L

Subject: Re: DHSS letter re. research protections violations (IUSM subcontract)

I have a little more info - is there a time this afternoon that I can give you a call?

Sent from my iPhone

On Feb 18, 2013, at 3:59 PM, "Axe, Shawn L" <saxe@iu.edu> wrote:

> Hi,
> Dr. Jose received the attached correspondence from OHRP today about the SUPPORT trial.
> Could one of you give me a call when you have a few minutes?
> Thank you,
> Shawn
>
> Shawn Axe, CIP
> Associate Director - Team 1
> IU Human Subjects Office
> Office of Research Administration
> Indiana University
> 980 Indiana Avenue | Lockefield Room 3322
> Indianapolis, IN 46202
> (317) 278-9211
> <mailto:saxe@iu.edu>
>
>
> <CopyMachineGreg@indiana.edu_20130218_110939.pdf>

From: [McGowan, Elisabeth C](#)
To: [Susan Hintz](#)
Cc: [Betty Vohr](#); [Newman, Jamie](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]
Subject: RE: April NRN meeting
Date: Monday, March 11, 2013 8:55:11 PM

Ok, once we know exact time I will pass along to Cecelia and Karen. Jamie, if you could just email me specifics on calling in, that would be great.

See you at PAS

Liz

PS Can't believe I am actually doing this, but (b)(6) Oh boy.....

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Monday, March 11, 2013 8:47 PM
To: McGowan, Elisabeth C
Cc: Betty Vohr; Newman, Jamie; higgins Higgins
Subject: Re: April NRN meeting

Hi Liz,

Thanks for the heads up. The psychologists will not be at the meeting, and we have been primarily dealing with psychology related issues with technical memos and updates. The follow up coordinators are not required to attend the April meeting, but they are of course welcome. The update at the meeting will be focused on logistics of the SUPPORT NEURO school age visits, certifications schedule, reminder of issues that have come up thus far with changes in forms/manual clarifications, discussions of plans for cross checks, and some of the major issues related to neuro exam and MABC exam problems (which have been detailed in a MABC q and a or "FAQ" type of memo.

I think the plan of having Cecelia conference in by phone (which Karen if she is available) would be great - I know that capability will be available at the meeting.

(b)(6)

Susan

On Mar 11, 2013, at 3:37 PM, "McGowan, Elisabeth C" <emcgowan@tuftsmedicalcenter.org> wrote:

Hi Betty & Susan,

Sorry to say that I'm going to be (b)(6) so won't be able to make it to the meeting. I'm not sure if the agenda was finalized regarding SUPPORT Neuro School Age discussions. Cecelia Sibley can be reachable by phone to be conferenced in for any M ABC II questions, and our coordinator Karen Murray can also be available with Cecelia – for the remainder of logistical concerns.

Would that be okay with everyone ? Does our psychologist need to be available as well ?

Liz

Elisabeth C. McGowan, MD
Director NICU Follow Up Program
Assistant Professor, Division of Newborn Medicine
Floating Hospital for Children
800 Washington Street, Box 044
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From: Kennedy, Kathleen A
To: [Finer, Neil](mailto:Finer_Neil); [Wrage, Lisa Ann \(wrage@rti.org\)](mailto:Wrage_LisaAnn@rti.org); dale_phelps@urmc.rochester.edu; [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins_Rosemary@NIH/NICHD); wcarlo@peds.uab.edu; [Das, Abhik](mailto:Das_Abhik); Roger.Faix@hsc.utah.edu; [Gantz, Marie](mailto:Gantz_Marie); alaptook@WIHRI.org; nxs5@cwru.edu; [Rich, Wade](mailto:Rich_Wade); kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer_Stephanie@NIH/NICHD)
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)
Date: Monday, March 11, 2013 1:08:54 PM

This was my previous response to the suggestion about surgery:

"I've been scratching my head about how to address the question about progression and surgery. I looked at the GDB forms and I don't think we record the date of PDA surgery. There is a date recorded for first episode of NEC and it's coded as medical vs surgical NEC but that's not exactly the same as recording the date of NEC surgery. Even if we had that date, and we could look at progression of ROP before and after NEC surgery, I don't know what we would compare it to. Are you seeing a way to do this that I'm not seeing?"

If we wanted to pursue this, I think we'd have to go back into the charts for the dates of surgery and ROP exams before and after surgery. That seems beyond the scope of this paper to me.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: [Finer, Neil \[mailto:nfiner@ucsd.edu\]](mailto:Finer_Neil)
Sent: Monday, March 11, 2013 11:46 AM
To: Kennedy, Kathleen A; [Wrage, Lisa Ann \(wrage@rti.org\)](mailto:Wrage_LisaAnn@rti.org); dale_phelps@urmc.rochester.edu; [Higgins, Rosemary \(NIH/NICHD\)](mailto:Higgins_Rosemary@NIH/NICHD); wcarlo@peds.uab.edu; [Das, Abhik](mailto:Das_Abhik); Roger.Faix@hsc.utah.edu; [Gantz, Marie](mailto:Gantz_Marie); alaptook@WIHRI.org; nxs5@cwru.edu; [Rich, Wade](mailto:Rich_Wade); kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Archer, Stephanie
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)

Hi Kathleen

This is a great paper, well written and full of information

I believe that I previously asked the following – but pardon my memory – Where you able to determine if later surgery – ie Hernia repair, ostomy closure etc was associated with more rapid progression of ROP

We have seen this repeatedly in infants we are preparing for discharge and following the surgery, the ROP at next exam is often worse.

Was this data available to be looked at?

Overall a great contribution

Thanks

Neil

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]

Sent: Friday, March 08, 2013 12:48 PM

To: Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; Finer, Neil; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; Rich, Wade; kurt.schibler@cchmc.org; Michele.Waish@UHhospitals.org; Bradley.Yoder@hsc.utah.edu

Cc: Archer, Stephanie

Subject: Onset of ROP Observational Study (SUPPORT Secondary)

I've attached what I hope is a final draft of the ROP Secondary Study. Thanks to those of you who submitted comments on the prior draft; it's been revised accordingly. This has now cleared all the administrative hurdles. If you have any additional suggestions, please send them to me by Monday March 18. I plan to submit it to Pediatrics on Tuesday March 19. Thanks again for your help on this.

Kathleen A. Kennedy, MD, MPH
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713 500-6708

From: [Gantz, Marie](#)
To: [Kennedy, Kathleen A](#); [Wrage, Lisa Ann](#); [dale_phelps@urmc.rochester.edu](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [wcarlo@peds.uab.edu](#); [Das, Abhik](#); [Roger.Faix@hsc.utah.edu](#); [nfiner@ucsd.edu](#); [alaptook@WIHRI.org](#); [nxs5@cwru.edu](#); [wrch@ucsd.edu](#); [kurt.schibler@cchmc.org](#); [Michele.Walsh@UHhospitals.org](#); [Bradley.Yoder@hsc.utah.edu](#)
Cc: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)
Date: Monday, March 11, 2013 12:25:59 PM
Attachments: ROP Natural History Study Manuscript (for submission without figures)_MG.doc

Nice job. A few comments are in the attached.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-547-5110

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Friday, March 08, 2013 3:48 PM
To: [Wrage, Lisa Ann](#); [dale_phelps@urmc.rochester.edu](#); [Higgins, Rosemary \(NIH/NICHD\)](#); [wcarlo@peds.uab.edu](#); [Das, Abhik](#); [Roger.Faix@hsc.utah.edu](#); [nfiner@ucsd.edu](#); [Gantz, Marie](#); [alaptook@WIHRI.org](#); [nxs5@cwru.edu](#); [wrch@ucsd.edu](#); [kurt.schibler@cchmc.org](#); [Michele.Walsh@UHhospitals.org](#); [Bradley.Yoder@hsc.utah.edu](#)
Cc: Archer, Stephanie
Subject: Onset of ROP Observational Study (SUPPORT Secondary)

I've attached what I hope is a final draft of the ROP Secondary Study. Thanks to those of you who submitted comments on the prior draft; it's been revised accordingly. This has now cleared all the administrative hurdles. If you have any additional suggestions, please send them to me by Monday March 18. I plan to submit it to Pediatrics on Tuesday March 19. Thanks again for your help on this.

Kathleen A. Kennedy, MD, MPH
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Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy, MD MPH¹; Lisa A. Wrage, MPH²; Rosemary D. Higgins, MD³ Neil N. Finer, MD⁴; Waldemar A. Carlo, MD⁵; Michele C. Walsh, MD MS⁶; Abbot R. Lupton, MD⁷; Roger G. Faix, MD⁸; Bradley A. Yoder, MD⁸; Kurt Schibler, MD⁹; Marie G. Gantz, PhD²; Abhik Das, PhD¹⁰; Nancy S. Newman, RN⁶; Wade Rich, RRT⁴; Dale L. Phelps, MD¹¹; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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³ *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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⁵ Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

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¹⁰ RTI International, Rockville, MD

¹¹ Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

Address correspondence to:

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Short title: Retinopathy of Prematurity Screening Criteria

Abbreviations:

ELBW – extremely low birth weight (<1000 g birth weight)
GA – gestational age
PMA – postmenstrual age
ROP – retinopathy of prematurity
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

Keywords: retinopathy of prematurity, screening, extremely premature infant

Funding source: The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT trial.

Financial disclosure: nothing to disclose

Conflict of interest: none

What's Known on this Subject

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Because earlier treatment is now recommended, updated information regarding the timing of onset of ROP is needed.

What This Study Adds

Our data support the timing of examinations in the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth. Ten percent of severe ROP cases occurred after discharge; close follow-up is important for infants who remain at risk after discharge.

Contributor's Statement:

Below we detail the contributions made by each author for this manuscript. The following authors have made significant contributions as determined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

Kathleen A. Kennedy, MD MPH is the principal investigator. She conceptualized and designed the observational study. As the site PI at the University of Texas Medical School at Houston, she oversaw recruitment and follow-up at this site which enrolled 85 infants in the trial. Dr. Kennedy drafted the initial manuscript, revised the manuscript, and approved the final manuscript as submitted.

Lisa A. Wrage, MPH served as the primary statistician for the observational study. She performed the analyses, prepared the data tables and figures, provided critical revision of the manuscript, and approved the final manuscript as submitted.

Rosemary D. Higgins, MD served as the Program Scientist for the NICHD NRN and a member of the SUPPORT Protocol Subcommittee. She participated in the design of the observational study, provided critical revision to the manuscript, and approved the final manuscript as submitted.

Neil N. Finer, MD was the Co-Lead Study Investigator for the SUPPORT trial and chair of the SUPPORT Protocol Subcommittee. He conceptualized and designed the parent randomized trial for this observational study. As the site PI at the University of California, San Diego, he oversaw recruitment and follow-up at this site which enrolled 74 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Waldemar A. Carlo, MD was the Co-Lead Study Investigator for the SUPPORT trial and vice chair of the SUPPORT Protocol Subcommittee. He conceptualized and designed the parent randomized trial for this observational study. As the site PI at the University of Alabama, Birmingham, he oversaw recruitment and follow-up at this site which enrolled 184 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Michele C. Walsh, MD MS was a member of the SUPPORT Protocol Subcommittee. She participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at Case Western Reserve University, she oversaw recruitment and follow-up at this site which enrolled 107 infants in the trial. She provided critical revision to the manuscript and approved the final manuscript as submitted.

Abbot R. Lupton, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at Brown University, he oversaw recruitment and follow-up at this site which enrolled 124 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Roger G. Faix, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at the University of Utah, he oversaw recruitment and follow-up at this site which enrolled 52 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Bradley A. Yoder, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site Co-PI at the University of Utah, he assisted in overseeing recruitment and follow-up at this site which enrolled 52 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Kurt Schibler, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at Cincinnati Children's Hospital, he oversaw recruitment and follow-up at this site which enrolled 90 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Marie G. Gantz, PhD served as the primary statistician for the parent trial and a member of the SUPPORT Protocol Subcommittee. She participated in the design and data processing for the parent randomized trial for this observational study. She performed the analyses for the parent randomized trial, reviewed the data tables and figures for this observational study, and approved the final manuscript as submitted.

Abhik Das, PhD is the principal investigator for the NRN Data Coordinating Center at RTI International and was a member of the SUPPORT Protocol Subcommittee. Dr. Das oversaw the statistical analyses, provided critical revisions to the manuscript, and approved the final version of the manuscript as submitted.

Nancy S. Newman, RN Nancy S. Newman, RN is the NRN Coordinator for Case Western Reserve University and a member of the SUPPORT Protocol Subcommittee. She contributed to the study manual and data forms for the parent randomized trial and served as a resource for data collection and implementation activities for the other NRN sites. She participated in the recruitment and implementation of the trial at Case Western Reserve University which enrolled 107 subjects. She approved the final version of the manuscript.

Wade Rich, RRT is the NRN Coordinator for the University of California, San Diego and a member of the SUPPORT Protocol Subcommittee. He contributed to the design of the project, the study manual and data forms for the parent randomized trial and served as a resource for data collection and implementation activities for the other NRN sites. He participated in the recruitment and implementation of the trial at the University of California, San Diego which enrolled 74 subjects. He approved the final manuscript as submitted.

Dale L. Phelps, MD was a member of the SUPPORT Protocol Subcommittee. She participated in the design and implementation of the parent randomized trial and in the design of the observational study. As the site PI at the University of Rochester, she oversaw recruitment and

follow-up at this site which enrolled 8 infants in the trial. She provided critical input into multiple revisions of this manuscript and approved the final manuscript as submitted.

Abstract

Objective: To determine if current ROP examination guidelines adequately identify treatable ROP in a contemporary cohort of extremely low gestation infants.

Methods: Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Inborn infants of 24 ⁰/₇ to 27 ⁶/₇ wks gestational age with consent prior to delivery were enrolled in 2005-2009. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was a primary outcome for the trial. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

Results: 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had a final ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

Conclusions: Our contemporary data support the 2013 screening guidelines. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines^{1,2} are based on natural history data from the CRYO-ROP³ and LIGHT-ROP⁴ studies. The CRYO-ROP study⁵ remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.⁶ Over the past two decades, survival of lower birth weight infants has increased.^{7,8} For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.⁷ The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age. It rarely occurs before 30 weeks postmenstrual age (PMA) or before 4 weeks chronological age. The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.⁴ Based on the results of the ET-ROP trial, earlier treatment is now recommended.⁹ With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP, defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial¹⁰ and a population-based cohort study of infants born 2004-2007 in Sweden¹¹ reported the age of onset of stages 1, 2, and 3 ROP; the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from the Canadian

Neonatal Network reported the age of onset of Type 1 ROP in a cohort of 214 infants ≤ 27 weeks gestation;¹² this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort¹³ reported that “No preterm infants required treatment before the 33th postmenstrual week or 8th postnatal week, respectively”; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 ⁶/₇ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)¹⁴ to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Methods

Comment [M61]: The methods section makes no mention of the comparisons that were made between GA groups or why those were done.

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O₂ saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24^{0/7} – 27^{6/7} weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Repeat examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up was curtailed at 55 wks (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than

2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for quantiles.¹⁵ Cumulative incidence curves were compared using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-five percent (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Comment [MG2]: Throughout the results section, the terms "ROP" and "severe ROP" seem to be used interchangeably. However, the distinction is important, and since the Methods section does talk about both "severe ROP" and "any ROP" the results section should be specific about which is meant.

Several previously reported risk factors for severe ROP are shown in Table 2.^{16,17,18}

Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown. The distributions for age of onset for each two-week interval of completed gestation at birth are shown in Figure 3. In contrast to prior studies,²³ our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP.

The distributions of PMA at onset of severe ROP is significantly later for ($p < 0.01$ for GA groups 26-27 weeks vs. 24-25 weeks ($p < 0.01$)). There is no significant difference in the distribution of chronologic age of onset by GA group.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status

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several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop severe ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,⁹ so updated information regarding the

timing of onset of ROP is needed. While our study findings differ from previous studies³³ in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

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In the CRYO-ROP natural history study³³ lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,¹ albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤ 1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.¹⁹ Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age²⁰ and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

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The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by

Austeng et al,¹¹ which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al¹² included 23-27 week infants; infants ≤ 25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants >25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (23-24-25 week) infants, whereas the medians for chronologic age are similar.

Comment [MG3]: Important edit

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest age of onset of Type 1 ROP is more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA (although 1 infant with unknown age of onset had severe ROP detected on an initial exam at 33 weeks PMA). These findings are consistent with the other recent studies. In the Canadian Network study,¹² the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al¹³ that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

Comment [MG4]: Include in results section?

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are

still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.²¹ The SUPPORT trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.^{21,24}

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Conclusion

Current screening guidelines, published in 2013,¹ recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged

from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines.

Comment [MG5]: Include in results section?

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

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Figure Legends:

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all 1316 infants in SUPPORT trial

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP ¹ Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/Moderate ROP	Severe (Type 1 or Treated) ROP
n	1316	997	353	506	138
Gestational age [mean (SD) ²]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	823 (180)	708 (148)
Small for gestational age ³ [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	153 (43)	179 (35)	42 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (44)
Hispanic	259 (20)	190 (19)	69 (20)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (56)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	340 (96)	480 (95)	135 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

¹ Retinopathy of prematurity

² Standard deviation

³ Based on Olsen²² growth curves

Table 2. Risk factors for ROP¹

Risk Factor	No ROP	Mild/Moderate ROP	Severe (Treated or Type 1) ROP
n	353	506	138
Days on supplemental oxygen [median (IQR ²)]	33 (10, 60)	62 (31, 94)	94 (66, 119)
Late-onset sepsis (+ culture) [n (%)]	75 (21)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	15 ³ (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	69 ³ (14)	29 (21)
Proven necrotizing enterocolitis [n (%)]	20 (6)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (35)	271 (54)	95 (69)

Comment [MG6]: Are infants who died included? If so, that could artificially shorten the number of days on oxygen in the group with no ROP. If not, then I would specify in the table that only survivors were included.

¹ Retinopathy of prematurity

² Interquartile range

³ Missing data for 1 infant

Table 3. Postmenstrual and chronological age of onset¹ [with 95% confidence intervals (CI²)] of any stage ROP³ (among infants with ROP age of onset determined)

		Postmenstrual Age (weeks)								
ROP type	n	Min ⁴	1%	5%	25%	50%	75%	95%	99%	Max ⁴
Any ROP (95%CI)	635	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP ⁵ (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

		Chronological Age (weeks)								
ROP type	n	min	1%	5%	25%	50%	75%	95%	99%	max
Any ROP (95%CI)	635	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP ⁵ (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP (95% CI)	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

¹ Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.

² Confidence interval

³ Retinopathy of prematurity

⁴ Min = minimum age at which designated severity of ROP was identified; max = maximum age.

⁵ Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Timing of first exam meeting severe ROP¹ criteria in relation to discharge and transfer

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital: n	1	4

¹ Retinopathy of prematurity

Table 5. ROP¹ exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I, n (%)	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone, n (%)	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP, n (%)	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone, n (%)	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP, n (%)	0	121 (23%)
Plus disease, n (%)	0	0
No exam prior to discharge, n (%)	0	3
Unknown (missing or incomplete information on exam prior to discharge), n (%)	0	5

¹ Retinopathy of prematurity

Table 6. Risk factors for ROP¹ for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA ² at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	59 (27)	47 (33)
Early onset sepsis, n (%)	0	10 (2)
Late onset sepsis, n (%)	7 (50)	148 (28)
Fungal sepsis, n (%)	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis, n (%)	1 (7)	36 (7)
Patent ductus arteriosus, n (%)	11 (79)	258 (48)
Discharge on oxygen, n (%)	2 (14)	88 (16)

¹ Retinopathy of prematurity

² Gestational age

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: Concerns from OHRP letter
Date: Monday, March 11, 2013 8:57:00 AM

I am available before 10, 12-1, 2-3 and 430-5 PM et

Rose

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, March 11, 2013 8:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Concerns from OHRP letter

Hi Rose:

I was going to contact you today because I read the TOP protocol also in addition to the consent form. The protocol addresses a lot of other potential risks of both high and low transfusion thresholds. I am concerned as even though both thresholds are commonly used, they both have pros and cons. This is similar to O2 sats ranges.

Wally

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 11, 2013 7:51 AM

To: Wally Carlo (wacarlo@uab.edu)
Subject: FW: Concerns from OHRP letter

Wally

I had talked to Monica and she was going to discuss this with you. I looked at the TOP model consent and it has the following language:

What are the possible risks or discomforts?

Your baby has been born very early, and is at risk for complications of extreme prematurity, and some of these babies die. This study does not carry any additional risks to your baby if you choose to take part. There are no extra blood tests being done on your baby. All blood tests are done as routine standard of care at your doctor's request. This study does not alter the routine care for your baby. The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy. If your baby needs blood for emergency reasons, where all doctors would routinely give blood, they will get the blood they need – irrespective of the study. After that urgent need is over, they will then return to the study protocol.

Blood transfusions are nowadays, in general extremely safe. It is simply that giving blood transfusions at too high a hemoglobin level may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. On the other hand, transfusing at too low a hemoglobin, could lead to the baby not having enough hemoglobin to carry enough oxygen around the body. We avoid these extremes by transfusing within the ranges of hemoglobin level that doctors nowadays already use.

During the entire study, an independent committee will review this study to make sure that it continues to be safe.

I am happy to discuss further and have a call in to Haresh to discuss.

Rose

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From: Monica Collins [<mailto:MCollins@peds.uab.edu>]
Sent: Saturday, February 23, 2013 9:39 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins
Subject: Concerns from OHRP letter

Rose,

As the coordinating site for which the OHRP letter was targeted, I have had many sleepless nights over this. Shirley and I have struggled with this for a while, reviewing whether the safety of the patients was compromised in order to get the study done. After months of consideration, we are comfortable that we did not compromise the care of any patient, given the information that we had at the time.

What to do now? I understand that the Steering Committee is going to have a conference call next week and I would like to suggest a few things, some of which I have heard from other coordinators and some are generated by Shirley and me. I am sending this to you before I speak with Wally about it because I want to be sure you understand all of my concerns. I have talked with Wally about some of these things, and he tries to reassure me that they have been considered, but I want to make sure someone else is aware of these issues.

First, the letter from OHRP, regardless of the sanity of the person who wrote the original letter to OHRP, brings up points that I think we should ponder. We authored a paper on targeted saturations and the publication states that "a target range of oxygen saturation of 85-89%, as compared with a range of 91-95%, 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." The current standards for our studies may not be the same as they were when SUPPORT protocols were originally written. For example, the TOP trial. [BB1] [BB1]

Second, I would like to ask that the group look at all of the consent forms that are currently being used to make sure that we have appropriately addressed the known risks and benefits of the study in each one. [BB2] [BB2] This concern stems from the OHRP letter and the publication of the saturation article that detailed that indeed, babies who were in the lower saturation group had a higher risk of mortality than those in the higher saturation group. That being said, I wonder if we have adequately addressed the risks to the babies who are kept in the restricted arm of the TOP trial. The consent form says that there is no more risk to these infants than current standard of care, as these thresholds are in the ranges of standard of care. The standard of care is what is common around nurseries in the US. What is common around the US is that different physicians take care of each baby in the nursery during their hospital stays. Many have a common threshold, but others in the same practices may have other thresholds. The infants are usually exposed to multiple philosophies during their stay. I am not sure we are not increasing their risks—we are segregating these babies to a

group where they will never receive a transfusion that might have been given at a higher hematocrit by a different physician during a different day in a different month. In the restrictive arm, these babies will not receive a transfusion unless they meet the threshold requirements determined by randomization, (of course, if there is an emergency, they will exit for a time). We will be keeping them in low oxygen carrying capacity despite who the attending is or what the attending's threshold may be. This is, in my opinion, different from standard of care, as when they are taken care of by many physicians, they might receive a transfusion at a higher level with one physician versus another. We are preventing this fluctuation in the standard of care by the study algorithm. Doesn't this increase their risk, based on the NRN publication about oxygen saturation? Should this be addressed in the consent form?

Third, for the babies who are in the liberal arm, those infants may receive more transfusions; and by necessity, more IV sticks (and associated risks of infection) than those in the restrictive arm. They also may be exposed to a greater number of donors, due to greater numbers of transfusions. This is also different from standard of care. Neither of these is addressed in the protocol or sample consent.

I am requesting the re-review of consents network-wide as we do have better information than we did when some of these protocols and informed consents were written. If there are no increased risks or benefits than current standard of care, I think we can say that with confidence and not just leave the "may be unknown risks that we discover later" to cover ourselves; however, if not, I think the consents should be modified. And I don't think it should be left to the individual site as unilateral modification of consents by the center, for risks and benefits might open a can of worms we don't want to open if we discover and publish something that one site felt was a known or suspected risk or benefit and another did not. The OHRP letter has made me realize that we should be paying more attention to our consent forms[BB3] .

(And just as a matter of course, the economic questionnaire is not mentioned in the current consent for TOP.)

Thanks for your consideration

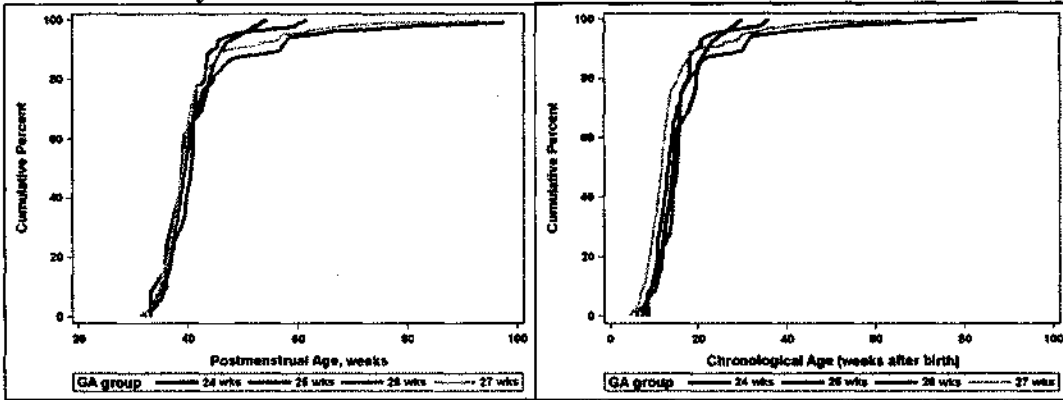
Monica

From: Kennedy, Kathleen A
To: [Wrage, Lisa Ann \(wrage@rti.org\)](mailto:Wrage_Lisa_Ann@rti.org); dale_phelps@urmc.rochester.edu; [Higgins, Rosemary \(NIH/NICHD\)](mailto:Higgins_Rosemary@NIH/NICHD)[E]; wcarlo@peds.uab.edu; [Das, Abhik](mailto:Das_Abhik@hsc.utah.edu); Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; [Gantz, Marie](mailto:Gantz_Marie@alaptok@WIHRI.org); alaptok@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cehmc.org; [Michele Walsh@UHHospitals.org](mailto:Michele.Walsh@UHHospitals.org); Bradley.Yoder@hsc.utah.edu
Cc: [Archer, Stephanie \(NIH/NICHD\)](mailto:Archer_Stephanie@NIH/NICHD)[E]
Subject: Onset of ROP Observational Study (SUPPORT Secondary)
Date: Friday, March 08, 2013 3:48:05 PM
Attachments: [Figure 4.pdf](#)
[Figure 1.pdf](#)
[Figure 2.pdf](#)
[Figure 3.pdf](#)
[ROP Natural History Study Manuscript \(for submission without figures\).doc](#)

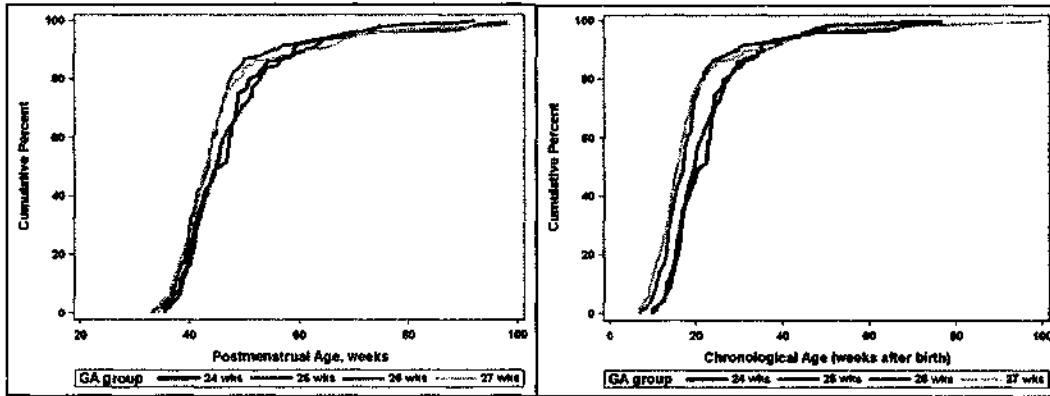
I've attached what I hope is a final draft of the ROP Secondary Study. Thanks to those of you who submitted comments on the prior draft; it's been revised accordingly. This has now cleared all the administrative hurdles. If you have any additional suggestions, please send them to me by Monday March 18. I plan to submit it to Pediatrics on Tuesday March 19. Thanks again for your help on this.

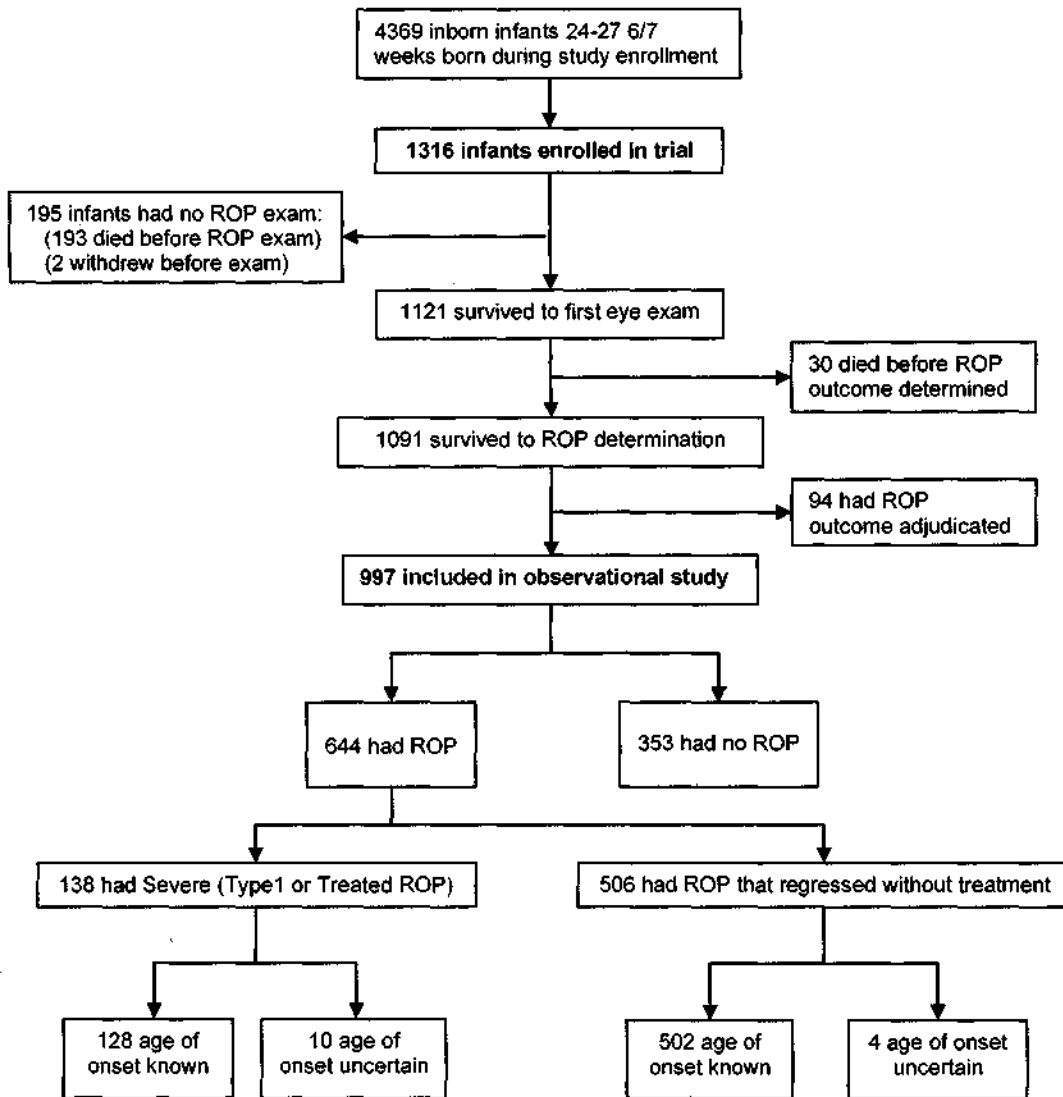
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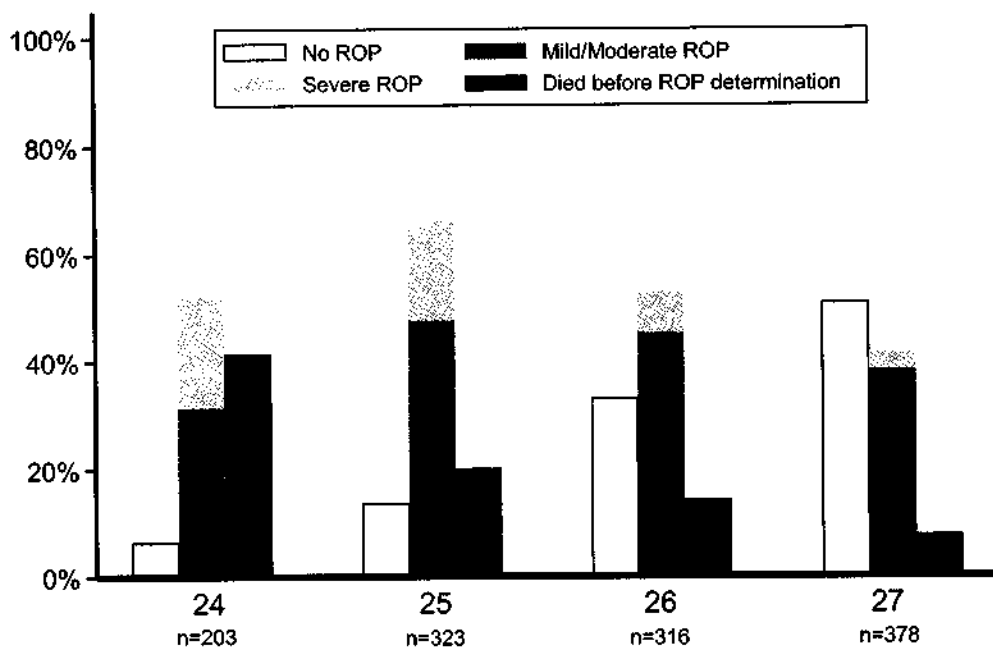
No ROP on any exam

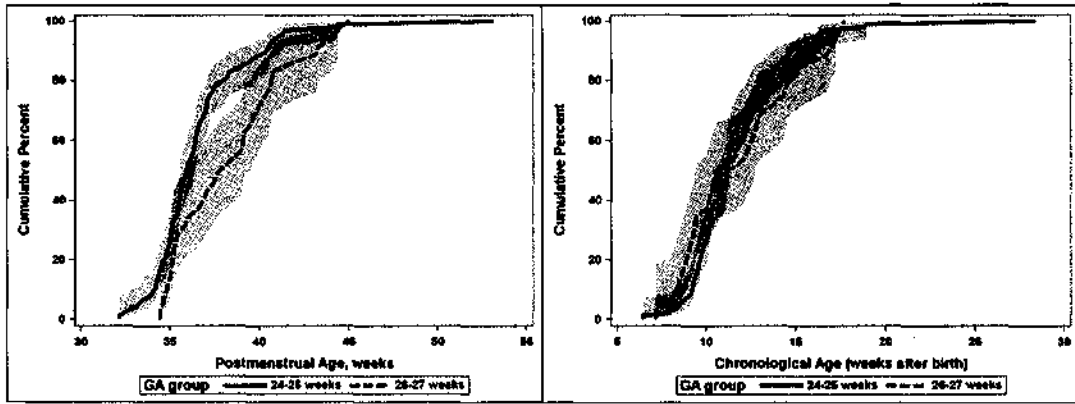


Mild/Moderate ROP









Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

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Short title: Retinopathy of Prematurity Screening Criteria

Abbreviations:

ELBW – extremely low birth weight (<1000 g birth weight)
GA – gestational age
PMA – postmenstrual age
ROP – retinopathy of prematurity
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

Keywords: retinopathy of prematurity, screening, extremely premature infant

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Conflict of interest: none

What's Known on this Subject

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Because earlier treatment is now recommended, updated information regarding the timing of onset of ROP is needed.

What This Study Adds

Our data support the timing of examinations in the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth. Ten percent of severe ROP cases occurred after discharge; close follow-up is important for infants who remain at risk after discharge.

Contributor's Statement:

Below we detail the contributions made by each author for this manuscript. The following authors have made significant contributions as determined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

Kathleen A. Kennedy, MD MPH is the principal investigator. She conceptualized and designed the observational study. As the site PI at the University of Texas Medical School at Houston, she oversaw recruitment and follow-up at this site which enrolled 85 infants in the trial. Dr. Kennedy drafted the initial manuscript, revised the manuscript, and approved the final manuscript as submitted.

Lisa A. Wrage, MPH served as the primary statistician for the observational study. She performed the analyses, prepared the data tables and figures, provided critical revision of the manuscript, and approved the final manuscript as submitted.

Rosemary D. Higgins, MD served as the Program Scientist for the NICHD NRN and a member of the SUPPORT Protocol Subcommittee. She participated in the design of the observational study, provided critical revision to the manuscript, and approved the final manuscript as submitted.

Neil N. Finer, MD was the Co-Lead Study Investigator for the SUPPORT trial and chair of the SUPPORT Protocol Subcommittee. He conceptualized and designed the parent randomized trial for this observational study. As the site PI at the University of California, San Diego, he oversaw recruitment and follow-up at this site which enrolled 74 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Waldemar A. Carlo, MD was the Co-Lead Study Investigator for the SUPPORT trial and vice chair of the SUPPORT Protocol Subcommittee. He conceptualized and designed the parent randomized trial for this observational study. As the site PI at the University of Alabama, Birmingham, he oversaw recruitment and follow-up at this site which enrolled 184 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Michele C. Walsh, MD MS was a member of the SUPPORT Protocol Subcommittee. She participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at Case Western Reserve University, she oversaw recruitment and follow-up at this site which enrolled 107 infants in the trial. She provided critical revision to the manuscript and approved the final manuscript as submitted.

Abbot R. Laptook, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at Brown University, he oversaw recruitment and follow-up at this site which enrolled 124 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Roger G. Faix, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at the University of Utah, he oversaw recruitment and follow-up at this site which enrolled 52 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Bradley A. Yoder, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site Co-PI at the University of Utah, he assisted in overseeing recruitment and follow-up at this site which enrolled 52 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Kurt Schibler, MD was a member of the SUPPORT Protocol Subcommittee. He participated in the design and implementation of the parent randomized trial for this observational study. As the site PI at Cincinnati Children's Hospital, he oversaw recruitment and follow-up at this site which enrolled 90 infants in the trial. He provided critical revision to the manuscript and approved the final manuscript as submitted.

Marie G. Gantz, PhD served as the primary statistician for the parent trial and a member of the SUPPORT Protocol Subcommittee. She participated in the design and data processing for the parent randomized trial for this observational study. She performed the analyses for the parent randomized trial, reviewed the data tables and figures for this observational study, and approved the final manuscript as submitted.

Abhik Das, PhD is the principal investigator for the NRN Data Coordinating Center at RTI International and was a member of the SUPPORT Protocol Subcommittee. Dr. Das oversaw the statistical analyses, provided critical revisions to the manuscript, and approved the final version of the manuscript as submitted.

Nancy S. Newman, RN Nancy S. Newman, RN is the NRN Coordinator for Case Western Reserve University and a member of the SUPPORT Protocol Subcommittee. She contributed to the study manual and data forms for the parent randomized trial and served as a resource for data collection and implementation activities for the other NRN sites. She participated in the recruitment and implementation of the trial at Case Western Reserve University which enrolled 107 subjects. She approved the final version of the manuscript.

Wade Rich, RRT is the NRN Coordinator for the University of California, San Diego and a member of the SUPPORT Protocol Subcommittee. He contributed to the design of the project, the study manual and data forms for the parent randomized trial and served as a resource for data collection and implementation activities for the other NRN sites. He participated in the recruitment and implementation of the trial at the University of California, San Diego which enrolled 74 subjects. He approved the final manuscript as submitted.

Dale L. Phelps, MD was a member of the SUPPORT Protocol Subcommittee. She participated in the design and implementation of the parent randomized trial and in the design of the observational study. As the site PI at the University of Rochester, she oversaw recruitment and

follow-up at this site which enrolled 8 infants in the trial. She provided critical input into multiple revisions of this manuscript and approved the final manuscript as submitted.

Abstract

Objective: To determine if current ROP examination guidelines adequately identify treatable ROP in a contemporary cohort of extremely low gestation infants.

Methods: Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Inborn infants of 24^{0/7} to 27^{6/7} wks gestational age with consent prior to delivery were enrolled in 2005-2009. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was a primary outcome for the trial. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

Results: 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had a final ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

Conclusions: Our contemporary data support the 2013 screening guidelines. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines^{1,2} are based on natural history data from the CRYO-ROP³ and LIGHT-ROP⁴ studies. The CRYO-ROP study⁵ remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.⁶ Over the past two decades, survival of lower birth weight infants has increased.^{7,8} For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.⁷ The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age. It rarely occurs before 30 weeks postmenstrual age (PMA) or before 4 weeks chronological age. The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.⁴ Based on the results of the ET-ROP trial, earlier treatment is now recommended.⁹ With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP, defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial¹⁰ and a population-based cohort study of infants born 2004-2007 in Sweden¹¹ reported the age of onset of stages 1, 2, and 3 ROP; the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from the Canadian

Neonatal Network reported the age of onset of Type 1 ROP in a cohort of 214 infants ≤ 27 weeks gestation;¹² this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort¹³ reported that “No preterm infants required treatment before the 33th postmenstrual week or 8th postnatal week, respectively”; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 ⁶/₇ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)¹⁴ to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O₂ saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24⁰/₇ – 27⁶/₇ weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Repeat examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up was curtailed at 55 wks (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, “age of onset” was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than

2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for quantiles.¹⁵ Cumulative incidence curves were compared using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-five percent (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to “onset” exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2.^{16,17,18}

Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown. The distributions for age of onset for each two-week of completed gestation at birth are shown in Figure 3. In contrast to prior studies,³ our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The distributions of PMA of onset of severe ROP is significantly later for ($p < 0.01$ for GA groups 26-27 weeks vs. 24-25 weeks). There is no difference in the distribution of chronologic age of onset by GA group.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status

several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop severe ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,⁹ so updated information regarding the

timing of onset of ROP is needed. While our study findings differ from previous studies³ in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,³ lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,¹ albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤ 1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.¹⁹ Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age²⁰ and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by

Austeng et al,¹¹ which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al¹² included 23-27 week infants; infants ≤ 25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants >25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (23-24 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest age of onset of Type 1 ROP is more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA (although 1 infant with unknown age of onset had severe ROP detected on an initial exam at 33 weeks PMA). These findings are consistent with the other recent studies. In the Canadian Network study,¹² the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al¹³ that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are

still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.²¹ The SUPPORT trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.²¹

Conclusion

Current screening guidelines, published in 2013,¹ recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged

from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

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Figure Legends:

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all 1316 infants in SUPPORT trial

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals

Figure 4. Postmenstrual and chronological age of “favorable outcome” (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP ¹ Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/Moderate ROP	Severe (Type 1 or Treated) ROP
n	1316	997	353	506	138
Gestational age [mean (SD ²)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	823 (180)	708 (148)
Small for gestational age ³ [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	153 (43)	179 (35)	42 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (44)
Hispanic	259 (20)	190 (19)	69 (20)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (56)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	340 (96)	480 (95)	135 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

¹ Retinopathy of prematurity

² Standard deviation

³ Based on Olsen²² growth curves

Table 2. Risk factors for ROP¹

Risk Factor	No ROP	Mild/Moderate ROP	Severe (Treated or Type 1) ROP
n	353	506	138
Days on supplemental oxygen [median (IQR ²)]	33 (10, 60)	62 (31, 94)	94 (66, 119)
Late-onset sepsis (+ culture) [(n (%))]	75 (21)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	15 ³ (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	69 ³ (14)	29 (21)
Proven necrotizing enterocolitis [n (%)]	20 (6)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (35)	271 (54)	95 (69)

¹ Retinopathy of prematurity

² Interquartile range

³ Missing data for 1 infant

Table 3. Postmenstrual and chronological age of onset¹ [with 95% confidence intervals (CI²)] of any stage ROP³ (among infants with ROP age of onset determined)

ROP type	n	Postmenstrual Age (weeks)								
		Min ⁴	1%	5%	25%	50%	75%	95%	99%	Max ⁴
Any ROP (95%CI)	635	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP ⁵ (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

ROP type	n	Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	max
Any ROP (95%CI)	635	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP ³ (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP (95% CI)	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

¹ Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.

² Confidence interval

³ Retinopathy of prematurity

⁴ Min = minimum age at which designated severity of ROP was identified; max = maximum age.

⁵ Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Timing of first exam meeting severe ROP¹ criteria in relation to discharge and transfer

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital: n	1	4

¹ Retinopathy of prematurity

Table 5. ROP¹ exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I, n (%)	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone, n (%)	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP, n (%)	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone, n (%)	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP, n (%)	0	121 (23%)
Plus disease, n (%)	0	0
No exam prior to discharge, n (%)	0	3
Unknown (missing or incomplete information on exam prior to discharge) , n (%)	0	5

¹ Retinopathy of prematurity

Table 6. Risk factors for ROP¹ for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA ² at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	59 (27)	47 (33)
Early onset sepsis, n (%)	0	10 (2)
Late onset sepsis, n (%)	7 (50)	148 (28)
Fungal sepsis, n (%)	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis, n (%)	1 (7)	36 (7)
Patent ductus arteriosus, n (%)	11 (79)	258 (48)
Discharge on oxygen, n (%)	2 (14)	88 (16)

¹ Retinopathy of prematurity

² Gestational age

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Laptook, Abbot"; "Zaterka-Baxter, Kristin"
Subject: RE: Steering Committee Call 3/4, M, 4:00 PM ET
Date: Wednesday, March 06, 2013 1:58:00 PM

Minutes will be posted

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Laptook, Abbot [mailto:ALaptook@Wihri.org]
Sent: Monday, March 04, 2013 8:41 PM
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Steering Committee Call 3/4, M, 4:00 PM ET

Rose, Kris

I could not be on the call; anything of note that I should be aware of? Tx, AL

From: Zaterka-Baxter, Kristin [kzaterka@rti.org]
Sent: Monday, March 04, 2013 2:16 PM
To: nxs5@case.edu; Vivek.Narendran@cchmc.org; Ivan Frantz; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; SDuara@med.miami.edu; Anthony.Piazza@oz.ped.emory.edu; Gantz, Marie; Poole, W. Kenneth; dstevenson@stanford.edu; morrisb1@tmfhs.org; nfiner@ucsd.edu; Wade RIch; dale_phelps@urmc.rochester.edu; Nirupama Laroia; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; [SCRN] Stoll, Barbara; Laptook, Abbot; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; Avroy Fanaroff; Dan Ellsbury; David Carlton; Eugenia Pallotto; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Luc Brion; Meena Garg; Michael Cotten; nambalavanan@peds.uab.edu; rohls@salud.unm.edu; Ronnie Guillet; Sood, Beena; Sudarshan Jadcherla
Cc: archerst@mail.nih.gov; Lewis-Evans, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Becky Brazeel; Vecchio, Brenda; Garcia, Deborah; gonza025@mc.duke.edu; Heidi Kleinbart; jwaidne@emory.edu; Kristie Smiley; jmoore@med.wayne.edu; Nancy.M.Smith@uth.tmc.edu; Theresa Banker
Subject: RE: Steering Committee Call 3/4, M, 4:00 PM ET

Reminder for the call below. Sorry for the late notice.

Thanks,

Kris

From: Gabrio, Jenna

Sent: Tuesday, February 26, 2013 4:15 PM

To: Cunningham, Meg; 'nxs5@case.edu'; '(Vivek.Narendran@cchmc.org)'; 'Ivan Frantz'; 'BradYoder (Bradley.yoder@hsc.utah.edu)'; 'RogerFaix (Roger.Faix@hsc.utah.edu)'; 'Shahnaz' (SDuara@med.miami.edu) 'Duara'; 'Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu)'; Gantz, Marie; Poole, W. Kenneth; 'dstevenson@stanford.edu'; 'Brenda Morris (morrisb1@tmfhs.org)'; 'nfiner@ucsd.edu'; 'Wade RIch'; 'dale_phelps@urmc.rochester.edu'; 'Nirupama Laroia'; 'moshea@wfubmc.edu'; 'richard.ehrenkranz@yale.edu'; [SCRN] Stoll, Barbara; Abbot Laptook (alaptook@WIHRI.org); 'Anne Marie Reynolds'; 'Barbara Schmidt'; Bell, Edward; 'Bill Truog'; Brenda Poindexter (bpoindex@iu.edu); 'Carl D'Angio'; Das, Abhik; goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Kathleen.A.Kennedy@uth.tmc.edu'; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; 'Leif Nelin'; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; 'RAP32@columbia.edu'; 'Satyan Lakshminrusimha'; 'sshankar@med.wayne.edu'; 'Uday Devaskar'; yanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; 'Avroy Fanaroff'; 'Dan Ellsbury'; 'David Carlton'; 'Eugenia Pallotto'; 'Greg Sokol'; 'Haresh Kirpalani'; 'John Barks'; jon.e.tyson@uth.tmc.edu; Keszler, Martin; 'Luc Brion'; 'Meena Garg'; 'Michael Cotten'; Namasivayam Ambalavanan (nambalavanan@peds.uab.edu); 'rohls@salud.unm.edu'; 'Ronnie Guillet'; 'Sood, Beena'; 'Sudarshan Jadcherla'

Cc: Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Lewis-Evans, Amanda; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Newman, Jamie; 'Becky Brazeel'; 'Brenda Vecchio'; 'Garcia, Deborah'; 'gonza025@mc.duke.edu'; 'Heidi Kleinbart'; 'jwaidne@emory.edu'; 'Kristie Smiley'; 'Imoore@med.wayne.edu'; Michelle Smith (Nancy.M.Smith@uth.tmc.edu); 'Theresa Banker'

Subject: Steering Committee Call 3/4, M, 4:00 PM ET

Hi All,

As discussed on today's SC call, we will have another Steering Committee call to follow up on this SUPPORT issue on **Monday, March 4th at 4:00pm ET.**

Dial:

Within the USA: (b)(6)

Or

Outside the USA: (b)(6)

Then, enter Participant Passcode: (b)(6)

Thanks,

Jenna

From: Gabrio, Jenna

Sent: Tuesday, February 26, 2013 9:27 AM

To: Cunningham, Meg; 'nxs5@case.edu'; '(Vivek.Narendran@cchmc.org)'; 'Ivan Frantz'; 'BradYoder (Bradley.yoder@hsc.utah.edu)'; 'RogerFaix (Roger.Faix@hsc.utah.edu)'; 'Shahnaz' (SDuara@med.miami.edu) 'Duara'; 'Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu)'; Gantz, Marie; Poole, W. Kenneth; 'dstevenson@stanford.edu'; 'Brenda Morris (morrisb1@tmfhs.org)'; 'nfiner@ucsd.edu'; 'Wade RIch'; 'dale_phelps@urmc.rochester.edu'; 'Nirupama Laroia'; 'moshea@wfubmc.edu'; 'richard.ehrenkranz@yale.edu'; [SCRN] Stoll, Barbara; Abbot Laptook (alaptook@WIHRI.org); 'Anne Marie Reynolds'; 'Barbara Schmidt'; Bell, Edward; 'Bill Truog'; Brenda Poindexter (bpoindex@iu.edu); 'Carl D'Angio'; Das, Abhik; goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Kathleen.A.Kennedy@uth.tmc.edu'; kurt.schibler@cchmc.org;

kwatterberg@salud.unm.edu; 'Leif Nelin'; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; 'RAP32@columbia.edu'; 'Satyan Lakshminrusimha'; sshankar@med.wayne.edu; 'Uday Devaskar'; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; 'Avroy Fanaroff'; 'Dan Ellsbury'; 'David Carlton'; 'Eugenia Pallotto'; 'Greg Sokol'; 'Haresh Kirpalani'; 'John Barks'; jon.e.tyson@uth.tmc.edu; Keszler, Martin; 'Luc Brion'; 'Meena Garg'; 'Michael Cotten'; Namasivayam Ambalavanan (nambalavanan@peds.uab.edu); rohls@salud.unm.edu; 'Ronnie Guillet'; 'Sood, Beena'; 'Sudarshan Jadcherla'

Cc: Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Lewis-Evans, Amanda; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Newman, Jamie; 'Becky Brazeel'; 'Brenda Vecchio'; 'Garcia, Deborah'; gonza025@mc.duke.edu; 'Heidi Kleinbart'; jwaidne@emory.edu; 'Kristie Smiley'; lmoore@med.wayne.edu; Michelle Smith (Nancy.M.Smith@uth.tmc.edu); 'Theresa Banker'

Subject: RE: Steering Committee Call 02/26 at 3 PM ET

Hi all,

A friendly reminder for today's call.

Jenna

From: Cunningham, Meg

Sent: Thursday, February 21, 2013 1:49 PM

To: nxs5@case.edu; (Vivek.Narendran@cchmc.org); Ivan Frantz; BradYoder (Bradley.yoder@hsc.utah.edu); RogerFaix (Roger.Faix@hsc.utah.edu); Shahnaz (SDuara@med.miami.edu) 'Duara; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu); Gantz, Marie; Poole, W. Kenneth; dstevenson@stanford.edu; Brenda Morris (morrisb1@tmfhs.org); nfiner@ucsd.edu; Wade Ritch; dale_phelps@urmc.rochester.edu; Nirupama Laroia; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; [SCRN] Stoll, Barbara; Abbot Laptook (alaptook@WIHL.org); Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; Brenda Poindexter (bpindex@iu.edu); Carl D'Angio; Das, Abhik; goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Kathleen.A.Kennedy@uth.tmc.edu'; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; Avroy Fanaroff; Dan Ellsbury; David Carlton; Eugenia Pallotto; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Luc Brion; Meena Garg; 'Michael Cotten'; Namasivayam Ambalavanan (nambalavanan@peds.uab.edu); rohls@salud.unm.edu; Ronnie Guillet; 'Sood, Beena'; Sudarshan Jadcherla

Cc: Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Gabrio, Jenna; Lewis-Evans, Amanda; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Newman, Jamie; Becky Brazeel; 'Brenda Vecchio'; Garcia, Deborah; gonza025@mc.duke.edu; Heidi Kleinbart; jwaidne@emory.edu; Kristie Smiley; lmoore@med.wayne.edu; Michelle Smith (Nancy.M.Smith@uth.tmc.edu); Theresa Banker

Subject: Steering Committee Call 02/26 at 3 PM ET

Hi All,

Below is an agenda for our SC call Tuesday, February 26th at 3:00pm ET.

Agenda

1. SUPPORT issue
2. (b)(5)
3. PAS
4. New business

Dial:

Within the USA:
or
Outside the USA:
Then, enter Participant Passcode:

Thanks!
Meg

*Meg Cunningham, CCRP
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<hr>
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delete this message and any attachment(s) immediately. Thank you for your consideration in this matter.

From: Michael Cotten, M.D.
To: Laughon, Matthew M
Cc: Michael Cotten, M.D.; Walsh, Michele; Gantz, Marie; Namasivayam Ambalavanan; Kennedy, Kathleen A; Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PaCO2 manuscript : Second draft of March 5, 2013
Date: Wednesday, March 06, 2013 11:32:28 AM

Complex yes,,, but maybe not so complex looking at one outcome at a time,,, or early, late, very late,,, or cns and Resp outcomes separately... I think it becomes more clinically applicable if you look more closely at Resp support x co2 than finding high paco2's are associated with bad outcomes

Mc

Sent from my mobile device
Dr. Michael Cotten

On Mar 6, 2013, at 11:02 AM, "Laughon, Matthew M" <matt_laughon@med.unc.edu> wrote:

Mike and Kathleen have good points; this would be a complicated analysis. Matt

From: Michael Cotten, M.D. [<mailto:michael.cotten@duke.edu>]
Sent: Wednesday, March 06, 2013 9:34 AM
To: Walsh, Michele; Gantz, Marie; Namasivayam Ambalavanan; Kennedy, Kathleen A
Cc: Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; NIH; Laughon, Matthew M; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Would you consider applying Matt's BPD estimator covariables at different days (or only day 3)....w/ addition of PaCO2 parameters as a way to provide a measure of respiratory illness severity?....maybe even stratify...max CO2 x type of vent when max co2 was measured (cpap, imv, hfv, cannula, room air)??

The dilemma is when you have low vent settings, but high co2's ...are you headed for trouble (ivh early, pvl, bpd, and ndi later).... w/ enough certainty that you should turn the support up?

mc

From: Walsh, Michele [<mailto:Michele.Walsh@uhhospitals.org>]
Sent: Wednesday, March 06, 2013 9:23 AM
To: Gantz, Marie; Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Not so severe....

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

From: Gantz, Marie [<mailto:mgantz@rti.org>]
Sent: Wednesday, March 06, 2013 8:43 AM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Severe illness was defined as $FiO_2 > 0.4$ and being on a ventilator for > 8 consecutive hours in the first 14 days after birth.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
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From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, March 05, 2013 7:50 PM
To: Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Das, Abhik; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Hi Kathleen,
Thank you for the comments. I agree - the main point that sicker babies have higher PCO2 and worse outcomes seems rather obvious. The "severe illness" definition was something that was used in the SUPPORT trial. We are somewhat limited by the data that were collected, and the fact that PCO2 was only indirectly addressed in SUPPORT.

Ambal

From: Kennedy, Kathleen A [Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, March 05, 2013 5:29 PM
To: Michael Cotten, M.D.; Namasivayam Ambalavanan
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

My, time flies. I've added my comments to Mike's. I think the biggest potential problem is that the reviewers may be put off by the complexity of the analyses and they may not be very excited by findings that seem to be exactly what you'd expect (sicker babies with higher PaCO2s do worse). I'm not sure I have a great solution. I've added some ideas in the comments in the attachment.

Kathleen A. Kennedy, MD, MPH

Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Michael Cotten, M.D. [<mailto:michael.cotten@duke.edu>]
Sent: Tuesday, March 05, 2013 2:42 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Hi everyone..sorry for my absence on the first round draft....

For the word overage...could you use S-IVH as an acronym for severe IVH? I think you'd get down to 250

Also...I put in a couple of places a query about considering a look at the vent support needed to get the PaCO2 that was measured (max)....i think if all the kids are lumped together, we might miss a signal that sometimes its not so bad....and maybe if you only need cpap or a rate of 20 and mean airway pressure of 7 to get pco2 of 65, that that doesn't have the same association as a kid w/ PaCO2 of 65 as a product of high frequency ventilation w/ a mean airway pressure of 18 and fio2 of 1.0....and there may be many more of those kids in the dataset....so much so that they overwhelm the possibility of leaving the baby on low vent support w/ a high PaCO2 alone....as it reads now, what we know is high PaCO2's are bad...so clinicians are likely to say...turn the vent up to get to 44 - 55...even if we tell them this is an association....

Can we think of an analysis that accounts for the respiratory support needed to get the PaCO2's were looking at?

mc

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, March 05, 2013 12:54 PM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Dear All,

Attached is the second draft of our manuscript (PCO2 SUPPORT March 5 2013.docx).

Thank you for all your comments - I have addressed most of them. The main changes are:

- 1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
- 2) Developed a new table of adjusted results
- 3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx) - some comments may need additional analysis (Lisa, would you look over the comments of Abhik Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,

Best regards,
Ambal

From: Namasivayam Ambalavanan
Sent: Thursday, February 21, 2013 10:37 AM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : first draft of Feb21, 2013
Importance: High

Dear All,
Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics. (Stephanie: Would you check the boilerplate and grant acknowledgments?)
Thank you for all your help,
Best regards,
Ambal

Namasivayam Ambalavanan MD
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Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology
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Fax Office (205) 934-3100 *Lab* (205) 996 2333
Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Wednesday, February 02, 2011 10:06 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,
Our PAS abstract on PaCO2 in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,
Thank you for all your help,
Ambal

From: Namasivayam Ambalavanan
Sent: Mon 11/8/2010 5:40 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,
Attached is the abstract on PaCO2 SUPPORT abstract for NICHD clearance.
Thank you,
Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO2 variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO2 in the CPAP arm from about 33 to 34. The Max PaCO2 was about the same in all groups)

Thanks,
Ambal

N. Ambalavanan MD
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Departments of Pediatrics, Cell Biology, and Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333
Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Sun 10/31/2010 6:25 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.

Ambal
(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

From: Namasivayam Ambalavanan
Sent: Sat 10/30/2010 8:15 PM
To: Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of

results.

Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,
Ambal

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Sat 10/30/2010 4:59 PM
To: Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]
Sent: Saturday, October 30, 2010 10:18 AM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
 2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)
- Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

Best Michele

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Fri 10/29/2010 5:28 PM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal

Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO₂ in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how).

Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?

Thanks,
Ambal

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Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333
Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Saturday, October 23, 2010 7:16 AM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO₂ (using highest FiO₂ on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?

Ambal

From: Namasivayam Ambalavanan
Sent: Fri 10/22/2010 8:58 PM
To: Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate

(permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO₂ (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO₂ and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO₂. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO₂ were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.

Ambal

From: Michael Cotten [<mailto:cotte010@mc.duke.edu>]
Sent: Fri 10/22/2010 7:57 PM
To: Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon
Subject: Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co₂? Some babies are easily hyperventilatable, and sometimes practitioners allow co₂ to be high on min settings,,,,and those kids are probably way different than kids on high settings or hfv who remain hypercarbic,,,

Mc

From: "Namasivayam Ambalavanan" [NAmbalavanan@peds.uab.edu]
Sent: 10/22/2010 03:59 PM EST
To: "Wrage, Lisa Ann" <wrage@rti.org>; <ambal@uab.edu>
Cc: "Das, Abhik" <adas@rti.org>; "Gantz, Marie" <mgantz@rti.org>; "Wally Carlo, M.D." <WCarlo@peds.uab.edu>; "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>; "Laptook, Abbot" <ALaptook@WIHRI.org>; "Higgins, Rosemary \ (NIH/NICHD\)" [E] <higginsr@mail.nih.gov>; <Michele.Walsh@UHhospitals.org>; Michael Cotten; "Laughon, Matthew M" <matt_laughon@med.unc.edu>
Subject: RE: PAS ABSTRACT

Hi Lisa,

(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO₂ (especially higher PaCO₂ and fluctuating PaCO₂) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO₂ is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in

space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO₂, minimal PaCO₂, time-weighted PaCO₂, and SD of PaCO₂ as independent continuous variables with actual time-weighted PaO₂ (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO₂ for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO₂ variables with outcome, after adjustment for the other variables. We probably do not need PaCO₂ values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO₂ and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO₂ terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO₂ to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO₂ category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO₂ categories and the numbers in each CO₂ category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,
Ambal

N. Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Email ambal@uab.edu

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 22, 2010 2:48 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,
I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO2 variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.
Thanks and have a great weekend.
Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Wednesday, October 20, 2010 10:58 AM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.
Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Wed 10/20/2010 9:42 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,
Thanks for the response. Regarding the time-weighted CO2, Wally and Marie did decide to cap the amount of time that on CO2 level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.
Thanks.

Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis butI think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

From: Gantz, Marie <mgantz@rti.org>

Sent: Tuesday, October 19, 2010 7:29 PM

To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>

Cc: Das, Abhik <adas@rti.org>; Wrage, Lisa Ann <wrage@rti.org>

Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5
75th 12
90th 21
95th 25.5
99th 80
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 15, 2010 2:56 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Lisa,

Thank you for the email.

- 1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
- 2) I think PROM>24h is ok
- 3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.
- 4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.

Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 15, 2010 1:46 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted CO2 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59).

The median time between blood gases is 8 hours, the mean is 12.4, the 95th %ile is 25.1 hours and the 99th %ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.
I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,
Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 05, 2010 2:45 PM
To: 'Namasivayam Ambalavanan'; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, October 05, 2010 2:38 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,

My answers (>>) are below your questions (**)

Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, October 05, 2010 12:36 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Thank you, this is helpful, I have a few more questions (see ** below).
Lisa

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Tuesday, October 05, 2010 12:42 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,
(Abhik/Wally/Marie – your comments are also welcome)
If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

****Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.**

>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices

- 2) For Aim (1): determine the association of PaCO₂ in the first 2 weeks with outcomes, we will use PaCO₂ as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

****Could you please clarify how you like to summarize PaCO₂ over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?**

>> I think max, min, time-weighted, and standard deviation should be ok.

- 3) For Aims (2) and (3), to determine the association of high/low PaCO₂ with outcomes, we will divide infants into quartiles based on their maximum PCO₂ and their minimum PCO₂ over the first two weeks. The infants in the highest quartile of max PCO₂ are "hypercapnic", and we can probably identify the threshold that

divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO₂ will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO₂ and minimum PCO₂. The outcomes will be assessed in the low and high SpO₂ groups in relation to PaCO₂ status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

***So, just to summarize, here we are using a 4-level categorical variable with categories of:*

Hypercapnic (in upper quartile of max PCO₂), >> Yes. fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators].

Hypocapnic (in lower quartile of min PCO₂), >> Yes. As above, I think we should have hypocapnia only, not fluctuators.

Fluctuators (in both upper quartile of max PCCO₂ lower quartile of min PCO₂)>> Yes.

Normocapnic (in middle two quartiles of max PCO₂ AND min PCCO₂)

To define Max PCO₂ and Min PCO₂ do you simply want me to use the maximum and minimum value of all values of PCO₂ for each infant using PCO₂ recorded during the 1st two weeks on the SUPP05 form?

>> Yes

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO₂, minPCO₂, time-weighted PCO₂, and SD of PCO₂ as independent continuous variables with SUPPORT group assignment

***OK.*

>>Great!

Thanks,
Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 05, 2010 10:32 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Dr. Ambalavanan,

I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO₂ to outcomes, plus how high / low CO₂ interacts with SpO₂. I see quite a

few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc. ", could you please provide a complete list?

Thank-you,
Lisa

Lisa Wrage, MPH
Research Statistician
Statistics & Epidemiology
RTI International
wrage@rti.org
919-220-2653

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 01, 2010 11:14 AM
To: Das, Abhik; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Hi Lisa, Marie,
What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?
Ambal

N. Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular
Pathology

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Tel Office (205) 934 4680 Lab (205) 934 0751 or 996 5419
Fax Office (205) 934-3100 Lab (205) 996 2333

Email ambal@uab.edu

From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Tuesday, September 21, 2010 3:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, September 21, 2010 11:15 AM
To: Ambal (ambal@uab.edu)
Cc: Wally Carlo, M.D.; Das, Abhik
Subject: PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.

November 8, 2010– Final abstracts to NICHD for clearance
Mid-November– PAS deadline
April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks
Rose

Rosemary D. Higgins, MD

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From: Michael Cotten, M.D.
To: Namasivayam Ambalavanan; Walsh, Michele; Gantz, Marie; Kennedy, Kathleen A
Cc: Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013
Date: Wednesday, March 06, 2013 10:43:43 AM

I think it's the 'not so sick kid' w/ a higher paco2 and not much support that we may worry about the most....

I'm trying to think of a way to model the PaCO2 like lex doyle's postnatal steroid paper..where risk of poor outcome associated w/ postnatal steroids was modified by risk level of BPD.

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@pedu.uab.edu]
Sent: Wednesday, March 06, 2013 10:20 AM
To: Michael Cotten, M.D.; Walsh, Michele; Gantz, Marie; Kennedy, Kathleen A
Cc: Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

I think that's a good idea. The BPD estimator equation will provide a continuous variable reflecting respiratory illness severity as opposed to a purely categorical "severe illness" variable.

For the BPD estimator, we will need GA, BW, Sex, Race/Ethnicity, Postnatal day (either 1, 3, 7 - as we have data only until d14), Ventilator type, and FiO2. I think we have all the data required. We can look at day 3 (for simplicity - would be complicated to look at all 3 timepoints) and calculate the predictive ability of BPD using just the estimator, and then the estimator in combination with the PaCO2 variables. This would inform us of the addition to predictive ability using PaCO2.

However, that would still not answer the underlying question - if there is a sick kid with high PaCO2, whether increasing vent settings to bring PaCO2 down to a "closer to normal" range reduces BPD, IVH, or NDI.

Let me think about this some more,
Ambal

From: Michael Cotten, M.D. [michael.cotten@duke.edu]
Sent: Wednesday, March 06, 2013 8:33 AM
To: Walsh, Michele; Gantz, Marie; Namasivayam Ambalavanan; Kennedy, Kathleen A
Cc: Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Would you consider applying Matt's BPD estimator covariables at different days (or only day 3)....w/ addition of PaCO2 parameters as a way to provide a measure of respiratory illness severity?....maybe even stratify...max CO2 x type of vent when max co2 was measured (cpap, imv, hfV, cannula, room air)??

The dilemma is when you have low vent settings, but high co2's ...are you headed for trouble (ivh early, pvl, bpd, and ndi later).... w/ enough certainty that you should turn the support up?
mc

From: Walsh, Michele [mailto:Michele.Walsh@uhhospitals.org]
Sent: Wednesday, March 06, 2013 9:23 AM
To: Gantz, Marie; Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa

Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Not so severe....

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

From: Gantz, Marie [<mailto:mgantz@rti.org>]
Sent: Wednesday, March 06, 2013 8:43 AM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Das, Abhik; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Severe illness was defined as $FiO_2 > 0.4$ and being on a ventilator for > 8 consecutive hours in the first 14 days after birth.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, March 05, 2013 7:50 PM
To: Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Das, Abhik; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Hi Kathleen,
Thank you for the comments. I agree - the main point that sicker babies have higher PCO2 and worse outcomes seems rather obvious. The "severe illness" definition was something that was used in the SUPPORT trial. We are somewhat limited by the data that were collected, and the fact that PCO2 was only indirectly addressed in SUPPORT.

Ambal

From: Kennedy, Kathleen A [Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, March 05, 2013 5:29 PM
To: Michael Cotten, M.D.; Namasivayam Ambalavanan
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

My, time flies. I've added my comments to Mike's. I think the biggest potential problem is that the reviewers may be put off by the complexity of the analyses and they may not be very excited by findings that seem to be exactly what you'd expect (sicker babies with higher PaCO₂s do worse). I'm not sure I have a great solution. I've added some ideas in the comments in the attachment.

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Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
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Houston, TX 77030
713 500-6708

From: Michael Cotten, M.D. [<mailto:michael.cotten@duke.edu>]
Sent: Tuesday, March 05, 2013 2:42 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO₂ manuscript : Second draft of March 5, 2013

Hi everyone..sorry for my absence on the first round draft....

For the word overage...could you use S-IVH as an acronym for severe IVH? I think you'd get down to 250

Also...I put in a couple of places a query about considering a look at the vent support needed to get the PaCO₂ that was measured (max)...I think if all the kids are lumped together, we might miss a signal that sometimes its not so bad...and maybe if you only need cpap or a rate of 20 and mean airway pressure of 7 to get pco₂ of 65, that that doesn't have the same association as a kid w/ PaCO₂ of 65 as a product of high frequency ventilation w/ a mean airway pressure of 18 and fio₂ of 1.0....and there may be many more of those kids in the dataset....so much so that they overwhelm the possibility of leaving the baby on low vent support w/ a high PaCO₂ alone....as it reads now, what we know is high PaCO₂'s are bad...so clinicians are likely to say...turn the vent up to get to 44 -- 55...even if we tell them this is an association....

Can we think of an analysis that accounts for the respiratory support needed to get the PaCO₂'s were looking at?

mc

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, March 05, 2013 12:54 PM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO₂ manuscript : Second draft of March 5, 2013

Dear All,

Attached is the second draft of our manuscript (PCO₂ SUPPORT March 5 2013.docx). Thank you for all your comments – I have addressed most of them. The main changes are:

- 1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into

- one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
- 2) Developed a new table of adjusted results
 - 3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx) - some comments may need additional analysis (Lisa, would you look over the comments of Abhik Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,

Best regards,
Ambal

From: Namasivayam Ambalavanan
Sent: Thursday, February 21, 2013 10:37 AM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : first draft of Feb21, 2013
Importance: High

Dear All,
Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.
(Stephanie: Would you check the boilerplate and grant acknowledgments?)
Thank you for all your help,
Best regards,
Ambal

Namasivayam Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology
University of Alabama at Birmingham
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619 South 19th Street
Birmingham, AL 35249-7335
Tel Office (205) 934 4680 *Lab* (205) 934 0751 or 996 5419
Fax Office (205) 934-3100 *Lab* (205) 996 2333
Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Wednesday, February 02, 2011 10:06 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,
Our PAS abstract on PaCO2 in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,
Thank you for all your help,
Ambal

From: Namasivayam Ambalavanan
Sent: Mon 11/8/2010 5:40 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,
Attached is the abstract on PaCO2 SUPPORT abstract for NICHD clearance.
Thank you,
Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO2 variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO2 in the CPAP arm from about 33 to 34. The Max PaCO2 was about the same in all groups)

Thanks,
Ambal

N. Ambalavanan MD
Professor, Division of Neonatology
Departments of Pediatrics, Cell Biology, and Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333
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From: Namasivayam Ambalavanan
Sent: Sun 10/31/2010 6:25 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.
Ambal
(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

From: Namasivayam Ambalavanan
Sent: Sat 10/30/2010 8:15 PM
To: Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.
Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,
Ambal

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Sat 10/30/2010 4:59 PM
To: Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
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From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]
Sent: Saturday, October 30, 2010 10:18 AM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.
Best Michele

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Fri 10/29/2010 5:28 PM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO2 in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how). Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT

subcommittees)?

Thanks,
Ambal

N. Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333
Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Saturday, October 23, 2010 7:16 AM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook;
NIH; Michele Walsh; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO2 (using highest FiO2 on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?
Ambal

From: Namasivayam Ambalavanan
Sent: Fri 10/22/2010 8:58 PM
To: Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook;
NIH; Michele Walsh; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO2 (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO2 and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO2. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO2 were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.
Ambal

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Fri 10/22/2010 7:57 PM
To: Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon
Subject: Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co2? Some babies are easily hyperventilatable, and sometimes practitioners allow co2 to be high on min settings,,,and those kids are probably way different than kids on high settings or hfv who remain hypercarbic,,,

Mc

From: "Namasivayam Ambalavanan" [NAmbalavanan@peds.uab.edu]
Sent: 10/22/2010 03:59 PM EST
To: "Wrage, Lisa Ann" <wrage@rti.org>; <ambal@uab.edu>
Cc: "Das, Abhik" <adas@rti.org>; "Gantz, Marie" <mgantz@rti.org>; "Wally Carlo, M.D." <WCarlo@peds.uab.edu>; "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>; "Laptook, Abbot" <ALaptook@WIHRI.org>; "Higgins, Rosemary \ (NIH/NICHD) [E]" <higginsr@mail.nih.gov>; <Michele.Walsh@UHHospitals.org>; Michael Cotten; "Laughon, Matthew M" <mat_laughon@med.unc.edu>
Subject: RE: PAS ABSTRACT

Hi Lisa,
(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO₂ (especially higher PaCO₂ and fluctuating PaCO₂) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO₂ is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO₂, minimal PaCO₂, time-weighted PaCO₂, and SD of PaCO₂ as independent continuous variables with actual time-weighted PaO₂ (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO₂ for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO₂

variables with outcome, after adjustment for the other variables. We probably do not need PaCO₂ values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO₂ and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO₂ terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO₂ to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO₂ category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO₂ categories and the numbers in each CO₂ category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,
Ambal

N. Ambalavanan MD
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Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333
Email ambal@uab.edu

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 22, 2010 2:48 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,

I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO₂ variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.

Thanks and have a great weekend.

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Wednesday, October 20, 2010 10:58 AM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.
Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Wed 10/20/2010 9:42 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,
Thanks for the response. Regarding the time-weighted CO₂, Wally and Marie did decide to cap the amount of time that on CO₂ level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.
Thanks.
Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis but I think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

From: Gantz, Marie <mgantz@rti.org>
Sent: Tuesday, October 19, 2010 7:29 PM
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>
Cc: Das, Abhik <adas@rti.org>; Wrage, Lisa Ann <wrage@rti.org>
Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted

CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5
75th 12
90th 21
95th 25.5
99th 80
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 15, 2010 2:56 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Lisa,

Thank you for the email.

- 1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
- 2) I think PROM>24h is ok
- 3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.

4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.
Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, October 15, 2010 1:46 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted CO2 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95th %ile is 25.1 hours and the 99th %ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.

I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,
Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 05, 2010 2:45 PM
To: 'Namasivayam Ambalavanan'; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,

Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, October 05, 2010 2:38 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,

My answers (>>) are below your questions (**)

Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 05, 2010 12:36 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,

Thank you, this is helpful, I have a few more questions (see ** below).

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, October 05, 2010 12:42 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,

(Abhik/Wally/Marie – your comments are also welcome)

If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

***Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.*

>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices

- 2) For Aim (1): determine the association of PaCO₂ in the first 2 weeks with outcomes, we will use PaCO₂ as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

***Could you please clarify how you like to summarize PaCO₂ over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?*

>> I think max, min, time-weighted, and standard deviation should be ok.

- 3) For Aims (2) and (3), to determine the association of high/low PaCO₂ with outcomes, we will divide infants into quartiles based on their maximum PCO₂ and their minimum PCO₂ over the first two weeks. The infants in the highest quartile of max PCO₂ are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO₂ will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO₂ and minimum PCO₂. The outcomes will be assessed in the low and high SpO₂ groups in relation to PaCO₂ status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

***So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PCO₂), >> Yes. fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators]. Hypocapnic (in lower quartile of min PCO₂), >> Yes. As above, I think we should have hypocapnia only, not fluctuators. Fluctuators (in both upper quartile of max PCO₂ lower quartile of min PCO₂) >> Yes. Normocapnic (in middle two quartiles of max PCO₂ AND min PCO₂)*

To define Max PCO₂ and Min PCO₂ do you simply want me to use the maximum and minimum value of all values of PCO₂ for each infant using PCO₂ recorded during the 1st two weeks on the SUPP05 form?

>> Yes

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO₂, minPCO₂, time-weighted PCO₂, and SD of PCO₂ as independent continuous variables with SUPPORT group assignment

****OK.**

>>Great!

Thanks,
Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, October 05, 2010 10:32 AM

To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Dr. Ambalavanan,

I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO2 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc."; could you please provide a complete list?

Thank-you,
Lisa

Lisa Wrage, MPH
Research Statistician
Statistics & Epidemiology
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919-220-2653

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 01, 2010 11:14 AM
To: Das, Abhik; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Hi Lisa, Marie,

What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?

Ambal

N. Ambalavanan MD

Division of Neonatology,
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Tuesday, September 21, 2010 3:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, September 21, 2010 11:15 AM
To: Ambal (ambal@uab.edu)
Cc: Wally Carlo, M.D.; Das, Abhik
Subject: PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.

November 8, 2010– Final abstracts to NICHD for clearance
Mid-November– PAS deadline
April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks
Rose

Rosemary D. Higgins, MD
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From: Lewis-Evans, Amanda
To: Susan Hintz; Bethany Ball; Betty Vohr; Das, Abhik; Gerry Taylor; Hammond, Jane; Higgins, Rosemary (NIH/NICHD) [E]; Jean Lowe; mxh7@cwru.edu; Neil Finer; Seetha Shankaran; vanmeurs@leland.stanford.edu; Wallace, Dennis; Archer, Stephanie (NIH/NICHD) [E]; Auman, Jeanette O.; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Imoore@med.wayne.edu; Newman, Jamie; Suzanne Sayers; Wrage, Lisa Ann; Zaterka-Baxter, Kristin
Cc: alewis@rti.org
Subject: REMINDER: SUPPORT Neuro School Age FU Subcommittee Call (3/6, Wednesday, 3:00 PM ET)
Date: Wednesday, March 06, 2013 9:56:41 AM

Dear all,

Just a friendly reminder about the SUPPORT Neuro School Age FU Conference Call today at 3:00pm ET.

Thanks,

Amanda

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, March 06, 2013 2:55 AM
To: Lewis-Evans, Amanda; Bethany Ball; Betty Vohr; Das, Abhik; Gerry Taylor; Hammond, Jane; Higgins, Rosemary (NIH/NICHD) [E]; Jean Lowe; mxh7@cwru.edu; Neil Finer; Seetha Shankaran; vanmeurs@leland.stanford.edu; Wallace, Dennis; Archer, Stephanie (NIH/NICHD) [E]; Auman, Jeanette O.; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Imoore@med.wayne.edu; Newman, Jamie; Suzanne Sayers; Wrage, Lisa Ann; Zaterka-Baxter, Kristin
Subject: Re: SUPPORT Neuro School Age FU Subcommittee Call (3/6, Wednesday, 3:00 PM ET)

Dear all,

For those who can make it on the call tomorrow (MARCH 6th) - this will be a brief call to update you on progress, and to get your input on a few issues.

The broad agenda points will be as follows:

- 1) Update on tracking and school age follow up
 - a) 3-4 year tracking
 - b) Monthly report table (attached)
 - i) Reminders given to sites with pending cases
 - ii) Future plans for reminders from Dr. Higgins
 - c) Windows closed, open, and upcoming - timeline
- 2) Progress of certification process
 - a) Certification procedures
 - b) Reminders for sites with open windows or upcoming
- 3) Cross check tables DRAFT (attached)
 - a) Review and request for feedback from subcommittee by **March 25th**
 - b) RTI review also needed
- 4) Follow up meeting in April - plans for updates/reminders, review key issues from neurologic and MABC certifications thus far.
- 5) Secondary studies review and status

Thank you all again for your continued work on this study, and your service to this committee.

Susan

Susan R. Hintz, M.D., M.S. Epi
Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
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750 Welch Road, Suite 315
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On Mar 1, 2013, at 6:47 AM, "Lewis-Evans, Amanda" <alewis@rti.org> wrote:

Dear all,

The SUPPORT Neuro School Age FU Conference Call has been scheduled for:

**Wednesday, 3/6
3:00pm ET**

Dial:

Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Thanks,

Amanda

From: [Kennedy, Kathleen A](#)
To: [Michael Cotten, M.D.](#); [Namasivayam Ambalavanan](#)
Cc: [Walsh, Michele](#); [Abhik Das](#); [Gantz, Marie](#); [Wally Carlo, M.D.](#); [Abbot Laptook](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Matt Laughon](#); [Seetha Shankaran](#); [Wrage, Lisa Ann](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013
Date: Tuesday, March 05, 2013 6:29:50 PM
Attachments: [PCO2_SUPPORT_March5_2013cmc \(KAK\).docx](#)

My, time flies. I've added my comments to Mike's. I think the biggest potential problem is that the reviewers may be put off by the complexity of the analyses and they may not be very excited by findings that seem to be exactly what you'd expect (sicker babies with higher PaCO2s do worse). I'm not sure I have a great solution. I've added some ideas in the comments in the attachment.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Michael Cotten, M.D. [<mailto:michael.cotten@duke.edu>]
Sent: Tuesday, March 05, 2013 2:42 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Hi everyone..sorry for my absence on the first round draft....

For the word overage...could you use S-IVH as an acronym for severe IVH? I think you'd get down to 250

Also...I put in a couple of places a query about considering a look at the vent support needed to get the PaCO2 that was measured (max)...i think if all the kids are lumped together, we might miss a signal that sometimes its not so bad....and maybe if you only need cpap or a rate of 20 and mean airway pressure of 7 to get pco2 of 65, that that doesn't have the same association as a kid w/ PaCO2 of 65 as a product of high frequency ventilation w/ a mean airway pressure of 18 and fio2 of 1.0....and there may be many more of those kids in the dataset....so much so that they overwhelm the possibility of leaving the baby on low vent support w/ a high PaCO2 alone....as it reads now, what we know is high PaCO2's are bad...so clinicians are likely to say...turn the vent up to get to 44 - 55...even if we tell them this is an association....

Can we think of an analysis that accounts for the respiratory support needed to get the PaCO2's were looking at?

mc

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, March 05, 2013 12:54 PM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Dear All,

Attached is the second draft of our manuscript (PCO2 SUPPORT March 5 2013.docx). Thank you for all your comments – I have addressed most of them. The main changes are:

- 1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
- 2) Developed a new table of adjusted results
- 3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx) - some comments may need additional analysis (Lisa, would you look over the comments of Abhik Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,

Best regards,
Ambal

From: Namasivayam Ambalavanan

Sent: Thursday, February 21, 2013 10:37 AM

To: Kennedy, Kathleen A; Namasivayam Ambalavanan

Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: PaCO2 manuscript : first draft of Feb21, 2013

Importance: High

Dear All,

Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.

(Stephanie: Would you check the boilerplate and grant acknowledgments?)

Thank you for all your help,

Best regards,
Ambal

Namasivayam Ambalavanan MD

Division of Neonatology,

Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology

University of Alabama at Birmingham

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Email ambal@uab.edu

From: Namasivayam Ambalavanan

Sent: Wednesday, February 02, 2011 10:06 PM

To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov

Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH;

Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

Subject: RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,

Our PAS abstract on PaCO2 in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,

Thank you for all your help,

Ambal

From: Namasivayam Ambalavanan

Sent: Mon 11/8/2010 5:40 PM

To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov

Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

Subject: RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,

Attached is the abstract on PaCO2 SUPPORT abstract for NICHD clearance.

Thank you,

Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO2 variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO2 in the CPAP arm from about 33 to 34. The Max PaCO2 was about the same in all groups)

Thanks,

Ambal

N. Ambalavanan MD

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Email ambal@uab.edu

From: Namasivayam Ambalavanan

Sent: Sun 10/31/2010 6:25 PM

To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu

Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

Subject: RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.

Ambal

(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

From: Namasivayam Ambalavanan

Sent: Sat 10/30/2010 8:15 PM

To: Kennedy, Kathleen A; ambal@uab.edu

Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH;

Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.

Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,
Ambal

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Sat 10/30/2010 4:59 PM
To: Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]
Sent: Saturday, October 30, 2010 10:18 AM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.
Best Michele

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Fri 10/29/2010 5:28 PM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO₂ in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how).

Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?

Thanks,

Ambal

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Email ambal@uab.edu

From: Namasivayam Ambalavanan

Sent: Saturday, October 23, 2010 7:16 AM

To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal

Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran

Subject: RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO₂ (using highest FiO₂ on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?

Ambal

From: Namasivayam Ambalavanan

Sent: Fri 10/22/2010 8:58 PM

To: Michael Cotten; Wrage, Lisa Ann; ambal

Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran

Subject: RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO₂ (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO₂ and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO₂. However, I don't

find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO₂ were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.
Ambal

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Fri 10/22/2010 7:57 PM
To: Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon
Subject: Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co₂? Some babies are easily hyperventilatable, and sometimes practitioners allow co₂ to be high on min settings,,,and those kids are probably way different than kids on high settings or hfv who remain hypercarbic,,,

Mc

From: "Namasivayam Ambalavanan" [NAmbalavanan@peds.uab.edu]
Sent: 10/22/2010 03:59 PM EST
To: "Wrage, Lisa Ann" <wrage@rti.org>; <ambal@uab.edu>
Cc: "Das, Abhik" <adas@rti.org>; "Gantz, Marie" <mgantz@rti.org>; "Wally Carlo, M.D." <WCarlo@peds.uab.edu>; "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>; "Laptook, Abbot" <ALaptook@WIHRI.org>; "Higgins, Rosemary \ (NIH/NICHD) [E]" <higginsr@mail.nih.gov>; <Michele.Walsh@UHhospitals.org>; Michael Cotten; "Laughon, Matthew M" <matt_laughon@med.unc.edu>
Subject: RE: PAS ABSTRACT

Hi Lisa,

(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO₂ (especially higher PaCO₂ and fluctuating PaCO₂) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO₂ is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO₂, minimal PaCO₂, time-weighted PaCO₂, and SD of PaCO₂ as independent continuous variables with actual time-weighted PaO₂ (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others),

prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO2 for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO2 variables with outcome, after adjustment for the other variables. We probably do not need PaCO2 values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO2 and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO2 terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO2 to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO2 category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO2 categories and the numbers in each CO2 category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,
Ambal

N. Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Email ambal@uab.edu

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 22, 2010 2:48 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,

I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract.

Since there are 5 CO2 variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.

Thanks and have a great weekend.

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Wednesday, October 20, 2010 10:58 AM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.

Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Wed 10/20/2010 9:42 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,

Thanks for the response. Regarding the time-weighted CO2, Wally and Marie did decide to cap the amount of time that on CO2 level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.

Thanks.

Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis but I think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

From: Gantz, Marie <mgantz@rti.org>
Sent: Tuesday, October 19, 2010 7:29 PM

To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>
Cc: Das, Abhik <adas@rti.org>; Wrage, Lisa Ann <wrage@rti.org>
Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5
75th 12
90th 21
95th 25.5
99th 80
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 15, 2010 2:56 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Lisa,

Thank you for the email.

- 1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
 - 2) I think PROM>24h is ok
 - 3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.
 - 4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.
- Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, October 15, 2010 1:46 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted CO2 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95th %ile is 25.1 hours and the 99th%ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.

I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,
Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 05, 2010 2:45 PM

To: 'Namasivayam Ambalavanan'; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, October 05, 2010 2:38 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,
My answers (>>) are below your questions (**)

Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 05, 2010 12:36 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Thank you, this is helpful, I have a few more questions (see ** below).
Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, October 05, 2010 12:42 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,
(Abhik/Wally/Marie – your comments are also welcome)
If we are going to do a condensed version for the PAS abstract, these would probably be the

priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

****Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.**

>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices

- 2) For Aim (1): determine the association of PaCO₂ in the first 2 weeks with outcomes, we will use PaCO₂ as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

****Could you please clarify how you like to summarize PaCO₂ over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?**

>> I think max, min, time-weighted, and standard deviation should be ok.

- 3) For Aims (2) and (3), to determine the association of high/low PaCO₂ with outcomes, we will divide infants into quartiles based on their maximum PCO₂ and their minimum PCO₂ over the first two weeks. The infants in the highest quartile of max PCO₂ are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO₂ will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO₂ and minimum PCO₂. The outcomes will be assessed in the low and high SpO₂ groups in relation to PaCO₂ status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

****So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PCO₂), >> Yes, fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators]. Hypocapnic (in lower quartile of min PCO₂), >> Yes. As above, I think we should have hypocapnia only, not fluctuators. Fluctuators (in both upper quartile of max PCCO₂ lower quartile of min PCO₂) >> Yes. Normocapnic (in middle two quartiles of max PCO₂ AND min PCCO₂)**

To define Max PCO₂ and Min PCO₂ do you simply want me to use the maximum and minimum value of all values of PCO₂ for each infant using PCO₂ recorded during the 1st two weeks on the SUPP05 form?

>> Yes

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO₂, minPCO₂, time-weighted PCO₂, and SD of PCO₂ as independent continuous variables with SUPPORT group assignment

****OK.**

>>Great!

Thanks,
Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 05, 2010 10:32 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Dr. Ambalavanan,

I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO2 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc. ", could you please provide a complete list?

Thank-you,
Lisa

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From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 01, 2010 11:14 AM
To: Das, Abhik; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Hi Lisa, Marie,

What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?

Ambal

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Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Tuesday, September 21, 2010 3:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, September 21, 2010 11:15 AM
To: Ambal (ambal@uab.edu)
Cc: Wally Carlo, M.D.; Das, Abhik
Subject: PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for

potential additional analysis.

November 8, 2010– Final abstracts to NICHD for clearance

Mid-November– PAS deadline

April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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Title:

Association of PaCO₂ with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Authors:

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Short Title: PaCO₂ and IVH

Abbreviations: BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

Keywords: Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis

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Conflicts of interest: The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

Word count: abstract: 260; text of manuscript: 2693 (Introduction, Methods, Results, and Discussion).

What's known on this subject: Variations in arterial partial pressure of carbon dioxide (PaCO_2) might contribute to or be associated with several clinical outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

What this study adds: Higher PaCO_2 and greater fluctuation in PaCO_2 were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment (and/or death). The correlation of PaCO_2 with FiO_2 and days of ventilation support higher maximum PaCO_2 as a marker of illness severity

ABSTRACT:

Objective: To determine the association of PaCO₂ with severe intraventricular hemorrhage (S-IVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 240/7 to 276/7 wks GA infants randomized in the SUPPORT trial to SpO₂ targets of 85-89% vs 91-95% and two ventilation strategies enrolled in the SUPPORT trial that included infants 24^{0/7} to 27^{6/7} wks GA randomized to SpO₂ targets of 85-89% vs 91-95% and two ventilation strategies. Five PaCO₂ variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO₂], hypocapnic [lowest quartile of Min PaCO₂], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO₂]). Unadjusted and adjusted analyses compared PaCO₂ variables for infants with and without severe IVH, BPD, and NDI (+/- death). **Results:** ~~S-Severe~~ IVH, BPD, and NDI (+/- death) were more common in hypercapnic infants and fluctuators. Other variables associated with ~~S-severe~~ IVH, BPD, and NDI (+/- death) included lower birth weight, male sex, and lower Apgars, but not treatment group. The relationship of Max PaCO₂ with outcomes persisted after adjustment (For ↑ of 10 mmHg: ~~S-Severe~~ IVH/death: OR 1.23 [1.12-1.36]; BPD/death: OR 1.38 [1.24-1.54]; NDI/death: OR 1.26 [1.13-1.39], all p < 0.0001). No interaction was found between PaCO₂ and SpO₂ or CPAP/surfactant group. Max PaCO₂ was positively correlated with maximum FiO₂ (r_s 0.55, p < 0.0001) & ventilator days (r_s 0.61, p < 0.0001). **Conclusions:** Higher PaCO₂ and greater fluctuation in PaCO₂ were associated with severe IVH, BPD, and NDI (+/- death). Correlation of PaCO₂ with FiO₂ and ventilator days supports higher Max PaCO₂ as a marker of illness severity rather than permissive hypercapnia.

Comment [reviewer1]: Could you call this S-IVH? You could save some room word count wise?

Comment [KKA2]: You could shorten this to "to different oxygenation and ventilation strategies."

Comment [KKA3]: Not sure the editor will allow this but I guess you can try.

Comment [KKA4]: Then change this to "oxygenation or ventilation"

Comment [KKA5]: I think this is a little confusing and you don't have room to explain it. Maybe you could just delete these words from the abstract.

(Abstract Word Count = 260: Need to shrink)

MANUSCRIPT TEXT

INTRODUCTION

Variations in arterial partial pressure of carbon dioxide (PaCO_2) are associated with and may possibly contribute to several important clinical outcomes of prematurity such as intraventricular hemorrhage (IVH)¹, periventricular leukomalacia (PVL)^{2,3}, bronchopulmonary dysplasia (BPD)⁴, and subsequent neurodevelopmental impairment (NDI)⁵. Increased PaCO_2 increases cerebral blood flow,⁶⁻⁸ while decreased PaCO_2 reduces cerebral blood flow, increases cerebral fractional oxygen extraction, and decreases cerebral electrical activity.⁹ We have previously shown that both high and low PaCO_2 levels and wide fluctuations in PaCO_2 are associated with a higher risk of severe IVH (IVH Grades III or IV).¹ Periventricular leukomalacia (PVL) is strongly linked to hypoxemia.^{2,3,10}

Cerebral blood flow decreases slightly with increased oxygenation⁸ but the interactions between PaCO_2 and PaO_2 have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher PaCO_2 as well as a lower PaO_2 , permitting earlier weaning from mechanical ventilation and reduced volutrauma.^{4,11,12} The combination of a higher PaCO_2 (permissive hypercapnia) as well as a lower PaO_2 (targeting a lower SpO_2 range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower PaO_2 alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants 24^{0/7} to 27^{6/7} weeks gestation and compared outcomes in infants randomly assigned to oxygen saturation targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (a $\text{PaCO}_2 > 65$ mm Hg permitted intubation, while a $\text{PaCO}_2 < 65$ mm Hg with a $\text{pH} > 7.20$ was a mandatory extubation criterion) or intubation and surfactant within 1

Comment [KKA6]: I would prefer "associated with".

Comment [KKA7]: Is there a reason you need to make these points about PaO_2 rather than SpO_2 ? You haven't referenced anything here that measured PaO_2 .

hour after birth (a $\text{PaCO}_2 < 50$ mm Hg with a $\text{pH} > 7.30$ was a mandatory extubation criterion).^{13, 14}

Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant

~~target groups although infants in the CPAP (higher PaCO_2 target) group less frequently required~~

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surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and

were more likely to be alive and free of mechanical ventilation by day 7 after birth. ~~In addition,~~

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~~Between the oxygenation target groups, death occurred more frequently in the lower oxygen~~

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saturation (low SpO_2) target group (19.9 vs. high SpO_2 16.2%; RR 1.27; CI 1.01, 1.60; $p = 0.04$)

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while severe retinopathy among survivors occurred less often in these infants (8.6 vs. 17.9%; RR

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0.52; CI 0.37, 0.73; $p < 0.001$), without significant differences in other outcomes.¹³ There were no

significant differences in the composite outcome of death or neurodevelopmental impairment (NDI) among infants in any of the treatment groups.¹⁵

It is possible that clinical outcomes that are not significantly different by SpO_2 target groups might be different when the combination of PaCO_2 and SpO_2 is analyzed. PaCO_2 is a

possible effect modifier, as PaCO_2 might modify the association between SpO_2 target and outcome, ~~due to interaction between PaCO_2 and outcome.~~ PaCO_2 might also be a confounder – it

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might distort the true relation between the SpO_2 group and outcome, as PaCO_2 might be related to both SpO_2 (as PaCO_2 influences the hemoglobin dissociation curve and thereby the SpO_2 for a given PaO_2) and outcome. We hypothesized that both extremes of PaCO_2 would be associated

with severe IVH, and that effect modification of SpO_2 will be observed, with hypercapnia associated with severe IVH in the low but not high SpO_2 group. We also hypothesized that BPD

would be lower in infants with hypercapnia and low SpO_2 , and that higher PaCO_2 will be associated with a higher risk of NDI.

Comment [KKAB]: I'm not sure you want to make this point. For PaCO_2 to be a confounder in the association between O_2 sat target and outcome, you would need to postulate that PaCO_2 differed between oxygen target groups because the randomization did not result in a balanced distribution.

Comment [KKAB]: If you're considering PaCO_2 as an effect modifier, don't you want to look at different PaCO_2 groups to see if the association between SaO_2 target and outcome is the same or different?

Comment [reviewer10]: Just as in the looks at pCO_2 and HIE...if you need a lot of ventilation and you're only getting a high pCO_2 out of all that mech ventilator energy delivery (on mean airway pressure of 15, fio_2 1.0, and rate of 40 w/ pCO_2 of 65.....that should be looked at differently than someone on a mean airway pressure of 7, fio_2 0.21 and imv of 20 w/ a pCO_2 of 65...right? I don't think looking at the pCO_2 alone, w/o accounting for the respiratory support needed to get to that pCO_2 is really that informative....

PATIENTS AND METHODS

Patient characteristics:

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.^{13, 14} Neonatal information collected for the SUPPORT trial ~~and in the generic database~~ included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical outcomes, and treatment. The baseline characteristics of this population¹³ and characteristics of the follow-up cohort¹⁵ have been previously reported.

PaCO₂ variables

Five PaCO₂ variables were defined for this observational study, using all PaCO₂ concentrations available from blood gases obtained every 8±4 hours up to 3 times a day on postnatal days 1-14: minimum level, maximum level (Max PaCO₂), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted PaCO₂ was calculated as described previously.¹ Time between blood gases was capped at 24 hours (~5% of all time difference measurements) so any one blood gas represents ~~up to~~ no more than 24 hours of time. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum PaCO₂ levels over days 1-14 into quartiles. Infants with minimum PaCO₂ levels in the lowest quartile who were not also in the highest quartile of maximum PaCO₂ level were then categorized as 'hypocapnic'. Infants with maximum PaCO₂ levels in the highest quartile who were not also in the lowest quartile of minimum PaCO₂ level were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum PaCO₂ and the highest quartile of maximum PaCO₂ were categorized as 'fluctuators', and the remaining infants, those whose minimum PaCO₂ level fall in quartiles 2-4 and maximum PaCO₂ levels fall in quartiles 1-3 were categorized as 'normocapnic'.

Comment [KKA11]: I couldn't enter a comment in these references. Why did you abbreviate the name of the Network? I don't think anyone will recognize those initials and that's not the way the authorship is listed.

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Comment [KKA12]: I think it's important to first say that decisions about blood gas measurements were not determined by the study protocol and give the frequency with which they were recorded for the study. Then I'd define how you used the data to construct independent variables for this study.

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Other variables

Maternal hypertension was defined as pregnancy induced hypertension. Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth. Prenatal steroids were defined as any use of antenatal steroids. Maximum FiO_2 was defined as the maximum of FiO_2 at 24 hours, day 3, 7, 14 and severe illness as $FiO_2 > 0.4$ and mechanical ventilation for 8+ hours in the 1st 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),¹⁶ and BPD was defined using the physiologic definition at 36 w PMA.^{17, 18} Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.¹⁵

Statistical Analysis

The $PaCO_2$ and other variables were compared by each of 6 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death. Specifically, the $PaCO_2$ and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance ($p < .05$) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis generating goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the Max $PaCO_2$ variable were obtained using a generalized estimating equation (GEE) model for the binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for the fact

Comment [KKA13]: Maybe you're going to deal with this later, but I think this is problematic as a marker of illness because it's going to be higher, for the same degree of illness, for babies in the high sat target group.

Comment [KKA14]: What's the rationale for this cut-off?

that multiple births were randomized to the same treatment arm in the SUPPORT trial. Variables included in the models along with Max PaCO₂ were: SUPPORT trial treatment groups (High/Low SpO₂, CPAP/ventilator), severe illness, birth weight, GA group, gender, race, prenatal steroid use, pregnancy induced hypertension, rupture of membranes > 24 hours, indicators for 1 & 5 minute Apgar scores < 3, and center. Interaction terms for Max PaCO₂ x SpO₂ treatment groups and Max PaCO₂ x CPAP/ventilator treatment groups were also included, to allow for the association between PaCO₂ and outcomes to differ by treatment arm. Results are expressed as adjusted odds ratios and 95% confidence intervals.

Why no variable for vent support at time of pco2...i'd be interested to know if pco2's were as predictive in permissive (low intervention) high pco2 group vs. too sick high pco2 group that had high pco2 despite high vent support...the clinical question will be is it ok to tolerate high co2's if you don't need much ventilation support...and maybe we throw the good out w/ the bad if we just look at the pco2 and not what it takes to get the pco2 we have to deal w/.

RESULTS

Unadjusted Results:

All PaCO₂ variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with severe IVH as compared to those without severe IVH (Table 1). In general, infants who developed severe IVH had a lower minimum, higher maximum and greater variation in PaCO₂ as compared to those without severe IVH (Table 1). Max PaCO₂ demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median Max PaCO₂ between infants with severe IVH and those without severe IVH. The magnitude of separation in minimum, standard deviation, and time-weighted

Comment [reviewer15]: Maybe one way to get at this would be to see if there is a bi-modal distribution of max pco2 or some vent support parameter at time of peak co2??? Some babies in the 'permissive group' and some in the 'just barely making it' group...it may be that high pco2 is the same bad influence in both groups...but I'm not convinced w/ the current analysis that lumps them all together.

Comment [KKA16]: I agree with Mike's point. I think this is a really complicated problem. Even if you have enough data on ventilator support to try to adjust for the difference between intentional hypercarbia and intractably bad lungs, I'm not sure you could sort this out in an observational study. As I said above, I'm particularly concerned about using FiO2 as an illness measure in babies randomized to different O2 sat goals. I think you might have less trouble trying to look for interaction. If you can assume (probably not entirely valid) that hypercarbia was not affected by the study interventions, you could ask whether the associations between sat goal target and outcomes were different in different PaCO2 groups. Sample size will be a problem but I don't think it's as badly confounded.

PaCO₂ were statistically highly significant (p<0.0001) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed severe IVH had higher maximum, standard deviation, and time-weighted PaCO₂ compared to survivors without severe IVH (Table 1).

Results for BPD (Table 2), BPD or death (Table 2), NDI (Table 3), and NDI or death (Table 3) were similar to those for severe IVH and severe IVH or death.

Adjusted Results (Table 4):

As the Max PaCO₂ variable was associated with outcome by bivariate analysis and demonstrated (of the PaCO₂ variables) the maximum separation between the groups with or without the outcomes, adjusted analyses were performed to determine if this variable was an independent predictor of outcome. Interaction terms for Max PaCO₂ x SpO₂ treatment groups and Max PaCO₂ x CPAP/ventilator treatment groups were also included but these interaction terms were not significant, and were therefore removed and excluded. Max PaCO₂ was significantly associated with higher odds of severe IVH/death (OR 1.23, 95% CI 1.12-1.36 for an increase in Max PaCO₂ of 10 mmHg, p <0.0001). Other variables significantly associated (p<0.05) with IVH/death included: low SpO₂ group, severe illness, lower birth weight, male gender, pregnancy induced hypertension, low 1 minute Apgar score, and center.

Max PaCO₂ was significantly associated with higher odds of BPD/death (OR 1.38, 95% CI 1.24-1.54 for an increase in Max PaCO₂ of 10 mmHg, p < 0.0001). Other variables significantly associated (p<0.05) with BPD/death included: severe illness, lower birth weight, male gender, non-white race, lower 1 minute Apgar score, and center.

Max PaCO₂ was also significantly associated with higher odds of NDI/death (OR 1.26, 95% CI 1.13-1.40, p<0.0001) for an increase in Max PaCO₂ of 10 mmHg. Other variables

Comment [KKA17]: Maybe I'm missing something here, but it seems like all this means is that babies who have severe IVH or BPD or NDI are sicker and more unstable than babies without those outcomes.

Comment [KKA18]: Could this be explained by "over-adjustment" for illness severity in the high O2 sat group?

significantly associated ($p < 0.05$) with NDI/death included: severe illness, lower birth weight, male gender, PIH, and lower 1 min Apgar score.

As higher Max PaCO₂ may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation) or due to more severe pulmonary disease (which may be associated with higher max FiO₂, days of mechanical ventilation, and severe illness), correlations of Max PaCO₂ with max FiO₂, days of ventilation, and severe illness (as previously defined) were calculated. Max PaCO₂ was positively correlated with both max FiO₂ (Spearman correlation coefficient = 0.55, $p < 0.0001$) and days of ventilation (Spearman correlation coefficient = 0.61, $p < 0.0001$). There was also a significant difference in PaCO₂ level by infants defined as having severe illness (median max PaCO₂=78) vs. infants defined as having no severe illness (median max PaCO₂=61), $p < 0.0001$ by Wilcoxon two sample test.

Comment [KKA19]: This seems like a pretty crude way to address this to me. Even if there were important differences among clinicians in desired PaCO₂ targets, it's likely that achieved PaCO₂ would be heavily influenced by illness severity and it would be hard to identify an inverse relationship between PaCO₂ and ventilator days.

DISCUSSION

We found that extremes of PaCO₂ were associated with worse outcome (severe IVH, BPD, and NDI) in extremely preterm infants. A higher maximum PaCO₂ in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO₂, days of ventilation, and severe illness).

Our study has the limitation that infants in the SUPPORT trial^{13, 14} were not primarily randomized to different specific PaCO₂ ranges as in the randomized trials of permissive hypercapnia^{4, 11, 19} but to interventions (Early CPAP or Prophylactic/Early Surfactant and conventional ventilation) with different PaCO₂ goals. However, it has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, criteria

Comment [reviewer20]: I think the kids w/ high co₂'s but no severe illness, whose vent support never rose above some 'serious' level might be a more accurate/valid # of than total days. ...did you account for death on the ventilator? Then the days on vent might not be so good. but the high fio₂ is likely to match up.

Comment [KKA21]: I think the point that the CPAP/surfactant intervention also included different PaCO₂ goals is not very apparent. You mention the extubation criteria in the Methods but then it doesn't come up again until here. That said, I'm not sure what you can do to try to make a point with the observational data. Since the main trial showed no difference in BPD/death between those two strategies, it seems like you're trying to investigate a mechanism for a difference that wasn't observed.

for intubation and extubation were used in the trial, and trained research coordinators collected data on blood gases and ventilator settings in addition to other routine clinical variables. Longer-term follow-up was achieved in the majority of infants, and was done by certified trained personnel. No interaction was observed between maximum PaCO₂ and SpO₂ groups, probably because randomization in this trial most likely led to a similar range of PaCO₂ in both SpO₂ groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in PaCO₂ secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.¹⁴

Previously, we have shown in a single-center retrospective analysis that both high and low PaCO₂ levels and wide fluctuations in PaCO₂ are associated with an increased risk of severe IVH.¹ The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of PaCO₂ were statistically significant, they were of small magnitude. Clinically relevant differences (~10 mm Hg) were only noted in the maximum PaCO₂. As maximum PaCO₂ was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum PaCO₂ had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation.

In this cohort, the average (time-weighted) PaCO₂ even in infants without severe IVH was ≥ 48 mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the "permissive hypercapnia" range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.¹¹ Our data indicate clinical practices in academic centers have evolved to maintain PaCO₂ in the permissive hypercapnia

range. However, as the maximum PaCO₂ exceeded this range even in infants without severe IVH, it is apparent that tight control of PaCO₂ within this narrow range is difficult.

A higher maximum and time-weighted PaCO₂ and a greater magnitude of fluctuation in PaCO₂ were associated with a greater risk of BPD and BPD/death. Similar to severe IVH, this is likely due to greater illness severity and more severe lung disease being associated with a higher PaCO₂ rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO₂ elimination for a given minute ventilation, due to a higher CO₂ in alveolar air (P_ACO₂). Also, due to the Bohr effect, the affinity of hemoglobin for oxygen decreases with increasing PaCO₂, and peripheral unloading of oxygen is improved with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in weaning preterm infants from the ventilator. There is also evidence that hypercapnic acidosis may attenuate ventilator-induced lung injury and inflammation by multiple molecular mechanisms.^{9, 12, 14} However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in BPD/death have been demonstrated.^{4, 11, 12, 19} In the largest randomized trial of permissive hypercapnia to date, which was terminated early due to unanticipated non-respiratory adverse events secondary to dexamethasone therapy, the relative risk for death or BPD in the minimal ventilation versus routine ventilation groups was 0.93 (63% vs. 68%; 95% CI 0.77-1.12, p = 0.43), despite ventilator support at 36 weeks being 1% in the minimal versus 16% in the routine group (p<0.01).⁴

Max PaCO₂ was also significantly associated with higher NDI/death, confirming our previous single-center study with a smaller sample size.⁵ This association may be secondary to Max PaCO₂ being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.²⁰ It is also possible that alterations in PaCO₂ may be a direct mediator of brain injury. A sudden marked increase in cerebral blood flow secondary to a spike in PaCO₂⁶⁻⁸ may result in severe IVH¹ and contribute to NDI. A reduction in cerebral blood flow due to decreased PaCO₂⁹ may contribute to lower white matter perfusion and result in periventricular leukomalacia (PVL).^{2, 3, 10} The brain injury associated with extremes of PaCO₂ may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.^{21, 22}

In conclusion, our work demonstrates that Max PaCO₂ is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO₂, Max PaCO₂ may be useful for risk-stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO₂ with outcomes at later time points and in other populations needs to be determined.

Comment [KKA22]: Maybe there's more that could be done with this point to make this study more attractive to reviewers. As it is, it seems only to confirm your single-center study and I'm afraid that the finding that higher PaCO₂ is associated with illness severity and bad outcomes won't seem very exciting. Do you think that Max PaCO₂ in the first 24 hrs or 48 hrs might have high enough sensitivity and specificity for BPD to be useful?

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Tables:

Table 1- Bivariate analyses for Severe IVH, and for Death or Severe IVH

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value ¹ (Severe IVH vs. No severe IVH)	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value ¹ (Death/severe IVH vs. No Death/severe IVH)
PaCO ₂ , minimum level	#	163	1098		325	971	
	Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
PaCO ₂ , maximum level	Median, IQR	32 (27-37)	34 (29-38)	.0047	33 (28-38)	34 (30-38)	.69
	#	163	1098		325	971	
PaCO ₂ , standard deviation	Mean (SD)	76.3 (19.8)	66.7 (17)		78.6 (21.8)	65 (15.9)	
	Median, IQR	75 (63-85)	65.5 (55-75)	<.0001	76 (65-88)	64 (54-74)	<.0001
PaCO ₂ , time-weighted	#	163	1077		314	951	
	Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
PaCO ₂ , time-weighted	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<.0001
	#	163	1098		325	971	
PaCO ₂ category:	Mean (SD)	49.6 (6.5)	48 (7.1)		52.3 (11.8)	47.5 (7.0)	
	Median, IQR	49.4 (45.8-54.2)	48.6 (43.6-52.9)	.0088	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<.0001
PaCO ₂ category:	# (%)			<.0001			<.0001
Hypocapnic		30 (18.4)	205 (18.7)		48 (14.8)	189 (19.5)	
Hypercapnic		42 (25.8)	168 (15.3)		102 (31.4)	127 (13.1)	
Fluctuator		26 (16.0)	70 (6.4)		45 (13.9)	52 (5.4)	
Normocapnic		65 (39.9)	658 (59.7)		130 (40.0)	603 (62.1)	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value ¹ (Severe IVH vs. No severe IVH)	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value ¹ (Death/severe IVH vs. No Death/severe IVH)
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	.13	166 (49.6)	496 (50.7)	.73
Treatment: SpO ₂ group, High or Low O ₂	#	164	1106		335	979	
	High O ₂ , # (%)	81 (49.4)	559 (50.5)	.78	156 (46.6)	505 (51.6)	.11
Birth Weight (g)	#	164	1106		335	979	
	Mean (SD)	802 (182)	838 (193)		763 (187)	853 (190)	
	Median (IQR)	783 (681-944)	830 (700-974)	.03	750 (640-881)	850 (710-990)	<.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	.08	197 (58.8)	514 (52.5)	.046
Race:	# (%)			.016			.092
NH Black		55 (33.5)	421 (38.1)		112 (33.4)	376 (38.4)	
NH White		55 (33.5)	442 (40.0)		133 (39.7)	387 (39.5)	
Hispanic		44 (26.8)	208 (18.8)		72 (21.5)	187 (19.1)	
Other		10 (6.1)	35 (3.2)		18 (5.4)	29 (3.0)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	.26	112 (33.4)	376 (38.4)	.104
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	.11	133 (39.7)	387 (39.5)	.96
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	.03	21 (6.6)	110 (12.0)	.0078

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value ¹ (Severe IVH vs. No severe IVH)	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value ¹ (Death/severe IVH vs. No Death/severe IVH)
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	.006	97 (30.4)	336 (34.9)	.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	.84	325 (97.3)	938 (95.8)	.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	.022	120 (35.9)	200 (20.4)	<.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	.04	29 (8.7)	29 (3.0)	<.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	.47	117 (37.9)	384 (39.2)	.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	.69	108 (32.2)	325 (33.2)	.74

¹ p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 2 - Bivariate analyses for BPD (in subset of survivors to 36 weeks) and Death or BPD (in all infants)

Characteristic		BPD (N=442)	No BPD (N=666)	p- value ¹ (BPD vs. No BPD)	Death or BPD (N=650)	No Death or BPD (N=666)	p-value ¹ (Death/BPD vs. No Death/BPD)
PaCO ₂ , minimum level	#	441	659		639	659	
	Mean (SD)	32.8 (6.6)	33.8 (6.6)		34.1 (10.6)	33.8 (6.6)	
	Median, IQR	33 (29-37)	34 (30-38)	.015	33 (29-38)	34 (30-38)	.25
PaCO ₂ , maximum level	#	441	659		639	659	
	Mean (SD)	74 (16)	61.2 (15.2)		75.9 (18.7)	61.2 (15.2)	
	Median, IQR	72 (64-83)	60 (50-69)	<.0001	73 (65-85)	60 (50-69)	<.0001
PaCO ₂ , standard deviation	#	438	642		625	642	
	Mean (SD)	10 (3.2)	8.1 (3.3)		10.9 (5.1)	8.1 (3.3)	
	Median, IQR	9.8 (7.8-11.8)	8.0(5.7-9.9)	<.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<.0001
PaCO ₂ , time-weighted	#	441	659		639	659	
	Mean (SD)	50.7 (6.2)	45.8 (6.8)		51.7 (9.4)	45.8 (6.8)	
	Median, IQR	51 (47.3-54.3)	46.2 (41.1-50.4)	<.0001	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<.0001
PaCO ₂ category:	# (%)						
	Hypocapnic	78 (17.7)	138 (20.9)	<.0001	100 (15.7)	138 (20.9)	<.0001
	Hypercapnic	101 (22.9)	59 (9.0)		170 (26.6)	59 (9)	
	Fluctuator	48 (10.9)	24 (3.6)		74 (11.6)	24 (3.6)	
Normocapnic	214 (46.5)	438 (66.5)		295 (46.2)	438 (66.5)		
Treatment: CPAP or Surfactant group	#	442	666		650	666	

Characteristic		BPD (N=442)	No BPD (N=666)	p- value ¹ (BPD vs. No BPD)	Death or BPD (N=650)	No Death or BPD (N=666)	p-value ¹ (Death/BPD vs. No Death/BPD)
	CPAP, # (%)	223 (50.4)	346 (52)	.62	317 (48.8)	346 (52.0)	.25
Treatment: SpO ₂ group, High or Low O ₂	#	442	666		650	666	
	High O ₂ , # (%)	237 (53.6)	331 (49.7)	.20	331 (50.9)	331 (49.7)	.66
Birth Weight (g)	#	442	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650- 870)	900 (770- 1020)	<.0001	740 (643- 870)	900 (770- 1020)	<.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	.043	375 (57.7)	337 (50.6)	.0098
Race:	# (%)						
NH Black		157 (35.5)	268 (40.2)	.013	221 (34)	268 (40.2)	.024
NH White		200 (45.3)	237 (35.6)		284 (43.7)	237 (35.6)	
Hispanic		73 (16.5)	137 (20.6)		122 (18.8)	137 (20.6)	
Other		12 (2.7)	24 (3.6)		23 (3.5)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non- Hispanic Black, # (%)	157 (35.5)	268 (40.2)	.11	221 (34)	268 (40.2)	.019
Race, collapsed: NH White vs. all other races	Non- Hispanic White, # (%)	200 (45.3)	237 (35.6)	.0013	284 (43.7)	237 (35.6)	.0026
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	.18	68 (11.1)	63 (10.1)	.58
Rupture of membranes > 24 hours prior to birth	#	431	659		626	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33	201 (32.1)	233 (35.4)	.22

Characteristic		BPD (N=442)	No BPD (N=666)	p- value¹ (BPD vs. No BPD)	Death or BPD (N=650)	No Death or BPD (N=666)	p-value¹ (Death/BPD vs. No Death/BPD)
Prenatal steroids	#	442	666		649	666	
	Yes, # (%)	427 (96.6)	636 (95.5)	.36	629 (96.9)	636 (95.5)	.18
1 minute Apgar < 3	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<.0001	207 (31.9)	114 (17.1)	<.0001
5 minute Apgar < 3	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	.11	41 (6.3)	17 (2.6)	.0009
Prophylactic indomethacin	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	.75	240 (38.5)	261 (39.2)	.79
Vaginal delivery	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240 (36.0)	.0044	193 (29.7)	240 (36.0)	.014

¹ p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 3 Bivariate analyses for NDI (in survivors) and Death or NDI (in all infants).

Characteristic		NDI (N=98)	No NDI (N=878)	p-value ¹ (NDI vs. No NDI)	Death or NDI (N=356)	No Death or NDI (N=878)	p-value ¹ (Death/NDI vs. No death or NDI)
PaCO ₂ , minimum level	#	98	872		346	872	
	Mean (SD)	31.3 (7.0)	33.6 (6.6)		34.9 (13.1)	33.6 (6.6)	
	Median, IQR	31 (26-36)	33 (30-38)	.0013	33 (28-38)	33 (30-38)	0.95
PaCO ₂ , maximum level	#	98	872		346	872	
	Mean (SD)	75.2 (19.6)	64.8 (16)		78.7 (21.4)	64.8 (16.0)	
	Median, IQR	74 (65-88)	64 (54-74)	<.0001	76 (66-88)	64 (54-74)	<.0001
PaCO ₂ , standard deviation	#	98	853		335	853	
	Mean (SD)	10.2 (3.6)	8.6 (3.4)		11.9 (6.2)	8.6 (3.4)	
	Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<.0001
PaCO ₂ , time-weighted	#	98	872		346	872	
	Mean (SD)	49.7 (7.3)	47.4 (6.9)		52.5 (11.6)	47.4 (6.9)	
	Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	.0014	51.7 (47.1-56)	48 (42.8-52.3)	<.0001

Characteristic		NDI (N=98)	No NDI (N=878)	p-value ¹ (NDI vs. No NDI)	Death or NDI (N=356)	No Death or NDI (N=878)	p-value ¹ (Death/NDI vs. No death or NDI)
PaCO ₂ category:	# (%)						
	Hypocapnic	22 (22.5)	171 (19.6)	<.0001	51 (14.7)	171 (19.6)	<.0001
	Hypercapnic	25 (25.5)	111 (12.7)		111 (32.1)	111 (12.7)	
	Fluctuator	17 (17.4)	44 (5.1)		49 (14.2)	44 (5.1)	
Normocapnic	34 (34.7)	546 (62.6)	135 (39.0)		546 (62.6)		
Treatment: CPAP or Surfactant group	#	98	878		356	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44
Treatment: SpO ₂ group, High or Low O ₂	#	98	878		356	878	
	High O ₂ , # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
Gender	Median (IQR)	754 (643-914)	850 (710-995)	<.0001	734 (621-870)	850 (710-995)	<.0001
	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	.013
Race:	# (%)						
	NH Black	37 (37.8)	333 (37.9)	0.89	125 (35.1)	333 (37.9)	0.47
	NH White	37 (37.8)	354 (40.3)		139 (39)	354 (40.3)	
	Hispanic	21 (21.4)	161 (18.3)		78 (21.9)	161 (18.3)	
Other	3 (3.1)	30 (3.4)	14 (3.9)		30 (3.4)		
Race, collapsed: NH Black vs. all other races	Non- Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97	125 (35.1)	333 (37.9)	0.35

Characteristic		NDI (N=98)	No NDI (N=878)	p-value ¹ (NDI vs. No NDI)	Death or NDI (N=356)	No Death or NDI (N=878)	p-value ¹ (Death/NDI vs. No death or NDI)
Race, collapsed: NH White vs. all other races	Non- Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62	139 (39)	354 (40.3)	0.68
HTN, pregnancy induced	#	88	829		335	829	
Rupture of membranes > 24 hours prior to birth	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
	#	97	863		341	863	
Prenatal steroids	Yes, # (%)	264 (26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16
	#	98	878		355	878	
1 minute Apgar < 3	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
	#	98	877		355	877	
5 minute Apgar < 3	Yes, # (%)	36 (36.7)	181 (20.6)	.0003	130 (36.6)	181 (20.6)	<.0001
	#	98	878		356	878	
Prophylactic indomethacin	Yes, # (%)	7 (7.1)	27 (3.1)	.037	29 (8.2)	27 (3.1)	.0001
	#	98	878		330	878	
Vaginal delivery	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
	#	98	878		356	878	
	Yes, # (%)	29 (29.6)	289 (32.9)	0.51	114 (32)	289 (32.9)	0.76

¹ p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 4: Adjusted analyses for max PaCO₂ in relation to outcomes of severe IVH/death, BPD/death, and NDI/death.

Severe IVH/death					
Characteristic	Estimate	Standard Error	95% Confidence Limits		P-value
Max PaCO ₂ (per mm Hg)	0.0209	0.0050	0.0111	0.0308	<.0001
High SpO ₂ group	-0.3892	0.1605	-0.7039	-0.0746	0.015
Severe illness	1.1170	0.1848	0.7548	1.4791	<.0001
Birth weight (per g)	-0.0014	0.0006	-0.0026	-0.0002	0.019
Male	0.3710	0.1669	0.0439	0.6982	0.026
Pregnancy induced hypertension	-1.1000	0.3187	-1.7247	-0.4753	0.0002
Apgar 1' < 3	0.4952	0.1832	0.1361	0.8543	0.01
Center	Variable (depending on center)				<.0001
BPD/death					
Characteristic	Estimate	Standard Error	95% Confidence Limits		P-value
Max PaCO ₂ (per mm Hg)	0.0325	0.0055	0.0216	0.0434	<.0001

Severe illness	1.1065	0.1881	0.7377	1.4752	<.0001
Birth weight (per g)	-0.0038	0.0005	-0.0048	-0.0027	<.0001
Male	0.4984	0.1545	0.1956	0.8011	0.001
Race (White)	0.4106	0.1696	0.0781	0.7431	0.017
Apgar 1'<3	0.4998	0.1878	0.1318	0.8677	0.01
Center	Variable (depending on center)				<.0001
NDI/death					
Characteristic	Estimate	Standard Error	95% Confidence Limits		P-value
Max PaCO ₂ (per mm Hg)	0.0227	0.0052	0.0126	0.0329	<.0001
Severe illness	0.7943	0.1802	0.4411	1.1476	<.0001
Birth weight (per g)	-0.0023	0.0006	-0.0034	-0.0011	0.0001
Male	0.5394	0.1801	0.1863	0.8925	0.002
Pregnancy induced hypertension	-0.7674	0.2886	-1.3331	-0.2017	0.005
Apgar 1'<3	0.4674	0.1871	0.1008	0.8340	0.014

PaCO₂/treatment interactions removed due to non-significance

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From: [Das, Abhik](#)
To: [Wally Carlo, M.D.](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wallace, Dennis](#); [Zaterka-Baxter, Kristin](#)
Subject: RE: OHRP letter_Revised_3 4 2013
Date: Tuesday, March 05, 2013 12:36:35 PM

Wally:

Unfortunately RTI legal folks have decided that they would not let RTI staff sign this letter. I don't agree with the decision, but these people are extremely risk averse and look at things from a completely different perspective than investigators. Hope this is not a big problem. We are still happy to work with you in refining the draft if you want.

Thanks a lot

Abhik

From: Becky Brazeel [<mailto:bbrazeel@ped.s.uab.edu>] **On Behalf Of** Wally Carlo, M.D.
Sent: Monday, March 04, 2013 5:35 PM
To: Das, Abhik; higginsr@mail.nih.gov
Cc: Wally Carlo, M.D.; Becky Brazeel (brazeel@uab.edu)
Subject: FW: OHRP letter_Revised_3 4 2013

Dear Drs. Das and Higgins:

Attached please find the revised letter.

Kind regards,
Becky

From: Wally Carlo, M.D.
Sent: Monday, March 04, 2013 3:54 PM
To: Das, Abhik; higginsr@mail.nih.gov
Cc: 'Becky Brazeel'
Subject: RE: OHRP letter

Great. I am sending a revised letter in a few minutes.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, March 04, 2013 3:28 PM
To: Wally Carlo, M.D.; higginsr@mail.nih.gov
Subject: RE: OHRP letter

One thing I forgot to mention. If RTI allows me to sign the letter, they will likely want to carefully review the final draft after it has been toned down.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, March 04, 2013 1:52 PM
To: Das, Abhik; higginsr@mail.nih.gov
Subject: RE: OHRP letter

Hi Abhik:

Even if you do not sign it, it may be best to water down these two paragraphs. Jon added them. I watered them a bit but should do it better.

Wally

Wally Carlo, M.D.
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From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, March 04, 2013 11:46 AM
To: Wally Carlo, M.D.; higginsr@mail.nih.gov
Subject: RE: OHRP letter

Wally and Rose:

We had a call with our IRB and institutional officials here today. Although they won't make a final decision (including on whether RTI needs to respond to the OHRP letter) until they have had an internal meeting later today, their preliminary thoughts were as follows:

1. They were not sure whether I needed to sign the letter to Dr. Marchase given that RTI's role in the NRN is mostly related to statistical, data management and logistical issues.
2. If I do sign, they recommended eliminating or significantly watering down the following two paragraphs in the summary section:

"Risk is defined in the OHRP IRB guidebook as "the probability of harm or injuryoccurring as a result of participation in a research study." As emphasized above, the best available evidence indicated no discernible increased probability of death or other harms as a result of participating in this trial comparing two methods of care widely used both within and outside the NICHD Neonatal Research Network. The SUPPORT consent form was thus appropriately written for this comparative effectiveness trial based on the relevant knowledge available at the time.

We believe it would be particularly unfortunate to criticize the consent form on ethical grounds when this trial has provided knowledge important to reducing the mortality of these infants. Leading ethicists including the eminent Tom Beauchamp have recently emphasized the need to promote comparative effectiveness trials and noted that "the terms 'research' and 'practice' are poor proxies for what should be our central moral concerns." "As they note a new ethical foundation needs to be developed that facilitates both care and research likely to benefit patients and that provides oversight that ...is commensurate with risk and burden in both realms" (Kass NE , Faden RR, Goodwin SN, Pronovost P, Tunis S, Beauchamp TL. Hastings Center Report Jan-Feb 2013. S4-S15)."

They think that if gets to OHRP, then it will appear that we are lecturing them on their job, and the fact that this trial has produced important results does not by itself mean that it was carried out ethically (which the 1st sentence in the 2nd quoted paragraph above could be taken to mean).

3. They appeared to be very much against the idea of copying OHRP on this letter and will likely not let me sign it if that were the case. A book written by the director of OHRP was pointed out, that seems very much in line with the letter we got from OHRP (see http://www.amazon.com/What-Doctor-Didnt-Say-Research/dp/B001PIHUCC/ref=sr_1_1?s=books&ie=UTF8&qid=1362418966&sr=1-1&keywords=what+the+doctor+didnt+say).

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, March 01, 2013 7:55 PM
To: Becky Brazeel; Das, Abhik; higginsr@mail.nih.gov
Cc: Becky Brazeel (brazeel@uab.edu)
Subject: RE: OHRP letter

Abhik and Rose:

We put the names as listed in the paper.

Rose may not want us to put NIH staff.

Wally

Wally Carlo, M.D.
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From: Becky Brazeel
Sent: Friday, March 01, 2013 4:25 PM
To: Wally Carlo, M.D.; Das, Abhik; higginsr@mail.nih.gov
Cc: Becky Brazeel (brazeel@uab.edu)
Subject: RE: OHRP letter

Dear Drs. Das and Higgins:

Attached please find the Draft rebuttal letter.

Best regards,
Becky

Becky Brazeel, CPS/CAP
University of Alabama at Birmingham
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PEDIATRICS



Children's
of Alabama

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Friday, March 01, 2013 11:15 AM
To: Das, Abhik; Becky Brazeel (brazeel@uab.edu); higginsr@mail.nih.gov

Subject: Re: OHRP letter

Abhik.

Yes. Becky will send the draft to you and Rose today.

Wally

-----Original message-----

From: "Das, Abhik" <adas@rti.org>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Fri, Mar 1, 2013 17:02:25 GMT+00:00
Subject: OHRP letter

Wally:

Will there be a revised draft from you along the lines that Ed had suggested? We meet with our IRB early on Monday, and I was wondering if I should wait to get another draft from you or share the previous one with them.

Thanks a lot

Abhik

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20852-3903
e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: [Das, Abhik](#)
To: [Wallace, Dennis](#); [Wally Carlo, M.D.](#); wacarlo@uab.edu
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: Thoughts on the OHRP Response
Date: Monday, March 04, 2013 6:13:27 PM

Makes sense to me.
Thanks
Abhik

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

From: Wallace, Dennis
Sent: Monday, March 04, 2013 05:17 PM Eastern Standard Time
To: Wally Carlo, M.D.; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: Thoughts on the OHRP Response

Wally,

I agree about not being controversial, which was why I framed things the way I did. Actually, I like the language that you used on the phone about incorrect facts (or I might rephrase it as factual misinterpretation). At the end of the day, I think that the statement in the paragraph on page 11 was relatively benign, as the language that they use says "it would have been appropriate" rather than saying something like the investigators misled participants. As such, I would use language like "our interpretation of the data is that . . ." which led us to exclude this particular statement from the consent (i.e. explain to them why we didn't include the language that they suggested). In that way, we are simply explaining why we did what we did rather than telling them that they are interpreting the data incorrectly. Again, my goal is to be as noncontroversial as possible, as I don't want to relive my junior high days of trying to fight the school bully (noble but misguided position ☺).

Dennis

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Monday, March 04, 2013 4:51 PM
To: Wallace, Dennis; wacarlo@uab.edu
Cc: Das, Abhik
Subject: RE: Thoughts on the OHRP Response

Dennis:

I appreciate your thoughtful comments. The problem is that those four points made by OHRP in their letter are based on incorrect facts as the prior data did not show an increased risk for blindness, serious brain injury, or death. Thus, we took the high road of clarifying the facts rather than go on a one by one rebuttal of their determinations that lack scientific support.

I am willing to modify the letter. We need to have the best letter. But I do not want to be confrontational.

What do you think?

Wally

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From: Wallace, Dennis [<mailto:dwallace@rti.org>]
Sent: Monday, March 04, 2013 1:02 PM
To: wacarlo@uab.edu
Cc: Das, Abhik
Subject: Thoughts on the OHRP Response

Wally,

I spent some time this weekend and this morning reading the OHRP letter again and reading the most recent response letter addressed to the UAB IRB that I received on Friday. After reviewing both of those carefully, I'm concerned that the letter as written very accurately presents good information about the risks of the SUPPORT trial as know at the start of that study; however, I don't think that it does an effective job of rebutting the findings that OHRP presents in the letter. As such, I'm concerned that we're creating a potential argument with OHRP about ancillary issues that won't lead to a dialog that will bring resolution to the finding.

Specifically, after reviewing fairly carefully both the OHRP letter and the response to the UAB IRB, I am very concerned that rather than addressing the OHRP findings directly, our response creates a straw-man argument that is unlikely to be helpful in furthering a dialog with OHRP. While the OHRP letter contains a substantial amount of information (some of which may indeed be misinformation), the key paragraph in the letter is the second paragraph starting on page 11 of 14 that starts with: "It would have been appropriate for the consent form to explain. . ." If we want the SC letter to rebut the OHRP finding effectively, we specifically need to demonstrate to them that it would not have been appropriate for the consent to address the 4 items that they specify in the remainder of that paragraph. I've read through the letter and I'm not convinced that we do that, or if we do rebut the specific 4 findings, I think that OHRP will have a hard time piecing together our argument. The letter either needs an introductory section that specifically rebuts one or more of those points (and probably agreeing to those that we can't rebut) or it needs a concluding section that does that. The remainder of the letter then provides the documentation for our conclusion.

Absent that direct address of the finding, the letter just appears that we want to argue with some of the details but that we don't have a conclusive argument that their fundamental finding was incorrect.

Those are just my thoughts after reading everything and probably are no more important

than the thoughts of others, but I wanted to at least let you know my impressions. Good luck with moving this forward, and I'm happy to try to craft some summary paragraphs if that would be helpful.

Dennis

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "kzaterka@rti.org"
Subject: Re: SC call
Date: Monday, March 04, 2013 5:07:10 PM

None of them were on
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, March 04, 2013 05:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SC call

Hi Rose,

Just for the minutes sake, these are the folks I did not hear on the call. Did you?

Nationwide

Dallas

UCLA

Brown

Indiana (Brenda known out)

CHOP (Barbara known out)

Support:

Neil

Roger/Brad

Shahnaz

Thanks,

Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
Clinical Research Specialist
Social Policy, Health, & Economic Research
RTI International
3040 Cornwallis Rd
Research Triangle Park, NC 27709
Phone: 919-485-7750
Fax: 919-485-7762

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Thoughts on the OHRP Response
Date: Monday, March 04, 2013 2:05:41 PM

FYI; I think he makes a good point. Did you get any guidance from NIH on whether you can be a signatory to such a letter, whether or not it is cc'd to OHRP?

Thanks

Abhik

From: Wallace, Dennis
Sent: Monday, March 04, 2013 2:02 PM
To: 'Wally Carlo (wacarlo@uab.edu)'
Cc: Das, Abhik
Subject: Thoughts on the OHRP Response

Wally,

I spent some time this weekend and this morning reading the OHRP letter again and reading the most recent response letter addressed to the UAB IRB that I received on Friday. After reviewing both of those carefully, I'm concerned that the letter as written very accurately presents good information about the risks of the SUPPORT trial as know at the start of that study; however, I don't think that it does an effective job of rebutting the findings that OHRP presents in the letter. As such, I'm concerned that we're creating a potential argument with OHRP about ancillary issues that won't lead to a dialog that will bring resolution to the finding.

Specifically, after reviewing fairly carefully both the OHRP letter and the response to the UAB IRB, I am very concerned that rather than addressing the OHRP findings directly, our response creates a straw-man argument that is unlikely to be helpful in furthering a dialog with OHRP. While the OHRP letter contains a substantial amount of information (some of which may indeed be misinformation), the key paragraph in the letter is the second paragraph starting on page 11 of 14 that starts with: "It would have been appropriate for the consent form to explain. . ." If we want the SC letter to rebut the OHRP finding effectively, we specifically need to demonstrate to them that it would not have been appropriate for the consent to address the 4 items that they specify in the remainder of that paragraph. I've read through the letter and I'm not convinced that we do that, or if we do rebut the specific 4 findings, I think that OHRP will have a hard time piecing together our argument. The letter either needs an introductory section that specifically rebuts one or more of those points (and probably agreeing to those that we can't rebut) or it needs a concluding section that does that. The remainder of the letter then provides the documentation for our conclusion. Absent that direct address of the finding, the letter just appears that we want to argue with some of the details but that we don't have a conclusive argument that their fundamental finding was incorrect.

Those are just my thoughts after reading everything and probably are no more important than the thoughts of others, but I wanted to at least let you know my impressions. Good luck with moving this forward, and I'm happy to try to craft some summary paragraphs if that would be helpful.

Dennis

From: Das, Abhik
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: OHRP letter
Date: Monday, March 04, 2013 1:55:08 PM

I agree. There is no use picking a nasty fight that may not have any winners.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, March 04, 2013 1:52 PM
To: Das, Abhik; higginsr@mail.nih.gov
Subject: RE: OHRP letter

Hi Abhik:

Even if you do not sign it, it may be best to water down these two paragraphs. Jon added them. I watered them a bit but should do it better.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, March 04, 2013 11:46 AM
To: Wally Carlo, M.D.; higginsr@mail.nih.gov
Subject: RE: OHRP letter

Wally and Rose:

We had a call with our IRB and institutional officials here today. Although they won't make a final decision (including on whether RTI needs to respond to the OHRP letter) until they have had an internal meeting later today, their preliminary thoughts were as follows:

1. They were not sure whether I needed to sign the letter to Dr. Marchase given that RTI's role in the NRN is mostly related to statistical, data management and logistical issues.
2. If I do sign, they recommended eliminating or significantly watering down the following two

paragraphs in the summary section:

"Risk is defined in the OHRP IRB guidebook as "the probability of harm or injuryoccurring as a result of participation in a research study." As emphasized above, the best available evidence indicated no discernible increased probability of death or other harms as a result of participating in this trial comparing two methods of care widely used both within and outside the NICHD Neonatal Research Network. The SUPPORT consent form was thus appropriately written for this comparative effectiveness trial based on the relevant knowledge available at the time.

We believe it would be particularly unfortunate to criticize the consent form on ethical grounds when this trial has provided knowledge important to reducing the mortality of these infants. Leading ethicists including the eminent Tom Beauchamp have recently emphasized the need to promote comparative effectiveness trials and noted that "the terms 'research' and 'practice' are poor proxies for what should be our central moral concerns." "As they note a new ethical foundation needs to be developed that facilitates both care and research likely to benefit patients and that provides oversight that ...is commensurate with risk and burden in both realms" (Kass NE , Faden RR, Goodwin SN, Pronovost P, Tunis S, Beauchamp TL. Hastings Center Report Jan-Feb 2013. S4-S15)."

They think that if gets to OHRP, then it will appear that we are lecturing them on their job, and the fact that this trial has produced important results does not by itself mean that it was carried out ethically (which the 1st sentence in the 2nd quoted paragraph above could be taken to mean).

3. They appeared to be very much against the idea of copying OHRP on this letter and will likely not let me sign it if that were the case. A book written by the director of OHRP was pointed out, that seems very much in line with the letter we got from OHRP (see http://www.amazon.com/What-Doctor-Didnt-Say-Research/dp/B001PIHUCC/ref=sr_1_1?s=books&ie=UTF8&qid=1362418966&sr=1-1&keywords=what+the+doctor+didnt+say).

Thanks

Abhik

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Friday, March 01, 2013 7:55 PM
To: Becky Brazeel; Das, Abhik; higginsr@mail.nih.gov
Cc: Becky Brazeel (brazeel@uab.edu)
Subject: RE: OHRP letter

Abhik and Rose:

We put the names as listed in the paper.

Rose may not want us to put NIH staff.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)


From: Becky Brazeel
Sent: Friday, March 01, 2013 4:25 PM
To: Wally Carlo, M.D.; Das, Abhik; higginsr@mail.nih.gov
Cc: Becky Brazeel (brazeel@uab.edu)
Subject: RE: OHRP letter

Dear Drs. Das and Higgins:

Attached please find the Draft rebuttal letter.

Best regards,
Becky

Becky Brazeel, CPS/CAP
University of Alabama at Birmingham
Division of Neonatology/Dr. Carlo's Office
1700 6th Avenue South/Suite 9380
Birmingham, AL 35233-7335
Phone: 205 934 4680/FAX: 205 934 3100

 Please consider the impact on the environment before printing this e-mail.

UAB MEDICINE

PEDIATRICS



Children's
of Alabama

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Friday, March 01, 2013 11:15 AM
To: Das, Abhik; Becky Brazeel (brazeel@uab.edu); higginsr@mail.nih.gov
Subject: Re: OHRP letter

Abhik.

Yes. Becky will send the draft to you and Rose today.

Wally

-----Original message-----

From: "Das, Abhik" <adas@rti.org>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Fri, Mar 1, 2013 17:02:25 GMT+00:00
Subject: OHRP letter

Wally:

Will there be a revised draft from you along the lines that Ed had suggested? We meet with our IRB early on Monday, and I was wondering if I should wait to get another draft from you or share the previous one with them.

Thanks a lot

Abhik

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20852-3903
e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: Ehrenkranz, Richard
To: rose higgins; Wally Carlo (wacarlo@uab.edu)
Cc: Hewett, Jan; Barney, Jeri
Subject: OHRP Follow-up call 3/4
Date: Friday, March 01, 2013 3:50:30 PM

Hi:

I will try to join the call on Monday, but in case I cannot I wanted to respond to the request to discuss this issue with our IRB/HRPP office. First of all, Jan Hewett and Jeri Barney from Yale's IRB/HRPP Office were present with me in my office during the majority of the call. We had additional discussions since that call. Since the SUPPORT trial was one of the studies reviewed during an OHRP audit at Yale, and since Yale had to specifically respond to questions from OHRP about the SUPPORT Trial, I have been requested not to sign any letter coming from the investigators. In addition, they suggested that Dr. Marchase, or some other UAB IRB official, consider calling OHRP and confirm the expected UAB response. They cautioned, that having the clinician investigators getting involved to defend the science piece might prove problematic. Have a good weekend.

Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: OHRP info
Date: Tuesday, February 26, 2013 6:06:06 PM

<http://www.hhs.gov/ohrp/compliance/evaluation/index.html>

Under

How OHRP Conducts For-Cause Compliance Oversight Evaluations:

(10) An institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation.

Under

How OHRP Conducts Not-For-Cause Compliance Oversight Evaluations:

(6) An institution may request that the Director of OHRP reconsider any determinations resulting from a not-for-cause compliance oversight evaluation

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

From: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: SUPPORT
Date: Tuesday, February 26, 2013 2:16:17 PM

Thx- let me know if I should dial in if you have to leave.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 2:16 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re: SUPPORT

Am at the meeting with cathy et al
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 01:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

That would be good to know. Am on a conference call in case you tried calling.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 1:17 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: RE: SUPPORT

Just spoke to Mona and Bob Bock – Bob is going to (b)(5)
based on the items in the last email I sent to the group (Ehrenkranz letter to OHRP, Guidelines for perinatal care, Carlo draft response).

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 12:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

I agree with Yvonne on this. Hope you can relax a little.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 12:49 PM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: SUPPORT

Hi

Yvonne and I spoke a few weeks ago about the OHRP letter sent – please look at the attached documents.

My understanding is that Yvonne was going to try to contact Sherrie Mills in building one.

The guidelines in 2007 refer to 85-95% saturation targets for premature infants. If you look at page 3 of the word document shows that mortality of enrolled infants was LOWER than the rates of our historical controls as well as infants eligible for the trial but not enrolled.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ehrenkranz, Richard [<mailto:richard.ehrenkranz@yale.edu>]
Sent: Thursday, February 21, 2013 4:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose:

The information that was sent, was sent in response to a letter requesting responses. Yale's last response was on Dec 9, 2011. We have heard nothing further from OHRP. I have attached that last response. I will let our IRB-Human Research Protection Program know that they can join with from my office.

Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine

333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 21, 2013 3:43 PM
To: Ehrenkranz, Richard
Subject: Re: SUPPORT

I am trying to balance those who need to be on the call with being open to sites- could they join from your office? Otherwise I will need a different call in or a different phone line to allow participation. Have you received any official correspondence from OHRP or was the information you sent in 11/2011 provided after their visit to Yale?

Let me know

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, February 21, 2013 01:46 PM
To: Kristi Watterberg <KWatterberg@salud.unm.edu>; nxs5@case.edu <nxs5@case.edu>; Kurt Schibler[kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Ivan Frantz <Ivan.Frantz@childrens.harvard.edu>; Michele Walsh(mcw3@cwru.edu) <mcw3@cwru.edu>; BradYoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; RogerFaix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Shahnaz' (SDuara@med.miami.edu) 'Duara <SDuara@med.miami.edu>; Beena[bsood@med.wayne.edu] Sood <bsood@med.wayne.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; M.D. Wally Carlo <WCarlo@peds.uab.edu>; Abhik Das(adas@rti.org) <adas@rti.org>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>; dstevenson@stanford.edu <dstevenson@stanford.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Brenda Morris (morrisb1@tmfhs.org) <morrisb1@tmfhs.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Wally Carlo (wacarlo@uab.edu) <wacarlo@uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Wade RIch <wrich@ucsd.edu>; Edward (Pediatrics) Bell <edward-bell@uiowa.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@URMC.Rochester.edu>; dale_phelps@urmc.rochester.edu <dale_phelps@URMC.Rochester.edu>; Nirupama Laroia <Nirupama_Laroia@URMC.Rochester.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; Abbot Laptok <Alaptok@wihri.org>
Cc: Archer, Stephanie (NIH/NICHD) [E]; Amanda (alewis@rti.org) Lewis-Evans <alewis@rti.org>; Jenna Gabrio (jgabrio@rti.org) <jgabrio@rti.org>; (kzaterka@rti.org) <kzaterka@rti.org>; (mcunningham@rti.org) <mcunningham@rti.org>; Carolyn Petrie <petrie@rti.org>

Subject: RE: SUPPORT

Wally,

I agree with Kristi-I have nothing further to add.

By the way, I have been asked by members of our IRB-Human Research Protection Program about participating in the call next week. I emailed their request to Rose; what are your thoughts? As you may remember, we were asked similar questions by OHRP; the final responses were submitted on Dec 9, 2011 and we have not heard back from them.

Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

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From: Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]

Sent: Thursday, February 21, 2013 1:28 PM

To: nxs5@case.edu; Kurt Schibler [kurt.schibler@cchmc.org]; (Vivek.Narendran@cchmc.org); Ivan Frantz; Michele Walsh (mcw3@cwru.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); bpointex@iupui.edu; Rosemary (NIH/NICHD)[E] Higgins; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz' (SDuara@med.miami.edu) 'Duara; Beena [bsood@med.wayne.edu] Sood; Seetha Shankaran; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); barbara_stoll@oz.ped.emory.edu; M.D. Wally Carlo; Abhik Das (adas@rti.org); mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; Krisa Van Meurs (vanmeurs@stanford.edu); Brenda Morris (morrisb1@tmfhs.org); Ambal (ambal@uab.edu); Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Wade RIch; Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; Nirupama Laroia; Jon.E.Tyson@uth.tmc.edu; Kathleen A Kennedy; Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; Abbot Laptook; Ehrenkranz, Richard

Cc: Stephanie (NIH/NICHD) [E] Archer; Amanda (alewis@rti.org) Lewis-Evans; Jenna Gabrio (jgabrio@rti.org); (kzaterka@rti.org); (mcunningham@rti.org); Carolyn Petrie

Subject: RE: SUPPORT

Very nice, Wally! - with the edits you've already received, I have nothing further to add.

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 2/21/2013 10:17 AM >>>

Wally,

Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.

Ed

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]

Sent: Thursday, February 21, 2013 10:27 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrish1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; Bell, Edward (Pediatrics); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu

Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn

Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

1700 6th Avenue South

176F Suite 9380R

Birmingham, AL 35233-7335

Phone: 205 934 4680

FAX: 205 934 3100

Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 19, 2013 8:25 AM

To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrish1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu

Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn

Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: OHRP draft letter from UAB
Date: Tuesday, February 26, 2013 2:04:00 PM
Attachments: Borrer_Carlo-RTI 7-18-10 TA editslwqrev1.doc
Importance: High

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, August 25, 2011 3:01 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wallace, Dennis
Subject: OHRP draft letter from UAB
Importance: High

This is the draft of our letter which is being sent confidentially to you. UAB adm officials thought it would be best to have individual responses.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Tracey Craddock [mailto:traddock@uab.edu]
Sent: Thursday, August 25, 2011 1:55 PM
To: Shirley Cosby; Wally Carlo, M.D.
Cc: Denise H Ball
Subject: FW: Borrer_Carlo-RTI 7-18-10 TA editslwqrev1.doc
Importance: High

Shirley,

Please have Dr. Carlo review the draft of the response to OHRP. We intend on sending this out tomorrow Fed Ex for delivery by the deadline on Monday.

Thanks,

Tracey Craddock, CCRP
Regulatory Compliance Manager
IRB
205/934-3789
FAX: 205/934-1301

From: Laretta Gerrity
Sent: Thursday, August 25, 2011 1:49 PM
To: Tracey Craddock
Subject: Borrer_Carlo-RTI 7-18-10 TA editslwgrev1.doc

August 25, 2011

Kristina C. Borrer, PhD
Director, Division of Compliance Oversight
Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Research Project entitled "The SURfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants, The SUPPORT Trial"

Principal Investigator: Dr. Waldemar Carlo

HHS Protocol #: 2U10HD034216

Dear Dr. Borrer:

This letter is provided in response to your letter dated July 18, 2011, wherein you requested that UAB investigate allegations of noncompliance with DHHS regulations at 45 CFR Part 46 ("HHS regulations") in connection with the above-referenced research. Below is a report of our investigation. We have completed our investigation, which included review of the IRB's file for this study and interviews with Dr. Carlo and Shirley Cosby, the study coordinator. We believe our findings, supported by the attached materials, indicate that the consent form used to enroll participants at UAB complied with 45 CFR 46.116(a).

In the report below, the sections are numbered as in your letter, and we have repeated (in italics) the specific allegations. Our response is bolded.

(1) DETAILED RESPONSE TO ALLEGATIONS:

Failure of the informed consent documents for this study to include or adequately address the following basic elements required by HHS regulations at 45 CFR 46.116(a):

- (a) *Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts. In specific, we are concerned that the informed consent document states "Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby." However this study involved randomizing subjects to either higher or lower ranges of oxygen saturation. This was clearly a departure from allowing a clinician to decide what oxygen saturation level they considered to be best for*

Kristina C. Borrer, PhD

August 16, 2011

each particular infant. Moreover, the researchers were well aware of the possibility of substantially different outcomes, resulting from the assignment to a treatment arm, at least based on mortality, and chance of blindness and other types of morbidity.

Response: While the sample consent form provided in the Manual of Operations to UAB included the language quoted above, UAB did not use that language in its consent form.

The trial involved randomization of infants to two ranges of saturation (85-89% and 91-95%). These ranges were thought at the time to not affect the risk of mortality to infants, and they were within the commonly recommended ranges (88-98%, 85-95%, or 80-95% among others) for the type of critically ill newborns as were enrolled in the trial. There was no consensus among clinicians regarding the appropriate oxygen saturation level for a particular infant such as those enrolled in this trial. Randomization aimed for saturations within the range used by clinicians. Moreover, the Data Safety and Monitoring Board (DSMB) met and reviewed data at specific time points. No concerns were raised about increased risk or benefit. Indeed, decreased risks were observed in both the intervention and control groups when compared to a historic control group, subsequently determined to be most likely due to selection bias.

There were no data from evidence-based trials to indicate increased risk or benefits between the two ranges of oxygen saturations tested. However, prevention of hyperoxia (usually keeping the oxygen saturations below 98%, aiming for oxygen saturations from 83-95%, and aiming for oxygen saturations below 90%) were associated with lower ROP rates in separate studies (reviewed in Carlo et al. NEJM: 2010; 362:1959-69).

See excerpts of the Introduction, Explanation of Procedures, and Possible Risks sections below. Complete copies of all UAB consent forms are available in Appendix B.

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 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.

Explanation of Procedures

Explanation of Procedures

them 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.

Duration of Study

Your baby will be involved in the ventilation part of this study for the first 14 days after birth.

Possible Risks

Possible Risks

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.

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 also will help decide when to put them 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.

Duration of Study

Your baby will be involved in the ventilation part of this study for the first 14 days after birth.

- (b) *Section 46.116(a)(1)(ii): an explanation of the purposes of the research. In specific, we are concerned that the informed consent document states as the purpose related to oxygen saturation "To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity), an eye disease that may result in impairment of vision or event blindness, which may be caused by excessive levels of oxygen" whereas the protocol stated "if 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. There*

Kristina C. Borrer, PhD

August 16, 2011

is no mention in the informed consent document related to the purpose the endpoints of survival differences.

Response: The UAB site did not use that language in its consent form provided in the Manual of Operations. A copy of the UAB IRB approved consent form is attached (Appendix B). The trial primary outcome is reported with the competing outcome of death as is customary in high-risk populations even though the investigators were not expecting a difference in mortality. None of the studies targeting saturations had reported a difference in mortality. Three other trials using the same design and intervention conducted concurrently in the United Kingdom; Australia/New Zealand; and Canada/many other countries, did not expect a difference in mortality as stated in their protocols. All trials analyzed the same outcomes including the competing outcome of death for each primary outcome measure. Indeed, the United Kingdom and Australia/New Zealand trials, which were recently published, confirmed the major results of this study (NEJM B Stenson 2011).

(2) COPY OF THE COMPLETE IRB FILE:

(See the referenced appendix for the requested documents)

- (a) *The IRB-approved protocol and applicable grant application (Appendix A)*
- (b) *The IRB-approved informed consent documents (Appendix B) UAB does not have access to consent forms approved for other enrollment sites.*
- (c) *The relevant IRB minutes, including initial review, continuing review, review of changes to the research or to the informed consent document, and review of any adverse or unanticipated events (Appendix C)*
- (d) *Correspondence between the IRB and investigator (Appendix D)*
- (e) *IRB continuing review reports (Appendix E)*
- (f) *List of subjects (code numbers only) and dates of enrollment (Appendix F)*
- (g) *Chronological summary of the dates of the IRB's actions (Appendix G)*
- (h) *Copy of publications or presentations which were derived from this research project (Appendix H)*
- (i) *Other pertinent information (none)*

(3) CLARIFICATION OF THE EXTENT TO WHICH THE RESEARCH WAS SUPPORTED IN ANY WAY, PARTIALLY OR INDIRECTLY, BY HHS OR OTHER FEDERAL AGENCY.

Response: This study was funded by the National Institute of Child Health and Development (NICHD) under grant # 5U10HD034216. Information posted on clinicaltrials.gov lists NCRR and NHLBI as collaborators.

(4) IF YOUR INVESTIGATION REVEALS NONCOMPLIANCE, A DESCRIPTION OF ANY CORRECTIVE ACTIONS THAT HAVE BEEN OR

Kristina C. Borrer, PhD

August 16, 2011

**WILL BE TAKEN BY THE INSTITUTION TO PREVENT SUCH
NONCOMPLIANCE FOR RECURRING.**

Response: We found no evidence of noncompliance.

For the reasons outlined above, the UAB maintains that the above-referenced study was conducted in accordance with HHS regulations, specifically, 45 CFR 46.116(a).

Thank you for your consideration. If you have any additional questions, please do not hesitate to contact me.

Sincerely,

Richard B. Marchase, PhD,
Vice President for Research and
Economic Development
Institutional Official

cc: Waldemar A Carlo, MD
Professor of Pediatrics
Pediatric Neonatology
Principal Investigator

Appendix A

IRB-approved protocol and applicable grant application

Appendix B

IRB-approved informed consent documents

Appendix C

IRB minutes, including initial review, continuing review, review of changes to the research or to the informed consent document, and review of any adverse or unanticipated events

Appendix D

Correspondence between the IRB and investigator

Appendix E

IRB continuing review reports

Appendix F

List of subjects and dates of enrollment

Appendix G

<u>IRB Meeting</u>	<u>Action</u>	<u>Final Action/Approval Issued</u>
9/22/04	Approved w/Limited Modifications	10/26/04
8/10/05	Approved	8/12/05
6/28/06	Approved w/Limited Modifications	7/15/06
5/9/07	Approved w/Limited Modifications	5/17/07
4/30/08	Approved w/Limited Modifications	5/18/08
2/25/09	Approved w/Limited Modifications	3/17/09
1/13/10	Approved	1/15/10
12/8/10	Approved	12/15/10

Appendix H

Publications and Presentations

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
Cc: [Rowe, Mona \(NIH/NICHD\) \[E\]](#)
Subject: RE: OHRP link
Date: Tuesday, February 26, 2013 2:02:00 PM

Other contacts –

703 (b)(6)
703 (cell)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 1:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: OHRP link

<http://www.hhs.gov/ohrp/compliance/evaluation/index.html>

Under

How OHRP Conducts For-Cause Compliance Oversight Evaluations:

(10) An institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation.

Under

How OHRP Conducts Not-For-Cause Compliance Oversight Evaluations:

(6) An institution may request that the Director of OHRP reconsider any determinations resulting from a not-for-cause compliance oversight evaluation

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, June 05, 2014 6:00 PM
To: Blansfield, Earl (NIH/NICHD) [E]
Subject: FW: SUPPORT OHRP request
Attachments: 20110726134644.pdf

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 1:59 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: SUPPORT OHRP request

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Tuesday, July 26, 2011 2:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT OHRP request

Hi Rose:

I assume everyone is going to get this. Can we discuss it today on the call?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Marcus Humphrey
Sent: Tuesday, July 26, 2011 1:47 PM
To: Wally Carlo, M.D.
Subject:

Marcus J. Humphrey

UAB Division of Neonatology
1700 6th Avenue South - 176F Suite 9380W
Birmingham, AL 35249-7333
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mhumphrey@peds.uab.edu



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: 240-453-8132
FAX: 240-453-6909
E-mail: Kristina.Berror@hhs.gov

July 18, 2011

Richard B. Marchase, PhD
VP for Research & Economic Development
University of Alabama at Birmingham (UAB)
AB 720E
701 20th Street South
Birmingham, AL 35294-0107

E. Ward Sax, M.B.A.
V.P., Treasurer and Chief Risk Officer
Research Triangle Institute (RTI)
3040 Cornwallis Road, P.O. Box 12194
Research Triangle Park, NC 27709-2194

**RE: Human Research Protections Under Federalwide Assurance FWA-5960 and -
FWA-3331**

**Research Project: The SURfactant Positive Airway Pressure and Pulse Oximetry
Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial**
Principal Investigator: Dr. Waldemar Carlo
HHS Protocol Number: 2U10HD034216

Dear Dr. Marchase:

We have received allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research.

The complainant alleges and we are concerned regarding the following:

Failure of the informed consent documents for this study to include or adequately address the following basic elements required by HHS regulations at 45 CFR 46.116(a):

Page 2 of 3

Richard B. Marchase, PhD-- University of Alabama at Birmingham

July 18, 2011

- (a) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts. In specific, we are concerned that the informed consent document states "Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby." However, this study involved randomizing subjects to either higher or lower ranges of oxygen saturation. This was clearly a departure from allowing a clinician to decide what oxygen saturation level they considered to be best for each particular infant. Moreover, the researchers were well aware of the possibility of substantially different outcomes, resulting from the assignment to a treatment arm, at least based on mortality, and chance of blindness and other types of morbidity.
- (b) Section 46.116(a)(1)(ii): an explanation of the purposes of the research. In specific, we are concerned that the informed consent document states as the purpose related to oxygen saturation "To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels 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" whereas the protocol stated "if 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." There is no mention in the informed consent document related to the purpose the endpoints of survival differences.

Consistent with its obligations under HHS regulations at 45 CFR 46.115(b) and under Public Law 99-158, I am requesting that your institutions investigate this matter and forward to us a written report of its investigation (see OHRP Compliance Oversight Procedures dated October 14, 2009 at

<http://www.hhs.gov/ohrp/compliance/evaluation/index.html>).

Please include the following with the report:

- (1) A detailed response to each allegation referenced above.
- (2) A copy of the complete IRB file for the research, including the following:
 - (a) The IRB-approved research protocol and any applicable grant applications.
 - (b) The IRB-approved informed consent documents from each enrollment site.
 - (c) The relevant IRB minutes, including initial review, continuing review, review of changes to the research or to the informed consent document, and review of any adverse or unanticipated events.
 - (d) All correspondence between the IRB and the investigators.
 - (e) All continuing review reports.

Page 3 of 3

Richard B. Marchase, PhD-- University of Alabama at Birmingham
July 18, 2011

- (f) A list of subjects (code numbers only) and dates of enrollment.
- (g) A chronological summary of the dates of the IRB's actions.
- (h) A copy of any publications or presentations which were derived from this research project.
- (i) Any other pertinent information.

(3) Clarification of the extent to which the research was supported in any way, even partially or indirectly, by HHS or any other federal agency.

(4) If your investigation reveals noncompliance, a description of any corrective actions that have been or will be taken by your institution to prevent such noncompliance from recurring.

Please forward your report so that we receive it no later than August 29, 2011.

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,



Kristina C. Borrer, Ph.D.
Director, Division of Compliance Oversight

cc:

Ms. Sheila D. Moore, Director, Office of the IRB, UAB

Dr. Ferdinand Urthaler, Chair, UAB IRBs

Dr. Waldemar Carlo, UAB

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

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 12:49 PM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: SUPPORT
Attachments: A Rudczynski ltr to OHRP 9Dec11.pdf; HIC-OHRP 2007 Perinatal Guidelines 6th Ed.pdf; HIC-OHRP 2002 Perinatal Guidelines 5th Ed.pdf; OHRP RESPONSE LETTER Ver 3 2-22-13wc_bb (4).doc

Hi

Yvonne and I spoke a few weeks ago about the OHRP letter sent – please look at the attached documents. My understanding is that Yvonne was going to try to contact Sherrie Mills in building one.

The guidelines in 2007 refer to 85-95% saturation targets for premature infants. If you look at page 3 of the word document shows that mortality of enrolled infants was LOWER than the rates of our historical controls as well as infants eligible for the trial but not enrolled.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, February 21, 2013 4:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose:

The information that was sent, was sent in response to a letter requesting responses. Yale's last response was on Dec 9, 2011. We have heard nothing further from OHRP. I have attached that last response. I will let our IRB-Human Research Protection Program know that they can join with from my office.

Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064

New Haven, CT 06520-8064

tele: 203-688-2320

fax: 203-688-5426

The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

Sent: Thursday, February 21, 2013 3:43 PM

To: Ehrenkranz, Richard

Subject: Re: SUPPORT

I am trying to balance those who need to be on the call with being open to sites- could they join from your office? Otherwise I will need a different call in or a different phone line to allow participation.

Have you received any official correspondence from OHRP or was the information you sent in 11/2011 provided after their visit to Yale?

Let me know

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Ehrenkranz, Richard [<mailto:richard.ehrenkranz@yale.edu>]

Sent: Thursday, February 21, 2013 01:46 PM

To: Kristi Watterberg <KWatterberg@salud.unm.edu>; nxs5@case.edu <nxs5@case.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Ivan Frantz <Ivan.Frantz@childrens.harvard.edu>; Michele Walsh (mcw3@cwru.edu) <mcw3@cwru.edu>; BradYoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; RogerFaix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; bpindex@iupui.edu <bpindex@iupui.edu>; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Shahnaz' (SDuara@med.miami.edu) 'Duara <SDuara@med.miami.edu>; Beena [bsood@med.wayne.edu] Sood <bsood@med.wayne.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; M.D. Wally Carlo <WCarlo@peds.uab.edu>; Abhik Das (adas@rti.org) <adas@rti.org>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>; dstevenson@stanford.edu <dstevenson@stanford.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Brenda Morris (morrisb1@tmfhs.org) <morrisb1@tmfhs.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Wally Carlo (wacarlo@uab.edu) <wacarlo@uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Wade RIch <wrich@ucsd.edu>; Edward (Pediatrics) Bell <edward-bell@uiowa.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@URMC.Rochester.edu>; dale_phelps@urmc.rochester.edu <dale_phelps@URMC.Rochester.edu>; Nirupama Laroia <Nirupama.Laroia@URMC.Rochester.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; Abbot Laptook <Alaptook@wihri.org>

Cc: Archer, Stephanie (NIH/NICHD) [E]; Amanda (alewis@rti.org) Lewis-Evans <alewis@rti.org>; Jenna Gabrio (jgabrio@rti.org) <jgabrio@rti.org>; (kzaterka@rti.org) <kzaterka@rti.org>; (mcunningham@rti.org) <mcunningham@rti.org>; Carolyn Petrie <petrie@rti.org>

Subject: RE: SUPPORT

Wally,

I agree with Kristi-I have nothing further to add.

By the way, I have been asked by members of our IRB-Human Research Protection Program about participating in the call next week. I emailed their request to Rose; what are your thoughts? As you may remember, we were asked similar questions by OHRP; the final responses were submitted on Dec 9, 2011 and we have not heard back from them.
Richard

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The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Thursday, February 21, 2013 1:28 PM
To: nxs5@case.edu; Kurt Schibler[kurt.schibler@cchmc.org]; (Vivek.Narendran@cchmc.org); Ivan Frantz; Michele Walsh(mcw3@cwru.edu); BradYoder (Bradley.yoder@hsc.utah.edu); RogerFaix (Roger.Faix@hsc.utah.edu); bpoindex@iupui.edu; Rosemary (NIH/NICHHD)[E] Higgins; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz' (SDuara@med.miami.edu) 'Duara; Beena[bsood@med.wayne.edu] Sood; Seetha Shankaran; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu); barbara_stoll@oz.ped.emory.edu; M.D. Wally Carlo; Abhik Das(adas@rti.org); mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; Krisa Van Meurs (vanmeurs@stanford.edu); Brenda Morris (morrish1@tmfhs.org); Ambal (ambal@uab.edu); Wally Carlo (wacarolo@uab.edu); nfiner@ucsd.edu; Wade RIch; Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; Nirupama Laroia; Jon.E.Tyson@uth.tmc.edu; Kathleen A Kennedy; Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; Abbot Laptook; Ehrenkranz, Richard
Cc: Stephanie(NIH/NICHHD) [E] Archer; Amanda (alewis@rti.org) Lewis-Evans; Jenna Gabrio (jgabrio@rti.org); (kzaterka@rti.org); (mcunningham@rti.org); Carolyn Petrie
Subject: RE: SUPPORT

Very nice, Wally! - with the edits you've already received, I have nothing further to add.

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 2/21/2013 10:17 AM >>>

Wally,
Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.
Ed

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 10:27 AM
To: Higgins, Rosemary (NIH/NICHHD) [E]; Wally Carlo (wacarolo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrish1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu);

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Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

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From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

Sent: Tuesday, February 19, 2013 8:25 AM

To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpointindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

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Yale Office of Research Administration

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December 9, 2011

Kristina Borrer, Ph.D.
Director, Division of Compliance Oversight
Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: Human Research Subject Protections under Federalwide Assurance (FWA) 00002571

Dear Dr. Borrer:

Thank you for your response letter dated November 15, 2011 in which you raised some questions and concerns with regard to Yale HIC Protocol # 0410027163. I appreciate the opportunity to address your questions with respect to that protocol. In this response letter, we have included your specific inquiry (in italicized font below) and our response follows.

Regarding protocol #0410027163, The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (the SUPPORT Trial), OHRP remains concerned that the informed consent documents for this study may have failed to include an adequate description of risks and discomforts, as required by HHS regulations at 45 CFR 46.116(a)(2) or an adequate explanation of the purposes of the research as required by HHS regulations at 45 CFR 46.116(a)(1)(ii). In regard to the concerns expressed in our previous letter, please clarify the standard of care used at your institution at the time the study was proposed (i.e., what levels of oxygen saturation were used at your institution for infants of 24 0/7ths to 27 6/7ths weeks at birth for which a decision has been made to provide full resuscitation).

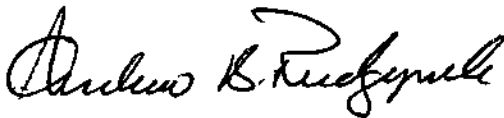
Response:

The standard of care for our institution in January 2005 (when the study was originally approved) was a clinical management approach that included pulse oximetry parameters (SpO₂) of 85-96% for preterm infants on supplemental oxygen. This study involved randomization of extremely low birth weight (ELBW) infants to two oxygen saturation ranges (85-89%) and (91-95%). Randomization aimed for saturation levels within the range used by clinicians. The American Academy of Pediatrics (AAP) Committee of Fetus and Newborn's Guidelines for Perinatal Care, 6th Edition (2007) states that the optimal ranges of SpO₂ are not known, but specifies that SpO₂ between 85-95% and PaO₂ values between 50 Hg and 80 mm Hg are ranges "pragmatically determined by some clinicians to guide oxygen therapy in preterm infants" (see attached). The prior edition of those Guidelines (2002) provided the same PaO₂ ranges, but did not specify SpO₂ ranges (see attached). The study protocol states that "there is no current agreement on the accepted SpO₂ ranges for managing the ELBW infants from birth." This was an

accurate statement. Nonetheless, despite the fact that no consensus existed among clinicians regarding the appropriate oxygen saturation levels to be used in managing a particular infant such as those enrolled in this study, the saturation ranges used in this study were within the commonly recommended ranges of oxygen saturation for such ELBW infants, as supported by the published AAP Committee of Fetus and Newborn's Guidelines for Perinatal Care.

Yale appreciates OHRP's commitment to ensuring that institutions engaged in human research have the appropriate infrastructure in place to ensure the protection of human research subjects. Please contact Dr. Sandra Alfano, Acting Director, Human Research Protection Program, at 203-785-4688 should you have any questions about this response.

Sincerely,



Andrew B. Rudczynski, Ph.D.
Associate Vice President for Research Administration

Enclosures: Relevant section of American Academy of Pediatrics (AAP) Committee of Fetus and Newborn's Guidelines for Perinatal Care, 6th Edition (2007), pp 259 – 262.
Relevant section of American Academy of Pediatrics (AAP) Committee of Fetus and Newborn's Guidelines for Perinatal Care, 5th Edition (2002), pp 244 – 246.

cc: Sandra Alfano, Pharm. D., Chair Human Investigation Committees I and III
Susan Bouregy, Ph. D., Vice Chair Human Subjects Committee
Joe Ellis, OER, National Institutes of Health
Margaret A. Hamburg M.D., Commissioner, Food and Drug Administration
Joanne Less Ph.D., Food and Drug Administration
Maurice J. Mahoney, M.D., J.D., Chair Human Investigation Committees II and IV
Sherry Mills, M.D., M.P.H., OER, National Institutes of Health

guidelines for
**PERINATAL
CARE**

Sixth Edition

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN™

The American College
of Obstetricians
and Gynecologists



WOMEN'S HEALTH CARE PHYSICIANS

Guidelines for Perinatal Care was developed through the cooperative efforts of the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn and the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice. The guidelines should not be viewed as a body of rigid rules. They are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or the type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

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Hydration

There is no evidence that excess fluid administered to the neonate decreases the serum bilirubin concentration. Some neonates who are admitted to the hospital with high bilirubin concentrations also may be mildly dehydrated and may need supplemental fluid intake to correct dehydration. In the absence of dehydration, routine supplementation (with dextrose-water) of neonates receiving phototherapy is not indicated. However, in sick, VLBW neonates receiving phototherapy, excess evaporative water loss is known to occur and frequently necessitates increased fluid intake, environmental humidity, or both for replacement or prevention of ongoing losses.

Phototherapy

Phototherapy is effective in reducing serum bilirubin concentrations in neonates with nonhemolytic jaundice. Phototherapy is less effective in neonates with ABO and CDE (Rh) group hemolytic disease, reducing, but not eliminating, the need for exchange transfusions in these neonates. Exchange transfusion is the treatment of choice when the bilirubin concentration appears to pose an imminent threat to the health of the neonate.

There is no standardized method for delivering phototherapy. However, detailed recommendations on phototherapy can be found in the hyperbilirubinemia practice parameters from the AAP. Commonly used phototherapy units contain daylight, cool white, blue, or "special blue" fluorescent tubes. Other units use tungsten-halogen lamps in different configurations, either freestanding or as part of a radiant-warming device. Fiber optic systems have been developed that deliver high-intensity light via a fiber optic blanket.

The efficacy of phototherapy is influenced by the energy output (irradiance) in the blue spectrum (measured in microwatt per centimeter squared), the spectrum of light source, and the surface area of the neonate exposed to the light source. The irradiance of a unit should be monitored and bulbs changed as needed to maintain maximum energy output. It is acceptable to interrupt phototherapy during feeding or brief parental visits. Intensive phototherapy can be achieved by use of blue lights, decreasing the distance of the source from the neonate and increasing the surface area exposed to the lights. The neonate's temperature should be monitored frequently while phototherapy is being applied.

Although phototherapy has many biologic effects, it has no known lasting toxic effects in the human neonate. Because experiments in animals have doc-

umented retinal damage from phototherapy, the neonate's eyes should be covered with opaque patches during exposure to phototherapy light. Known potential complications from improper monitoring of eye-patch placement include exposure to high-energy light, malposition and obstruction of the nares, inadequate securing of the patch that allows lid opening and resultant corneal abrasion, and conjunctivitis from use without intermittent removal to assess the condition of the covered tissues.

The determination of a neonate's suitability for early discharge requires heightened awareness of the normal course of physiologic hyperbilirubinemia. Recent data suggest that there is some predictability to the progressive increase in serum bilirubin concentrations from nonpathologic sources. It is suggested that for neonates who are otherwise candidates for early discharge, a pre-discharge serum bilirubin determination can be helpful in predicting risk for a subsequent increase to more concerning concentrations. A neonate with early onset jaundice (within the first 24 hours) should have hemolysis excluded as a cause before being considered for early discharge. After the newborn is discharged from the birthing hospital, the mother and child should receive a seamless continuation of care as outlined in the AAP guideline.

Some neonates with uncomplicated nonhemolytic jaundice may be treated with phototherapy at home. Guidelines should be developed by each institution to define criteria for neonates who are eligible for home phototherapy. Home care requires appropriate follow-up and supervision by a health care professional with access to serum bilirubin determinations as clinically indicated. With proper instruction of the parents or guardians, phototherapy can be provided by using a freestanding device or a fiber optic blanket. If serum bilirubin concentrations do not decrease in response to conventional phototherapy, admission to the hospital may be indicated for more intensive phototherapy or exchange transfusion and for evaluation of the underlying cause (Fig. 8-1 and Fig. 8-2).

Clinical Considerations in the Use of Oxygen

The hazards associated with nonindicated administration of supplemental oxygen to preterm neonates have been recognized for many years. Studies conducted in the 1950s indicated that prolonged oxygen therapy without clinical indication was associated with increased rates of retinopathy of prematurity, formerly called retrolental fibroplasia. The ensuing blanket restriction of ambient oxygen therapy resulted in a marked decrease in retinopathy of prematurity at the cost of an increase in morbidity and mortality. Current practice includes

the prudent use of supplemental oxygen as needed, based on an objective determination of oxygen requirements.

When supplemental oxygen therapy is considered, the potential risks, in terms of both hypoxia and hyperoxia, should be weighed. Clinical judgment of physical signs alone as a guide to the amount of supplemental oxygen needed is acceptable for short periods, emergencies, or abrupt clinical changes. However, ongoing use of supplemental oxygen should be guided by an objective assessment of patient oxygenation.

Administration and Monitoring

In an emergency, high concentrations of supplemental oxygen may be administered by a face mask, nasal prongs, or endotracheal tube. When a neonate requires oxygen therapy beyond the emergency period, the oxygen should be warmed and humidified and the concentration or flow should be monitored and regulated. Supplemental oxygen can be delivered via endotracheal tube, oxygen hood, nasal prongs, or incubator. Oxygen analyzers should be calibrated in accordance with manufacturers' recommendations. Orders for oxygen therapy should include desired ambient concentration, flow, or both. The concentration or flow rate of oxygen should be checked routinely. Alternatively, orders should be written to adjust fraction of inspired oxygen (FIO_2) or flow within a stated range to maintain oxygen saturation within specific limits. There should be an institutional guideline for ordering, delivering, and documenting oxygen therapy and monitoring.

An important development in the care of neonates who require oxygen therapy is the ability to monitor oxygenation continuously with noninvasive techniques. The pulse oximeter measures oxyhemoglobin saturation and the transcutaneous oxygen analyzer provides an indirect measurement of PaO_2 . Because neither technique measures PaO_2 directly, they should be used as adjuncts to, rather than substitutes for, arterial blood gas sampling, especially in neonates with moderate to severe respiratory distress.

Periodic or continuous measurement of PaO_2 in samples from an umbilical or peripheral artery catheter is the most reliable method of assessing the effectiveness of oxygen therapy. If an indwelling arterial catheter is not in place, peripheral artery puncture can be used, but this is painful and repeated sampling from these sites is not always possible. Oxygenation is not accurately estimated in arterialized capillary samples. However, arterialized capillary sampling provides fairly reliable estimates of arterial pH and $PaCO_2$. The combined use of continuous, transcutaneous oxygen saturation monitoring and intermittent

percutaneous arterial or arterialized blood gases to guide oxygen therapy is an attractive pragmatic strategy when invasive arterial catheters are not in place.

In neonates whose condition is unstable, noninvasive measurements should be correlated with PaO_2 as often as every 8–24 hours. More frequent analyses of arterial blood gas may be indicated for the assessment of pH and $PaCO_2$. In neonates whose condition is stable, correlation with arterial blood gas samples may be performed when clinically indicated.

The use of either pulse oximetry or transcutaneous oxygen measurement may shorten the time required to determine optimum inspired oxygen concentration and ventilator settings in the acute care setting. Both measurements are particularly useful in monitoring oxygen therapy in neonates who are recovering from respiratory distress or who require long-term supplemental oxygen. Pulse oximetry is particularly advantageous for long-term monitoring of oxygen therapy because transcutaneous oxygen measurements underestimate oxygenation in older neonates with bronchopulmonary dysplasia (BPD) and may cause burns. Pulse oximetry also is widely available.

In consideration of the current, but incomplete, understanding of the effects of oxygen administration, the following recommendations are offered:

- Supplemental oxygen should be used for specific indications, such as cyanosis, low PaO_2 , or low oxygen saturation.
- The continuous use of supplemental oxygen, other than for resuscitation, should be monitored by assessments of PaO_2 , oxygen saturation, or both.
- Oxygenation monitoring should be available whenever oxygen is continuously administered to newborns.
- For neonates who require oxygen therapy for acute care, measurements of blood pH and $PaCO_2$ should accompany measurements of PaO_2 . In addition, a record of blood gas measurements, noninvasive measurements of oxygenation, details of the oxygen delivery system (eg, ventilator, continuous positive airway pressure, nasal cannula, hood, mask, settings), and ambient oxygen concentrations (FIO_2 , liter of flow per minute, or both) should be maintained.
- The optimal range for oxygen saturation and PaO_2 that balances tissue metabolism, growth and development, and toxicity has not been elucidated fully for preterm infants receiving supplemental oxygen. Oxygen saturation values between 85–95% and PaO_2 values between 50 mm Hg and 80 mm Hg are examples of ranges pragmatically determined by some

clinicians to guide oxygen therapy in preterm infants. Additional research to determine the "optimal" oxygenation ranges for oxygen saturation and PaO₂ is needed. Of note, even with careful monitoring, oxygen saturation and PaO₂ may fluctuate outside specified ranges, particularly in neonates with cardiopulmonary disease.

- Regular and periodic (every 1–4 hours) measurement and recording of the concentration of oxygen delivered to the neonate receiving supplemental oxygen is recommended.
- Except for an emergency situation, air–oxygen mixtures should be warmed and humidified before being administered to newborns.

Retinopathy of Prematurity

A myriad of factors, including but not limited to hyperoxia, may contribute to the pathogenesis of retinopathy of prematurity. Prematurity, low birth weight, twin gestation, severity of illness, prolonged ventilatory support (especially when accompanied by episodes of hypoxia and hypercapnia) and clinical conditions, including acidosis, shock, sepsis, apnea, anemia, chronic lung disease, intraventricular hemorrhage, patent ductus arteriosus, and vitamin E deficiency, also have been associated with retinopathy of prematurity.

To date, a safe level of PaO₂ in relation to retinopathy of prematurity has not been established. Retinopathy of prematurity has occurred in preterm neonates who have never received supplemental oxygen therapy and in neonates with cyanotic, congenital heart disease in whom PaO₂ levels never exceeded 50 mm Hg. Conversely, retinopathy of prematurity has not developed in some preterm neonates after prolonged periods of hyperoxemia. Data have demonstrated no additional progression of active prethreshold retinopathy of prematurity when supplemental oxygen was administered at pulse oximetry saturations between 96% and 99%. Further, continuous, close monitoring of transcutaneous oxygen tension has not resulted in a decrease in the incidence of retinopathy of prematurity when compared with intermittent transcutaneous monitoring. However, recent data in extremely low birth weight infants between 23 weeks and 29 weeks of gestation suggest that oxygen saturation in the lowest range (70–90%) compared with highest range (88–98%) was associated with significantly less threshold retinopathy of prematurity. A one-year follow-up showed similar neurodevelopmental outcome. Randomized, controlled-trial studies will need to be done before this lower range of oxygenation can be recommended.

On the basis of published data, the following statements regarding retinopathy of prematurity and oxygen use are warranted:

- Retinopathy of prematurity is not preventable in some neonates, especially extremely premature neonates.
- Many factors other than hyperoxia contribute to the pathogenesis of retinopathy of prematurity.
- Transient hyperoxemia alone cannot be considered sufficient to cause retinopathy of prematurity.
- Strict adherence to existing guidelines for supplemental oxygen therapy will not completely prevent complications or side effects.
- An ophthalmologist with experience in retinopathy of prematurity and indirect ophthalmoscopy should examine the retinas of all preterm neonates born at 30 weeks of gestation or less or weighing less than 1,500 g at birth, as well as selected infants between 1,500–2,000 g birth weight with an unstable clinical course who are thought to be at risk by their attending pediatrician or neonatologist. The examination should be performed at 4–6 weeks of chronologic age or at 31–33 weeks postmenstrual age (gestational age at birth plus chronologic age), as determined by the neonate's attending pediatrician or neonatologist. The use of a digital, wide-field camera system to photograph retinas of neonates at high risk is being evaluated and may prove valuable to facilitate analysis by experienced off-site ophthalmologists.

Table 8–1 represents a suggested schedule for timing of initial eye examinations based on postmenstrual age and chronologic (postnatal) age to detect retinopathy of prematurity before it becomes severe enough to result in retinal detachment and to allow for earlier intervention, while minimizing the number of examinations, which potentially are traumatic to the baby.

The timing of follow-up examinations is best determined from the findings of the first examination, using the International Classification of Retinopathy of Prematurity. Treatment generally should be accomplished, when possible, within 72 hours of diagnosed treatable disease so as to minimize the risk of retinal detachment. The retinal findings requiring strong consideration of ablative treatment recently have been revised as follows:

- Zone I retinopathy of prematurity: any stage with plus disease
- Zone I retinopathy of prematurity: stage 3, no plus disease
- Zone II: stage 2 or 3 with plus disease

guidelines for
**PERINATAL
CARE**

Fifth Edition



Guidelines for Perinatal Care was developed through the cooperative efforts of the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn and the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice. The guidelines should not be viewed as a body of rigid rules. They are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

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hospital may be indicated for more intensive phototherapy or exchange transfusion and for evaluation of the underlying cause.

Clinical Considerations in the Use of Oxygen

The hazards associated with the nonindicated administration of supplemental oxygen to preterm neonates have been recognized for many years. Studies conducted in the 1950s indicated that prolonged oxygen therapy without clinical indication was associated with increased rates of retinopathy of prematurity, formerly called retrolental fibroplasia. The ensuing blanket restriction of ambient oxygen therapy resulted in a marked decrease in retinopathy of prematurity at the cost of a marked increase in morbidity and mortality. Current practice includes the prudent use of supplemental oxygen as needed, based on an objective determination of oxygen requirements.

When supplemental oxygen therapy is considered, the potential risks, in terms of both hypoxia and hyperoxia, should be weighed. Clinical judgment of physical signs alone as a guide to the amount of supplemental oxygen needed is acceptable for short periods, emergencies, or abrupt clinical changes. However, the ease of noninvasive determinations of oxygen saturation should preclude the continued use of supplemental oxygen without an objective assessment.

ADMINISTRATION AND MONITORING

In an emergency, high concentrations of supplemental oxygen may be administered by a face mask or endotracheal tube. When a neonate requires oxygen therapy beyond the emergency period, the oxygen should be warmed and humidified, and the concentration or flow should be carefully regulated and monitored. Oxygen can be delivered via an endotracheal tube, oxygen hood, nasal prong, or incubator. Oxygen analyzers should be calibrated in accordance with manufacturers' recommendations. Orders for oxygen therapy should be written in terms of desired ambient concentration or flow and should indicate the intervals at which the concentration (or flow rate, when nasal prongs

are used) should be routinely checked. Alternatively, orders should be written to adjust F_{iO_2} or flow within a stated range to maintain oxygen saturation within specific limits. There should be an institutional policy for ordering, delivering, and documenting oxygen therapy and monitoring.

An important development in the care of neonates who require oxygen therapy has been the ability to monitor oxygenation continuously with noninvasive techniques. The transcutaneous oxygen analyzer provides an indirect measurement of P_{aO_2} , and the pulse oximeter measures oxyhemoglobin saturation. Because neither technique measures P_{aO_2} directly, they should be used as adjuncts to, rather than substitutes for, arterial blood gas sampling, especially in neonates with moderate to severe respiratory distress.

Periodic measurement of P_{aO_2} in samples from an umbilical or peripheral artery catheter is the most reliable method of assessing the effectiveness of oxygen therapy. If an indwelling arterial catheter is not in place, peripheral artery puncture can be used, but repeated sampling from these sites is not always possible. When arterial blood sampling is not possible, arterialized capillary sampling is an acceptable alternative. This measurement produces fairly reliable estimates of arterial pH and arterial carbon dioxide (P_{aCO_2}) but usually underestimates true P_{aO_2} .

In neonates whose condition is unstable, noninvasive measurements should be correlated with P_{aO_2} at least every 8-12 hours. More frequent analyses of arterial blood gas may be indicated for the assessment of pH and P_{aO_2} . In neonates whose condition is stable, correlation with arterial blood gas samples may be performed less frequently.

The use of either transcutaneous oxygen measurement or pulse oximetry may shorten the time required to determine optimum inspired oxygen concentration and ventilator settings in the acute care setting. Both measurements are particularly useful in monitoring oxygen therapy in neonates who are recovering from respiratory distress or who require long-term supplemental oxygen. Because transcutaneous oxygen measurements underestimate oxygenation in older neonates with bronchopulmonary dysplasia (BPD), pulse oximetry may be a more suitable method for monitoring oxygen therapy in these neonates.

In consideration of the current, but incomplete, understanding of the effects of oxygen administration, the following recommendations are offered:

- Supplemental oxygen should not be used without a specific indication, such as cyanosis, low P_{aO_2} , or low oxygen saturation.
- The use of supplemental oxygen other than for resuscitation should be monitored by regular assessments of P_{aO_2} and oxygen saturation.
- The duration of time that oxygen therapy may be administered in nurseries lacking the capability of appropriate P_{aO_2} or oxygen saturation monitoring before consideration of transfer to a higher level unit is contingent on the gestational age of the neonate and the severity of the oxygenation deficit. In general, neonates delivered at less than 36 weeks of gestation or those requiring more than 40% ambient oxygen should be stabilized and transferred promptly.
- For neonates who require oxygen therapy for acute care, measurements of blood pressure levels, blood pH, and P_{aCO_2} should accompany measurements of P_{aO_2} . In addition, a record of blood gas measurements, details of the oxygen delivery system (eg, ventilator, settings, continuous positive airway pressure), and ambient oxygen concentrations (or liter of flow per minute, if nasal prongs are used) should be maintained.
- When supplemental oxygen is administered to a preterm neonate, attempts should be made to maintain P_{aO_2} at 50–80 mm Hg. Oxygen tensions in this range should be adequate for tissue needs given normal hemoglobin concentrations and blood flow. Even with careful monitoring, however, P_{aO_2} may fluctuate outside this range, particularly in neonates with cardiopulmonary disease.
- It is prudent when oxygen therapy is needed for a preterm neonate to discuss the reasons for using supplemental oxygen and the associated risks and benefits with parents.
- Hourly measurement and recording of the concentration of oxygen delivered to the neonate is recommended.
- Except for an emergency situation, air-oxygen mixtures should be warmed and humidified before being administered to newborns.

RETINOPATHY OF PREMATURETY

Myriad factors other than hyperoxia may contribute to the pathogenesis of retinopathy of prematurity. Prolonged ventilatory support (especially when accompanied by episodes of hypoxia and hypercapnia) and clinical conditions, including acidosis, shock, sepsis, apnea, anemia, patent ductus arteriosus, and vitamin E deficiency also have been associated with retinopathy of prematurity.

To date, a safe level of P_{aO_2} in relation to retinopathy of prematurity has not been established. Retinopathy of prematurity has occurred in preterm neonates who have never received supplemental oxygen therapy and in neonates with cyanotic congenital heart disease in whom P_{aO_2} levels never exceeded 50 mm Hg. Conversely, retinopathy of prematurity has not developed in some preterm neonates after prolonged periods of hyperoxia. Recent data have demonstrated no additional progression of active prethreshold retinopathy of prematurity when supplemental oxygen was administered at pulse oximetry saturations between 96% and 99%. Further, continuous close monitoring of transcutaneous oxygen tension has not resulted in a decrease in the incidence of retinopathy of prematurity.

On the basis of published data, the following statements regarding retinopathy of prematurity and oxygen use are warranted:

- Retinopathy of prematurity is not preventable in some neonates, especially extremely LBW neonates.
- Many factors other than hyperoxia are important in the pathogenesis of retinopathy of prematurity.
- Transient hyperoxia alone cannot be considered sufficient to cause retinopathy of prematurity.
- Strict adherence to existing standard of care for supplemental oxygen therapy will not completely prevent complications or side effects.
- An ophthalmologist with experience in retinopathy of prematurity and indirect ophthalmoscopy should examine the retinas of all preterm neonates (ie, those delivered at ≤ 28 weeks of gestation or weighing $\leq 1,500$ g at birth). The examination should be performed at 4–6 weeks of chronologic age or at 31–33 weeks post-

In response to the letter dated February 8, 2013 sent to Dr. Marchase (UAB) and Mr. Saz (RTI) we would like to respectfully submit a rebuttal of several of its assertions and interpretations.

Limitations in the Historical Background as Documented in the OHRP Letter

The summary statement on page 4 of the review of the literature states that, "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 preterm infant developing ROP and other aspects of morbidity and mortality."

The evidence of increased mortality with restriction of oxygen was based on observational studies. The trials comparing a practice that restricted oxygen supplementation to $\leq 50\%$ inspired oxygen concentration regardless of the condition of the preterm infants did not report an increase in mortality. The unrestricted oxygen policy provided oxygen routinely for 2 to 7 weeks at over 50% concentration. The meta-analysis of these 5 trials (1950 to 1970) showed that oxygen restriction decreased the incidence and severity of retinopathy without an effect on mortality (Askie LM, Henderson-Smart DJ, Ko H. *Cochrane Database Syst Rev.* 2009. Jan 21;1: CD001077). These trials included few extremely preterm infants whereas the SUPPORT trial enrolled only extremely preterm infants. Restriction of oxygen using an arbitrary cut-off of inspired oxygen concentration has not been a standard clinical practice in US NICUs for many decades, and this was not a practice tested in the SUPPORT trial. Furthermore, oxygen monitoring in the 1950s was done by monitoring the infants skin color whereas continuous oxygen saturation monitoring was used in SUPPORT. In addition, most NICU practices have changed substantially since the 1950s. Notice that the references used in the "Background" in the OHRP letter are for 1956 (ref. 4), 1973 (ref. 5), and 1984 (ref. 6). Reference 8 published in 2006 states, "marked variability in opinion exists with respect to oxygen targets" but does not include references to support the statement or new data.

Evidence Available Prior to SUPPORT to Determine Reasonably Expected Risk and Benefits

The best prior evidence for the design of the SUPPORT trial included the following cohort studies:

The study by Tin *et al.* (Tin W, Milligan DW, Pennefather P, Hey E. *Arch Dis Child Fetal Neonatal Ed.* 2001;84:F106-10) was the most rigorous study that tested targets of oxygen saturation less than 95% before SUPPORT was performed. The Tin study was a multicenter population-based prospective cohort study of infants <28 weeks (just like SUPPORT). The Tin study was the only one with follow-up assessments to at least 10 months of age.

The policy for oxygen saturation targets and alarm limits varied among the centers. ROP was decreased in the 70-90% saturation target patients **without a difference in survival (51.6% survival in the 70-90% O₂ saturation target group vs. 51.7% in 84-95% group, Table 1).**

Table 1.

Saturation Alarm Targets	N	Survival	Survival with ROP	Survival with Cerebral Palsy
70-90%	126	51.6%	6.2%	15.4%
84-95%	319	51.7%	15.8%	15.5%
88-98%	123	52.8%	27.7%	16.9%

It should be noted that impaired neurodevelopmental outcome was not higher with oxygen saturation targets as low as 70-90%. Furthermore, not a single case of blindness was reported in infants at targets up to 95% despite the difference in ROP.

The Chow *et al.* study (Chow LC, Wright KW, Sola A, CSMC Oxygen Administration Study Group. *Pediatrics*. 2003;111:339-45) was a single center prospective cohort study to assess the impact of implementation of an oxygen monitoring and administration policy for very low birth weight infants. Outcomes for very low birth weight infants with a lower saturation target (83-93%) were compared to outcomes of very low birth weight infant during a previous period when the oxygen saturation target was 90-98%. With the lower oxygen saturation target, severe ROP decreased from 12.5% to 2.5% and the need for ROP laser treatment decreased from 4.5% to 0%. Over the years of the study, there was a trend **for increased survival following implementation of the restrictive oxygen policy** (contrary to what we found in SUPPORT). Survival improved from 48 to 75% in the infants 500-749 g and from 74 to 81% in the infants 750-999 g from 1997 to 2001. The policy was changed in the middle of 1998 (Table 2).

Table 2.

Birth Weight (g)	1997		1998		1999		2000		2001		Total	
	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival
500-749	14	48	15	40	18	73	15	87	12	75	74	58
750-999	25	74	27	78	18	78	21	82	17	81	108	83
1000-1249	24	88	20	100	26	96	28	100	21	94	119	95
1250-1500	29	97	27	100	26	100	28	100	36	97	146	99
Total	92	81	89	83	88	85	92	93	86	90	447	86

The American Academy of Pediatrics Guidelines for Perinatal Care recommended targets oxygen saturation for preterm infants although they acknowledge that the optimal range had not been elucidated (Guidelines for Perinatal Care, 6th Edition (2007)). Their recommendation specified oxygen saturation target of 85-95% and PaO₂ values between 50 and 80 mm Hg as “pragmatically determined by some clinicians to guide oxygen therapy in preterm infants”. The prior edition of those Guidelines (2002) provides the same PaO₂ ranges but did not specify an oxygen saturation target. Thus, the SUPPORT Trial treatments were in compliance with the Guidelines for Perinatal Care.

Disclosure of Risks

The best available studies, those with the highest level of evidence, when SUPPORT was designed and conducted suggested that lower oxygen saturation targets would lead to a decrease in ROP and decreased BPD. Furthermore, there was not even suggestive evidence from relevant prior literature that would suggest an increase in death, blindness, or other serious morbidity with either set of oxygen saturation targets used in SUPPORT.

Based on these and other studies, many clinicians started to recommend lower oxygen saturation targets and developed educational programs promoting the same. The most prominent program was developed by Dr. Jay Goldsmith from Ochsner Clinic (not published in the peer-reviewed literature). In this program Dr. Goldsmith and colleagues recommended oxygen saturation targets of 85 to 93%. The benefits stated were decreased ROP, decreased days on a ventilator and on oxygen, and decreased hospitalization duration. Risk for adverse effects or increased mortality was not included in the materials.

Four other multicenter trials were designed after the SUPPORT trial was conceived. These trials were led by investigators based in the United Kingdom, Australia, New Zealand, and Canada. These protocols were also designed without the expectation of increased mortality in the lower oxygen saturation group.

The SUPPORT consent template, the UAB consent forms, and those of other clinical centers were appropriately written based on the relevant knowledge available at the time. Furthermore, throughout the trial, survival was better than the historical reference group used prospectively to monitor the trial by the independent Neonatal Research Network (NRN), DSMC, and the NRN Steering Committee. Rates of morbidities and mortality compared to historic controls were reviewed during each quarterly NRN Steering Committee meeting and found to be lower than the historical reference group. Concurrent infants not enrolled in the SUPPORT Trials had a mortality rate of 24.1% compared to infants in the higher saturation group (16.2%) and infants in the lower oxygen saturation group (19.9%) although these differences were not statistically significant in adjusted regression analyses (Table 3).

Table 3.

	Mortality Rates
Historic reference group	21.1%
SUPPORT 85-89% target group	19.9%
SUPPORT 91-95% target group	16.2%
Concurrent eligible not enrolled in SUPPORT	24.1%

Death was included in the primary outcomes of the SUPPORT Trial because it is a competing outcome of retinopathy of prematurity and bronchopulmonary dysplasia not because an increase in mortality was expected in either case. Inclusion of death as part of the primary outcome measures is done in almost all large randomized controlled trials in the NICHD Neonatal Research Network and other major neonatal research groups when research involves extremely preterm infants.

Summary

In summary, the existing published data that were pertinent when the SUPPORT Trial was designed and conducted did not portend an increase in mortality or blindness in either treatment group. Other morbidities had not been reported in the published studies.

Risk is defined in the OHRP IRB guidebook as “the probability of harm or injury ...occurring as a result of participation in a research study.” As emphasized above, the best available evidence indicated no discernible increased probability of death or other harms as a result of participating in this trial comparing two methods of care widely used both within and outside the NICHD Neonatal Research Network. The SUPPORT consent form was thus appropriately written for this comparative effectiveness trial based on the relevant knowledge available at the time.

We believe it would be particularly unfortunate to criticize the consent form on ethical grounds when this trial has provided knowledge important to reducing the mortality of these infants. Leading ethicists including the eminent Tom Beauchamp have recently emphasized the need to promote comparative effectiveness trials and noted that “the terms ‘research’ and ‘practice’ are poor proxies for what should be our central moral concerns.” “As they note a new ethical foundation needs to be developed that facilitates both care and research likely to benefit patients and that provides oversight that ...is commensurate with risk and burden in both realms” (Kass NE , Faden RR, Goodwin SN, Pronovost P, Tunis S, Beauchamp TL. Hastings Center Report Jan-Feb 2013. S4-S15).

Thus, we stand by our original position that the consent forms were appropriate based on the knowledge at the time. The SUPPORT Trial is the best evidence currently available to inform physicians how to manage oxygen administration in these vulnerable infants.

Respectfully submitted,

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, February 26, 2013 12:03 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: FW: Heads-Up RE: OHRP Determination letter posting

Just an FYI – at this point

Bob and I were given heads up about this letter being posted just in case NIH receives any media questions. Bob is reaching out to Renate Myeles in Building 1 to coordinate how best to handle. Bob will be touching base later as needed.

Mona

Mona Jaffe Rowe, M.C.P.
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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; he also may address proposed regulatory changes that OHRP believes will strengthen the consent process. We propose to refer to NICHD any queries about the SUPPORT study and to UAB any questions 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 RTI 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
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Cc: [Willinger, Marian \(NIH/NICHD\) \[E\]](mailto:Willinger.Marian@NIH/NICHD)
Subject: FW: SUPPORT
Date: Tuesday, February 26, 2013 12:48:00 PM
Attachments: [A Rudczynski ltr to OHRP 9Dec11.pdf](#)
[HIC-OHRP 2007 Perinatal Guidelines 6th Ed.pdf](#)
[HIC-OHRP 2002 Perinatal Guidelines 5th Ed.pdf](#)
[OHRP RESPONSE LETTER Ver 3 2-22-13wc bb \(4\).doc](#)

Hi

Yvonne and I spoke a few weeks ago about the OHRP letter sent – please look at the attached documents.

My understanding is that Yvonne was going to try to contact Sherrie Mills in building one.

The guidelines in 2007 refer to 85-95% saturation targets for premature infants. If you look at page 3 of the word document shows that mortality of enrolled infants was LOWER than the rates of our historical controls as well as infants eligible for the trial but not enrolled.

Rose

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From: Ehrenkranz, Richard [<mailto:richard.ehrenkranz@yale.edu>]
Sent: Thursday, February 21, 2013 4:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose:

The information that was sent, was sent in response to a letter requesting responses. Yale's last response was on Dec 9, 2011. We have heard nothing further from OHRP. I have attached that last response. I will let our IRB-Human Research Protection Program know that they can join with from my office.

Richard

Richard A. Ehrenkranz, MD
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The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 21, 2013 3:43 PM
To: Ehrenkranz, Richard
Subject: Re: SUPPORT

I am trying to balance those who need to be on the call with being open to sites- could they join from your office? Otherwise I will need a different call in or a different phone line to allow participation. Have you received any official correspondence from OHRP or was the information you sent in 11/2011 provided after their visit to Yale?

Let me know

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, February 21, 2013 01:46 PM
To: Kristi Watterberg <KWatterberg@salud.unm.edu>; nxs5@case.edu <nxs5@case.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Ivan Frantz <Ivan.Frantz@childrens.harvard.edu>; Michele Walsh (mcw3@cwru.edu) <mcw3@cwru.edu>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Roger Faix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Shahnaz' (SDuara@med.miami.edu) 'Duara <SDuara@med.miami.edu>; Beena [bsood@med.wayne.edu] Sood <bsood@med.wayne.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; M.D. Wally Carlo <WCarlo@peds.uab.edu>; Abhik Das (adas@rti.org) <adas@rti.org>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>; dstevenson@stanford.edu <dstevenson@stanford.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Brenda Morris (morrisb1@tmfhs.org) <morrisb1@tmfhs.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Wally Carlo (wacarlo@uab.edu) <wacarlo@uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Wade RIch <wrich@ucsd.edu>; Edward (Pediatrics) Bell <edward-bell@uiowa.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@URMC.Rochester.edu>; dale_phelps@urmc.rochester.edu <dale_phelps@URMC.Rochester.edu>; Nirupama Laroia <Nirupama_Laroia@URMC.Rochester.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; Abbot Laptook <Alaptook@wihri.org>
Cc: Archer, Stephanie (NIH/NICHD) [E]; Amanda (alewis@rti.org) Lewis-Evans <alewis@rti.org>; Jenna Gabrio (jgabrio@rti.org) <jgabrio@rti.org>; (kzaterka@rti.org) <kzaterka@rti.org>; (mcunningham@rti.org) <mcunningham@rti.org>; Carolyn Petrie <petrie@rti.org>

Subject: RE: SUPPORT

Wally,

I agree with Kristi-I have nothing further to add.

By the way, I have been asked by members of our IRB-Human Research Protection Program about participating in the call next week. I emailed their request to Rose; what are your thoughts? As you may remember, we were asked similar questions by OHRP; the final responses were submitted on Dec 9, 2011 and we have not heard back from them.

Richard

Richard A. Ehrenkranz, MD
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333 Cedar Street
PO Box 208064
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fax: 203-688-5426

The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]

Sent: Thursday, February 21, 2013 1:28 PM

To: nxs5@case.edu; Kurt Schibler [kurt.schibler@cchmc.org]; (Vivek.Narendran@cchmc.org); Ivan Frantz; Michele Walsh (mcw3@cwru.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); bpoindex@iupui.edu; Rosemary (NIH/NICHD)[E] Higgins; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz' (SDuara@med.miami.edu) 'Duara; Beena [bsood@med.wayne.edu] Sood; Seetha Shankaran; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); barbara_stoll@oz.ped.emory.edu; M.D. Wally Carlo; Abhik Das (adas@rti.org); mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; Krisa Van Meurs (vanmeurs@stanford.edu); Brenda Morris (morrisb1@tmfhs.org); Ambal (ambal@uab.edu); Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Wade RIch; Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; Nirupama Laroia; Jon.E.Tyson@uth.tmc.edu; Kathleen A Kennedy; Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; Abbot Laptook; Ehrenkranz, Richard

Cc: Stephanie(NIH/NICHD) [E] Archer; Amanda (alewis@rti.org) Lewis-Evans; Jenna Gabrio (jgabrio@rti.org); (kzaterka@rti.org); (mcunningham@rti.org); Carolyn Petrie

Subject: RE: SUPPORT

Very nice. Wally! - with the edits you've already received, I have nothing further to add.

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 2/21/2013 10:17 AM >>>

Wally,

Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.

Ed

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 10:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Bell, Edward (Pediatrics); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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FAX: 205 934 3100
Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 19, 2013 8:25 AM
To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edwardbell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6)

with pass code

(b)(6)

Rose

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From: Das, Abhik
To: Wally Carlo, M.D.; Namasivayam Ambalavanan
Cc: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : first draft of Feb21, 2013
Date: Monday, February 25, 2013 1:46:22 PM
Attachments: PCO2_SUPPORT_Feb21_2013wc_AD.docx

My comments are appended in the attached.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@ped.s.uab.edu]
Sent: Thursday, February 21, 2013 8:43 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A
Cc: Walsh, Michele; Michael Cotten; Das, Abhik; Gantz, Marie; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : first draft of Feb21, 2013

Ambal:

Great job putting this paper together so promptly. I only have minor suggestions which are tracked.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Newborn Nurseries
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Phone: 205 934 4680
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From: Namasivayam Ambalavanan
Sent: Thursday, February 21, 2013 10:37 AM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : first draft of Feb21, 2013
Importance: High

Dear All,

Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.

(Stephanie: Would you check the boilerplate and grant acknowledgments?)
Thank you for all your help,
Best regards,
Ambal

Namasivayam Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology
University of Alabama at Birmingham

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Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Wednesday, February 02, 2011 10:06 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,
Our PAS abstract on PaCO2 in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,
Thank you for all your help,
Ambal

From: Namasivayam Ambalavanan
Sent: Mon 11/8/2010 5:40 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,
Attached is the abstract on PaCO2 SUPPORT abstract for NICHD clearance.
Thank you,
Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO2 variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO2 in the CPAP arm from about 33 to 34. The Max PaCO2 was about the same in all groups)

Thanks,
Ambal

N. Ambalavanan MD
Professor, Division of Neonatology
Departments of Pediatrics, Cell Biology, and Pathology

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From: Namasivayam Ambalavanan
Sent: Sun 10/31/2010 6:25 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.

Ambal

(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

From: Namasivayam Ambalavanan
Sent: Sat 10/30/2010 8:15 PM
To: Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.

Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher

CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,
Ambal

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Sat 10/30/2010 4:59 PM
To: Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]
Sent: Saturday, October 30, 2010 10:18 AM

To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook;
NIH; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

Best Michele

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@ped.s.uab.edu>]

Sent: Fri 10/29/2010 5:28 PM

To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal

Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran

Subject: RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO2 in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how). Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?

Thanks,

Ambal

N. Ambalavanan MD

Division of Neonatology,

Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Email ambal@uab.edu

From: Namasivayam Ambalavanan

Sent: Saturday, October 23, 2010 7:16 AM

To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal

Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook;

NIH; Michele Walsh; Matt Laughon; Seetha Shankaran

Subject: RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of

ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO2 (using highest FiO2 on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?
Ambal

From: Namasivayam Ambalavanan
Sent: Fri 10/22/2010 8:58 PM
To: Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO2 (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO2 and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO2. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO2 were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.
Ambal

From: Michael Cotten [<mailto:cotte010@mc.duke.edu>]
Sent: Fri 10/22/2010 7:57 PM
To: Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon
Subject: Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co2? Some babies are easily hyperventilatable, and sometimes practitioners allow co2 to be high on min settings...and those kids are probably way different than kids on high settings or hfvc who remain hypercarbic,,,

Mc

From: "Namasivayam Ambalavanan" [NAmbalavanan@peds.uab.edu]
Sent: 10/22/2010 03:59 PM EST
To: "Wrage, Lisa Ann" <wrage@rti.org>; <ambal@uab.edu>
Cc: "Das, Abhik" <adas@rti.org>; "Gantz, Marie" <mgantz@rti.org>; "Wally Carlo, M.D." <WCarlo@peds.uab.edu>; "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>; "Laptook, Abbot" <ALaptook@WIHRI.org>; "Higgins, Rosemary (NIH/NICHD)" [E] <higginsr@mail.nih.gov>; <Michele.Walsh@UHHospitals.org>; Michael Cotten; "Laughon, Matthew M" <matt_laughon@med.unc.edu>
Subject: RE: PAS ABSTRACT

Hi Lisa,

(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO₂ (especially higher PaCO₂ and fluctuating PaCO₂) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO₂ is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO₂, minimal PaCO₂, time-weighted PaCO₂, and SD of PaCO₂ as independent continuous variables with actual time-weighted PaO₂ (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO₂ for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO₂ variables with outcome, after adjustment for the other variables. We probably do not need PaCO₂ values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO₂ and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO₂ terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO₂ to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO₂ category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO₂ categories and the numbers in each CO₂ category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,
Ambal

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 22, 2010 2:48 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,

I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO2 variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.

Thanks and have a great weekend.

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Wednesday, October 20, 2010 10:58 AM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.

Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Wed 10/20/2010 9:42 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,

Thanks for the response. Regarding the time-weighted CO2, Wally and Marie did decide to cap the amount of time that on CO2 level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.
Thanks.
Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis but I think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

From: Gantz, Marie <mgantz@rti.org>

Sent: Tuesday, October 19, 2010 7:29 PM

To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>

Cc: Das, Abhik <adas@rti.org>; Wrage, Lisa Ann <wrage@rti.org>

Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5
75th 12
90th 21
95th 25.5
99th 80
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
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828-254-6255

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 15, 2010 2:56 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Lisa,

Thank you for the email.

- 1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
 - 2) I think PROM>24h is ok
 - 3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.
 - 4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.
- Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 15, 2010 1:46 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted CO2 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95th %ile is 25.1 hours and the 99th%ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.

I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,
Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 05, 2010 2:45 PM
To: 'Namasivayam Ambalavanan'; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.

Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, October 05, 2010 2:38 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,
My answers (>>) are below your questions (**)

Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]

Sent: Tuesday, October 05, 2010 12:36 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Thank you, this is helpful, I have a few more questions (see ** below).
Lisa

From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Tuesday, October 05, 2010 12:42 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,
(Abhik/Wally/Marie – your comments are also welcome)
If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

***Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.*

>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices

- 2) For Aim (1): determine the association of PaCO₂ in the first 2 weeks with outcomes, we will use PaCO₂ as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

***Could you please clarify how you like to summarize PaCO₂ over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?*

>> I think max, min, time-weighted, and standard deviation should be ok.

- 3) For Aims (2) and (3), to determine the association of high/low PaCO₂ with outcomes, we will divide infants into quartiles based on their maximum PCO₂ and their minimum PCO₂ over the first two weeks. The infants in the highest quartile of max PCO₂ are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO₂ will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO₂ and minimum PCO₂. The outcomes will be assessed in the low and high SpO₂ groups in relation to PaCO₂ status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

***So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PCO₂), >> Yes. fluctuators will be a subset of this*

group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators]. Hypocapnic (in lower quartile of min PCO2,>> Yes. As above, I think we should have hypocapnia only, not fluctuators. Fluctuators (in both upper quartile of max PCCO2 lower quartile of min PCO2)>> Yes. Normocapnic (in middle two quartiles of max PCO2 AND min PCCO2)

To define Max PCO2 and Min PCO2 do you simply want me to use the maximum and minimum value of all values of PCO2 for each infant using PCO2 recorded during the 1st two weeks on the SUPP05 form?

>> **Yes**

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO2, minPCO2, time-weighted PCO2, and SD of PCO2 as independent continuous variables with SUPPORT group assignment

****OK.**

>>**Great!**

Thanks,
Ambal

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 05, 2010 10:32 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Dr. Ambalavanan,

I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO2 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc. ", could you please provide a complete list?

Thank-you,
Lisa

Lisa Wrage, MPH
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From: Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]
Sent: Friday, October 01, 2010 11:14 AM
To: Das, Abhik; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Hi Lisa, Marie,
What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?
Ambal

N. Ambalavanan MD
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From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Tuesday, September 21, 2010 3:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, September 21, 2010 11:15 AM
To: Ambal (ambal@uab.edu)
Cc: Wally Carlo, M.D.; Das, Abhik
Subject: PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.

November 8, 2010– Final abstracts to NICHD for clearance
Mid-November– PAS deadline
April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks
Rose

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Title:

Association of PaCO₂ with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Authors:

Namasivayam Ambalavanan MD¹; Waldemar A. Carlo MD¹; Lisa Wrage MPH²; Abhik Das PhD²; Matthew Laughon MD MPH³; C. Michael Cotten MD⁴; Kathleen Kennedy MD⁵; Abbot Laptook MD⁶; Seetha Shankaran MD⁷; Michele Walsh MD MS⁸; Rosemary D. Higgins MD⁹; For the SUPPORT Study Group of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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Short Title: PaCO₂ and IVH

Abbreviations: BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

Keywords: Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis

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Funding source: Supported by grants from the National Institute of Child Health and Human Development and the Department of Health and Human Services (U10 HD21385, U10 HD40689, U10 HD27871, U10 HD21373, U01 HD36790, U10 HD40498, U10 HD40461, U10 HD34216, U10 HD21397, U10 HD27904, U10 HD40492, U10 HD27856, U10 HD40521, U10 HD27853, U10 HD27880, U10 HD27851) and from the National Institutes of Health (GCRC M01 RR 08084, M01 RR 00125, M01 RR 00750, M01 RR 00070, M01 RR 0039-43, M01 RR 00039, and 5 M01 RR00044). (Stephanie Archer – Would you please confirm/correct?)

Conflicts of interest: The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

Word count: abstract: 320; text of manuscript: 2613 (Introduction, Methods, Results, and Discussion).

What's known on this subject: Variations in arterial partial pressure of carbon dioxide (PaCO_2) might contribute to or be associated with several clinical outcomes of prematurity such as IVH, PVL, BPD, and subsequent NDI.

What this study adds: Higher PaCO_2 and greater fluctuation in PaCO_2 were associated with severe IVH, BPD, and NDI (and/or death). The correlation of PaCO_2 with FiO_2 and days of ventilation support indicate that higher Max PaCO_2 as may be a marker of illness severity.

Comment [AD1]: Do we need to spell out any of this, because this is the first time they are mentioned?

Comment [WC2]: It would be best to use a more generic term rather than Max which is a term from your paper and not all readers will get.

ABSTRACT:

Objective: To determine the association of PaCO₂ with severe intraventricular hemorrhage (IVH), physiologic bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) each alone and in combination with the competing outcome of death in extremely premature infants. **Methods:** Blood gas data from postnatal days 0-14 were analyzed in 1316 infants enrolled in the SUPPORT trial that included infants 24^{0/7} to 27^{6/7} wks GA randomized to SpO₂ targets of 85-89% vs 91-95% and two ventilation strategies. 5 PaCO₂ variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO₂], hypocapnic [lowest quartile of Min PaCO₂], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO₂]). For unadjusted analyses, we compared PaCO₂ variables for infants with and without the outcomes of severe IVH, BPD, and NDI (+/- death). Multivariable regression was done for severe IVH/death, BPD/death, and NDI/death using Max PaCO₂, birth weight, GA, sex, race, prenatal steroids, PIH, ROM>24h, 1 & 5 min Apgars, center, severe illness (FiO₂>0.4, ventilation for >8 h in first 14d), & treatment group (CPAP/Surfactant, High/low SpO₂). **Results:** Severe IVH, BPD, and NDI (+/- death) were more common in hypercapnic infants and fluctuators. Other variables associated with severe IVH, BPD, and NDI (+/- death) included lower birth weight, male sex, and lower Apgars, but not treatment group. The relationship of Max PaCO₂ with outcomes persisted after adjustment (For ↑ of 10 mmHg: Severe IVH/death: OR 1.23 [1.12-1.36]; BPD/death: OR 1.38 [1.24-1.54]; NDI/death: OR 1.26 [1.13-1.39], all p < 0.0001). No interaction was found between PaCO₂ and SpO₂ or CPAP/surfactant group. Max PaCO₂ was positively correlated with maximum FiO₂ (r_s 0.55, p < 0.0001) & days of ventilation (r_s 0.61, p < 0.0001). **Conclusions:** Higher PaCO₂ and greater fluctuation in PaCO₂ were independently associated with severe IVH, BPD, and NDI (+/- death). The correlation of PaCO₂ with FiO₂ and days of ventilation support higher Max PaCO₂ as a marker of illness severity rather than permissive hypercapnia.

Comment [AD3]: If you spell these out before, then you will save some words!

Comment [AD4]: Perhaps can delete here if you need to cut?

Comment [WC5]: You could leave this out to get a shorter abstract

Comment [AD6]: Can shorten by saying something like "The outcomes of ... were compared using unadjusted and adjusted analyses (adjusting for ...)." I am also not sure I would put much emphasis on unadjusted comparisons from an observational study here or in the Results.

(Abstract Word Count = 320: Need to shrink)

MANUSCRIPT TEXT

INTRODUCTION

Comment [AD7]: This is good, but can you also explicitly address why it is important to know about this association. What difference could it make clinically?

Variations in arterial partial pressure of carbon dioxide (PaCO_2) ~~may contribute to or~~ be associated with several important clinical outcomes of prematurity such as intraventricular hemorrhage (IVH)¹, periventricular leukomalacia (PVL)^{2,3}, bronchopulmonary dysplasia (BPD)⁴, and subsequent neurodevelopmental impairment (NDI)⁵. Increased PaCO_2 increases cerebral blood flow,⁶⁻⁸ while decreased PaCO_2 reduces cerebral blood flow, increases cerebral fractional oxygen extraction, and decreases cerebral electrical activity.⁹ We have previously shown that both high and low PaCO_2 levels and wide fluctuations in PaCO_2 are associated with a higher risk of severe IVH (IVH Grades III or IV).¹ Periventricular leukomalacia (PVL) is strongly linked to hypocapnia.^{2,3,10} Cerebral blood flow decreases slightly with increased oxygenation⁸ but the interactions between PaCO_2 and PaO_2 have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher PaCO_2 as well as a lower PaO_2 , permitting reduced volutrauma and earlier weaning from mechanical ventilation.^{4,11,12} The combination of a higher PaCO_2 (permissive hypercapnia) as well as a lower PaO_2 (targeting a lower SpO_2 range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower PaO_2 alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants 24^{0/7} to 27^{6/7} weeks gestation and compared outcomes in infants randomly assigned to~~managed with~~ oxygen saturation targets of either 85-89% or 91-95%, while also being randomly assigned to either early CPAP and a protocol-driven limited ventilation strategy (a $\text{PaCO}_2 > 65$ mm Hg permitted intubation, while a $\text{PaCO}_2 < 65$ mm Hg with a $\text{pH} > 7.20$ was a mandatory extubation criterion) or intubation and surfactant within 1 hour after birth (a $\text{PaCO}_2 < 50$ mm Hg with a $\text{pH} > 7.30$ was a

mandatory extubation criterion).^{13,14} Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant target groups although infants in the CPAP (higher PaCO₂ target) group less frequently required surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and were more likely to be alive and free of mechanical ventilation by day 7 after birth. In addition, death occurred more frequently in the lower oxygen saturation (low SpO₂) target group (19.9 vs. high SpO₂ 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs. 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001), without significant differences in other outcomes.¹³ There were no significant differences in the composite outcome of death or neurodevelopmental impairment (NDI) among infants in any of the treatment groups assigned to the lower or higher target range of oxygen saturation.¹⁵

It is possible that clinical outcomes that are not significantly different by SpO₂ target groups might be different when the combination of PaCO₂ and SpO₂ is analyzed. PaCO₂ is a possible effect modifier, as PaCO₂ might modify the association between SpO₂ and outcome, due to interaction between PaCO₂ and outcome. PaCO₂ might also be a confounder – it might distort the true relation between the SpO₂ group and outcome, as PaCO₂ might be related to both SpO₂ (as PaCO₂ influences the hemoglobin dissociation curve and thereby the SpO₂ for a given PaO₂) and outcome. We hypothesized that both extremes of PaCO₂ would be associated with severe IVH; and that effect modification of SpO₂ will be observed, with PaCO₂ associated with severe IVH in the low but not high SpO₂ group. We also hypothesized that BPD would be lower in infants with hypercapnia and low SpO₂—and that higher PaCO₂ will be associated with a higher risk of NDI.

PATIENTS AND METHODS

Patient characteristics:

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.¹³ Neonatal information collected for the SUPPORT trial and in the generic database included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical outcomes, and treatment. The baseline characteristics of this population¹³ and characteristics of the follow-up cohort¹⁵ have been previously reported.

PaCO₂ variables

Five PaCO₂ variables were defined: minimum level, maximum level (Max PaCO₂), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted PaCO₂ (calculated as described previously¹) was estimated using all PaCO₂ levels available from blood gases obtained every 8±4 hours up to 3 times a day on postnatal days 1-14. Time between blood gases was capped at 24 hours (~5% of all time difference measurements) so any one blood gas represents up to 24 hours of time. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum PaCO₂ levels into quartiles. Infants with minimum PaCO₂ levels in the lowest quartile who were not also in the highest quartile of maximum PaCO₂ level were then categorized as 'hypocapnic'. Infants with maximum PaCO₂ levels in the highest quartile who were not also in the lowest quartile of minimum PaCO₂ level were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum PaCO₂ and the highest quartile of maximum PaCO₂ were categorized as 'fluctuators', and the remaining infants, those whose minimum

Comment [WCB]: Maybe both initial papers should be quoted here.

Comment [AD9]: Is there a way to show this graphically? The text made my eyes glaze over a little!

Comment [AD10]: Before going into this, I think we need a description first of what PaCO₂ data was collected over what time frame.

PaCO₂ level fall in quartiles 2-4 and maximum PaCO₂ levels fall in quartiles 1-3 were categorized as 'normocapnic'.

Other variables

Maternal hypertension was defined as pregnancy induced hypertension. Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth. Prenatal steroids were defined as any use of antenatal steroids. Maximum FiO₂ was defined as the maximum of FiO₂ at 24 hours, day 3, 7, 14 and severe illness as FiO₂ >0.4 and mechanical ventilation for 8+ hours in the 1st 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),¹⁶ and BPD was defined using the physiologic definition at 36 w PMA.^{17,18} Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.¹⁵

Statistical Analysis

The PaCO₂ and other variables were compared by each of 6 outcomes: severe IVH, death or severe IVH, BPD, death or BPD, NDI, and death or NDI. Specifically, the PaCO₂ and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance (p<.05) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis generating goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the Max PaCO₂ variable were obtained using a GEE model for the binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for the fact that the SUPPORT trial randomized multiple births to the same treatment arm. Variables included in the models along with Max PaCO₂ were: SUPPORT trial treatment groups (High/Low SpO₂, CPAP/ventilator), severe illness, birth weight, GA group, gender, race, prenatal steroid use, pregnancy induced hypertension, rupture of membranes > 24 hours, indicators for 1 & 5 minute Apgar scores < 3, and center. Interaction terms for Max PaCO₂ x SpO₂ treatment groups and Max PaCO₂ x CPAP/ventilator treatment groups were also included to allow for the association between PaCO₂ and outcomes to differ by treatment arm. However, these interaction terms were not significant (p > 0.1?), and were therefore removed and excluded. Results are expressed as adjusted odds ratios and associated 95% confidence intervals.

Comment [AD11]: Defined as?

Comment [AD12]: Specify

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RESULTS

Unadjusted Results:

All PaCO₂ variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with severe IVH as compared to those without severe IVH (Table 1). In general, infants who developed severe IVH had a lower minimum, higher maximum and greater variation in PaCO₂ as compared to those without severe IVH (Table 1). ~~The~~ Max PaCO₂ demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median Max PaCO₂ between infants with severe IVH and those without severe IVH. The magnitude of separation in minimum, standard deviation, and time-weighted PaCO₂ were statistically highly significant (p < 0.0001) but clinically small (~2 mm Hg). Bivariate

Comment [AD13]: Are unadjusted results meaningful for an observational study such as this one? Should we give them so much 'ink'?

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analysis showed that infants who died or developed severe IVH had higher maximum, standard deviation, and time-weighted PaCO₂ compared to survivors without severe IVH (Table 2). Results for BPD (Table 3), death or BPD (Table 4), NDI (Table 5), and death or NDI (Table 6) were similar to those for severe IVH and death or severe IVH.

Adjusted Results:

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As the Max PaCO₂ variable was associated with outcome by bivariate analysis and demonstrated (of the PaCO₂ variables) the maximum separation between the groups with or without the outcomes, adjusted analyses were done to determine if this variable was an independent predictor of outcome. Max PaCO₂ was significantly associated with higher odds of death/IVH (OR 1.23, 95% CI 1.12-1.36 for an increase in Max PaCO₂ of 10 mmHg, p < 0.0001). Other variables significantly associated (p < 0.05) with death/IVH included: low SpO₂ group, severe illness, lower birth weight, male gender, pregnancy induced hypertension, low 1 minute Apgar score, and center.

Comment [AD14]: For all these reported associations, have we explored whether they are all caused by differences in mortality that may be driving the significance for all these composite outcomes? Did we look at just severe IVH, BPD and NDI among survivors?
The conclusion lists both max and fluctuation in PaCO₂. For the latter to hold, I think we need to do and report adjusted analyses for that variable as well. You may need to adjust your conclusions if this adjusted analysis was not significant.

Max PaCO₂ was significantly associated with higher odds of death/BPD (OR 1.38, 95% CI 1.24-1.54 for an increase in Max PaCO₂ of 10 mmHg, p < 0.0001). Other variables significantly associated (p < 0.05) with death/BPD included: severe illness, lower birth weight, male gender, non-white race, lower 1 minute Apgar score, and center.

Max PaCO₂ was also significantly associated with higher odds of death/NDI (OR 1.26, 95% CI 1.13-1.40, p < 0.0001) for an increase in Max PaCO₂ of 10 mmHg. Other variables significantly associated (p < 0.05) with death /NDI included: severe illness, lower birth weight, male gender, PIH, and lower 1 min Apgar score.

As higher Max PaCO₂ may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation) or due to

more severe pulmonary disease (which may be associated with higher max FiO₂, days of mechanical ventilation, and severe illness), correlations of Max PaCO₂ with max FiO₂, days of ventilation, and severe illness (as previously defined) were calculated. Max PaCO₂ was positively correlated with both max FiO₂ (Spearman correlation coefficient = 0.55, p<0.0001) and days of ventilation (Spearman correlation coefficient = 0.61, p<0.0001). There was also a significant difference in PaCO₂ level by infants defined as having severe illness (median max PaCO₂=78) vs. infants ~~not defined~~ as having no severe illness (median max PaCO₂=61), p <0.0001 by Wilcoxon two sample test.

DISCUSSION

We found that extremes of PaCO₂ were associated with worse outcome (severe IVH, BPD, and NDI) in extremely preterm infants. A higher maximum PaCO₂ in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO₂, days of ventilation, and severe illness).

Comment [AD15]: See 2nd part of previous comment.

Our study has the limitation that infants in the SUPPORT trial^{13, 14} were not primarily randomized to different specific PaCO₂ ranges as in the randomized trials of permissive hypercapnia^{4, 11, 19} but to interventions (Early CPAP or Prophylactic/Early Surfactant and conventional ventilation) ~~with which had~~ different PaCO₂ goals. However, it has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, criteria for intubation and extubation were used in the trial, and trained research coordinators collected data on blood gases and ventilator settings in addition to other routine clinical variables. Longer-term follow-up was achieved in the majority of infants; and was done by certified trained personnel. Randomization in this trial has most likely led to a similar range of

PaCO₂ in both SpO₂ groups as no interaction was observed between maximum PaCO₂ and SpO₂ groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in PaCO₂ secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.¹⁴

Previously, we have shown in a single-center retrospective analysis that both high and low PaCO₂ levels and wide fluctuations in PaCO₂ ~~are associated with an increased~~ increase the risk of severe IVH.¹ The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of PaCO₂ were statistically significant, they were of small magnitude and clinically relevant differences (~10 mm Hg) were only noted in the maximum PaCO₂. As maximum PaCO₂ was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum PaCO₂ had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation.

In this cohort, the average (time-weighted) PaCO₂ even in infants without severe IVH was ≥ 48 mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the "permissive hypercapnia" range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.¹¹ Our data indicate clinical practices in academic centers have evolved to maintain PaCO₂ in the permissive hypercapnia range. However, as the maximum PaCO₂ exceeded this range even in infants without severe IVH, it is apparent that tight control of PaCO₂ within this narrow range is difficult.

A higher maximum and time-weighted PaCO₂ and a greater magnitude of fluctuation in PaCO₂ were associated with a greater risk of BPD and death/BPD. Similar to severe IVH, this is

likely due to greater illness severity and more severe lung disease being associated with a higher PaCO₂; rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO₂ elimination for a given minute ventilation, due to a higher CO₂ in alveolar air (P_ACO₂). Also, due to the Bohr effect, the affinity of hemoglobin for oxygen decreases with increasing PaCO₂, and peripheral unloading of oxygen is improved with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in weaning preterm infants from the ventilator. There is also evidence that hypercapnic acidosis may attenuate ventilator-induced lung injury and inflammation by multiple molecular mechanisms.^{9, 12, 14} However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in death/BPD have been demonstrated.^{4, 11, 12, 19} In the largest randomized trial of permissive hypercapnia to date, which was terminated early due to unanticipated non-respiratory adverse events secondary to dexamethasone therapy, the relative risk for death or BPD in the minimal ventilation versus routine ventilation groups was 0.93 (63% vs. 68%; 95% CI 0.77-1.12, p = 0.43), and ventilator support at 36 weeks was 1% in the minimal versus 16% in the routine group (p<0.01).⁴

Max PaCO₂ was also significantly associated with higher death/NDI, confirming our previous single-center study with a smaller sample size.⁵ This association may be secondary to Max PaCO₂ being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.²⁰ It is also possible that alterations in PaCO₂ may be a direct mediator of brain injury. A sudden marked increase in cerebral blood flow secondary to a spike in PaCO₂⁶⁻⁸ may result in severe IVH¹ and contribute to NDI. A

Comment [WC16]: 1.You can add the meta-analysis by Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev.* 2012;(3):CD000510
2.It shows decreased death/BPD

reduction in cerebral blood flow due to decreased PaCO₂⁹ may contribute to lower white matter perfusion and result in periventricular leukomalacia (PVL).^{2,3,10} The brain injury associated with extremes of PaCO₂ may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.^{21,22}

In conclusion, our work demonstrates that Max PaCO₂ is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO₂, Max PaCO₂ may be useful for risk-stratification in clinical trials; or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO₂ with outcomes at later time points and in other populations needs to be determined.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Lisa Wrage (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Tables:

Table 1- Bivariate analyses for Severe IVH

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value¹
PaCO₂, minimum level	#	163	1098	
	Mean (SD)	31.8 (7)	33.6 (6.7)	
	Median, IQR	32 (27-37)	34 (29-38)	.0047
PaCO₂, maximum level	#	163	1098	
	Mean (SD)	76.3 (19.8)	66.7 (17)	
	Median, IQR	75 (63-85)	65.5 (55-75)	<.0001
PaCO₂, standard deviation	#	163	1077	
	Mean (SD)	10.9 (4.2)	9 (3.7)	
	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<.0001
PaCO₂, time-weighted	#	163	1098	
	Mean (SD)	49.6 (6.5)	48 (7.1)	
	Median, IQR	49.4 (45.8-54.2)	48.6 (43.6-52.9)	.0088
PaCO₂ category:	# (%)			<.0001
	Hypocapnic	30 (18.4)	205 (18.7)	
	Hypercapnic	42 (25.8)	168 (15.3)	
	Fluctuator	26 (16.0)	70 (6.4)	
	Normocapnic	65(39.9)	658 (59.7)	
Treatment: CPAP or Surfactant group	#	164	1106	
	CPAP, # (%)	92 (56.1)	550 (49.7)	.13
Treatment: SpO₂ group, High or Low O₂	#	164	1106	
	High O ₂ , # (%)	81 (49.4)	559 (50.5)	.78
Birth Weight (g)	#	164	1106	
	Mean (SD)	802 (182)	838 (193)	
	Median (IQR)	783 (681-944)	830 (700-974)	.03
Gender	#	164	1106	
	Male, # (%)	99 (60.4)	588 (53.2)	.08

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value¹
Race:	# (%)			.016
NH Black		55 (33.5)	421 (38.1)	
NH White		55 (33.5)	442 (40.0)	
Hispanic		44 (26.8)	208 (18.8)	
Other		10 (6.1)	35 (3.2)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	.26
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	.11
HTN, pregnancy induced	#	155	1041	
	Yes, # (%)	9 (5.8)	121 (11.6)	.03
Rupture of membranes > 24 hours prior to birth	#	160	1083	
	Yes, # (%)	38 (23.8)	376(34.7)	.006
Prenatal steroids	#	164	1105	
	Yes, # (%)	158 (96.3)	1061 (96.0)	.84
1 minute Apgar < 3	#	164	1105	
	Yes, # (%)	49 (29.9)	241 (21.8)	.022
5 minute Apgar < 3	#	164	1106	
	Yes, # (%)	10 (6.1)	33 (3.0)	.04
Prophylactic indomethacin	#	164	1106	
	Yes, # (%)	60 (36.6)	437 (39.5)	.47
Vaginal delivery	#	164	1106	
	Yes, # (%)	57 (34.8)	367 (33.2)	.69

Table 2 - Bivariate analyses for Death or Severe IVH

Characteristic		Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value ¹
PaCO ₂ , minimum level	#	325	971	
	Mean (SD)	34.9 (13.4)	33.6 (6.6)	
	Median, IQR	33 (28-38)	34 (30-38)	.69
PaCO ₂ , maximum level	#	325	971	
	Mean (SD)	78.6 (21.8)	65 (15.9)	
	Median, IQR	76 (65-88)	64 (54-74)	<.0001
PaCO ₂ , standard deviation	#	314	951	
	Mean (SD)	12 (6.3)	8.6 (3.4)	
	Median, IQR	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<.0001
PaCO ₂ , time-weighted	#	325	971	
	Mean (SD)	52.3 (11.8)	47.5 (7.0)	
	Median, IQR	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<.0001
PaCO ₂ category:	# (%)			<.0001
Hypocapnic		48 (14.8)	189 (19.5)	
Hypercapnic		102 (31.4)	127 (13.1)	
Fluctuator		45 (13.9)	52 (5.4)	
Normocapnic		130 (40.0)	603 (62.1)	
Treatment: CPAP or Surfactant group	#	335	979	
	CPAP, # (%)	166 (49.6)	496 (50.7)	.73
Treatment: SpO ₂ group, High or Low O ₂	#	335	979	
	High O ₂ , # (%)	156 (46.6)	505 (51.6)	.11
Birth Weight (g)	#	335	979	
	Mean (SD)	763 (187)	853 (190)	
	Median (IQR)	750 (640-881)	850 (710-990)	<.0001
Gender	#	335	979	
	Male, # (%)	197 (58.8)	514 (52.5)	.046

Characteristic		Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value ¹
Race:	# (%)			.092
NH Black		112 (33.4)	376 (38.4)	
NH White		133 (39.7)	387 (39.5)	
Hispanic		72 (21.5)	187 (19.1)	
Other		18 (5.4)	29 (3.0)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	112 (33.4)	376 (38.4)	.104
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	133 (39.7)	387 (39.5)	.96
HTN, pregnancy induced	#	317	920	
	Yes, # (%)	21 (6.6)	110 (12.0)	.0078
Rupture of membranes > 24 hours prior to birth	#	319	964	
	Yes, # (%)	97 (30.4)	336 (34.9)	.15
Prenatal steroids	#	334	979	
	Yes, # (%)	325 (97.3)	938 (95.8)	.22
1 minute Apgar < 3	#	334	978	
	Yes, # (%)	120 (35.9)	200 (20.4)	<.0001
5 minute Apgar < 3	#	335	979	
	Yes, # (%)	29 (8.7)	29 (3.0)	<.0001
Prophylactic indomethacin	#	309	979	
	Yes, # (%)	117 (37.9)	384 (39.2)	.67
Vaginal delivery	#	335	979	
	Yes, # (%)	108 (32.2)	325 (33.2)	.74

Table 3 - Bivariate analyses for BPD - subset of survivors to 36 weeks

Characteristic		BPD (N=442)	No BPD (N=666)	p-value ¹
PaCO ₂ , minimum level	#	441	659	
	Mean (SD)	32.8 (6.6)	33.8 (6.6)	
	Median, IQR	33 (29-37)	34 (30-38)	.015
PaCO ₂ , maximum level	#	441	659	
	Mean (SD)	74 (16)	61.2 (15.2)	
	Median, IQR	72 (64-83)	60 (50-69)	<.0001
PaCO ₂ , standard deviation	#	438	642	
	Mean (SD)	10 (3.2)	8.1 (3.3)	
	Median, IQR	9.8 (7.8-11.8)	8.0(5.7-9.9)	<.0001
PaCO ₂ , time-weighted	#	441	659	
	Mean (SD)	50.7 (6.2)	45.8 (6.8)	
	Median, IQR	51 (47.3-54.3)	46.2 (41.1-50.4)	<.0001
PaCO ₂ category:	# (%)			
Hypocapnic		78 (17.7)	138 (20.9)	<.0001
Hypercapnic		101 (22.9)	59 (9.0)	
Fluctuator		48 (10.9)	24 (3.6)	
Normocapnic		214 (46.5)	438 (66.5)	
Treatment: CPAP or Surfactant group	#	442	666	
	CPAP, # (%)	223 (50.4)	346 (52)	.62
Treatment: SpO ₂ group, High or Low O ₂	#	442	666	
	High O ₂ , # (%)	237 (53.6)	331 (49.7)	.20
Birth Weight (g)	#	442	666	
	Mean (SD)	769 (177)	898 (181)	
	Median (IQR)	750 (650-870)	900 (770-1020)	<.0001
Gender	#	442	666	
	Male, # (%)	251 (56.8)	337 (50.6)	.043

Characteristic		BPD (N=442)	No BPD (N=666)	p-value¹
Race:	# (%)			
NH Black		157 (35.5)	268 (40.2)	.013
NH White		200 (45.3)	237 (35.6)	
Hispanic		73 (16.5)	137 (20.6)	
Other		12 (2.7)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	.11
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	.0013
HTN, pregnancy induced	#	415	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	.18
Rupture of membranes > 24 hours prior to birth	#	431	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33
Prenatal steroids	#	442	666	
	Yes, # (%)	427 (96.6)	636 (95.5)	.36
1 minute Apgar < 3	#	442	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<.0001
5 minute Apgar < 3	#	442	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	.11
Prophylactic indomethacin	#	442	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	.75
Vaginal delivery	#	442	666	
	Yes, # (%)	123 (27.8)	240 (36.0)	.0044

Table 4 - Bivariate analyses for Death or BPD

Characteristic		Death or BPD (N=650)	No Death or BPD (N=666)	p-value ¹
PaCO ₂ , minimum level	#	639	659	
	Mean (SD)	34.1 (10.6)	33.8 (6.6)	
	Median, IQR	33 (29-38)	34 (30-38)	.25
PaCO ₂ , maximum level	#	639	659	
	Mean (SD)	75.9 (18.7)	61.2 (15.2)	
	Median, IQR	73 (65-85)	60 (50-69)	<.0001
PaCO ₂ , standard deviation	#	625	642	
	Mean (SD)	10.9 (5.1)	8.1 (3.3)	
	Median, IQR	10.2 (8.1-12.7)	8 (5.7-9.9)	<.0001
PaCO ₂ , time-weighted	#	639	659	
	Mean (SD)	51.7 (9.4)	45.8 (6.8)	
	Median, IQR	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<.0001
PaCO ₂ category:	# (%)			
Hypocapnic		100 (15.7)	138 (20.9)	<.0001
Hypercapnic		170 (26.6)	59 (9)	
Fluctuator		74 (11.6)	24 (3.6)	
Normocapnic		295 (46.2)	438 (66.5)	
Treatment: CPAP or Surfactant group	#	650	666	
	CPAP, # (%)	317 (48.8)	346 (52.0)	.25
Treatment: SpO ₂ group, High or Low O ₂	#	650	666	
	High O ₂ , # (%)	331 (50.9)	331 (49.7)	.66
Birth Weight (g)	#	650	666	
	Mean (SD)	760 (180)	898 (181)	
	Median (IQR)	740 (643-870)	900 (770-1020)	<.0001
Gender	#	650	666	
	Male, # (%)	375 (57.7)	337 (50.6)	.0098

Characteristic		Death or BPD (N=650)	No Death or BPD (N=666)	p-value ¹
Race:	# (%)			
NH Black		221 (34)	268 (40.2)	.024
NH White		284 (43.7)	237 (35.6)	
Hispanic		122 (18.8)	137 (20.6)	
Other		23 (3.5)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	221 (34)	268 (40.2)	.019
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	284 (43.7)	237 (35.6)	.0026
HTN, pregnancy induced	#	615	624	
	Yes, # (%)	68 (11.1)	63 (10.1)	.58
Rupture of membranes > 24 hours prior to birth	#	626	659	
	Yes, # (%)	201 (32.1)	233 (35.4)	.22
Prenatal steroids	#	649	666	
	Yes, # (%)	629 (96.9)	636 (95.5)	.18
1 minute Apgar < 3	#	649	665	
	Yes, # (%)	207 (31.9)	114 (17.1)	<.0001
5 minute Apgar < 3	#	650	666	
	Yes, # (%)	41 (6.3)	17 (2.6)	.0009
Prophylactic indomethacin	#	624	666	
	Yes, # (%)	240 (38.5)	261 (39.2)	.79
Vaginal delivery	#	650	666	
	Yes, # (%)	193 (29.7)	240 (36.0)	.014

Table 5 Bivariate analyses for NDI in survivors.

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value ¹
PaCO ₂ , minimum level	#	98	872	
	Mean (SD)	31.3 (7.0)	33.6 (6.6)	
	Median, IQR	31 (26-36)	33 (30-38)	.0013
PaCO ₂ , maximum level	#	98	872	
	Mean (SD)	75.2 (19.6)	64.8 (16)	
	Median, IQR	74 (65-88)	64 (54-74)	<.0001
PaCO ₂ , standard deviation	#	98	853	
	Mean (SD)	10.2 (3.6)	8.6 (3.4)	
	Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<.0001
PaCO ₂ , time-weighted	#	98	872	
	Mean (SD)	49.7 (7.3)	47.4 (6.9)	
	Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	.0014
PaCO ₂ category:	# (%)			
Hypocapnic		22 (22.5)	171 (19.6)	<.0001
Hypercapnic		25 (25.5)	111 (12.7)	
Fluctuator		17 (17.4)	44 (5.1)	
Normocapnic		34 (34.7)	546 (62.6)	
Treatment: CPAP or Surfactant group	#	98	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34
Treatment: SpO ₂ group, High or Low O ₂	#	98	878	
	High O ₂ , # (%)	53 (54.1)	451 (51.4)	0.61
Birth Weight (g)	#	98	878	
	Mean (SD)	774 (192)	859 (187)	
	Median (IQR)	754 (643-914)	850 (710-995)	<.0001
Gender	#	98	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value ¹
Race:	# (%)			
NH Black		37 (37.8)	333 (37.9)	0.89
NH White		37 (37.8)	354 (40.3)	
Hispanic		21 (21.4)	161 (18.3)	
Other		3 (3.1)	30 (3.4)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62
HTN, pregnancy induced	#	88	829	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64
Rupture of membranes > 24 hours prior to birth	#	97	863	
	Yes, # (%)	26 (26.8)	300 (34.8)	0.12
Prenatal steroids	#	98	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26
1 minute Apgar < 3	#	98	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	.0003
5 minute Apgar < 3	#	98	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	.037
Prophylactic indomethacin	#	98	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92
Vaginal delivery	#	98	878	
	Yes, # (%)	29 (29.6)	289 (32.9)	0.51

Table 6: Bivariate analyses for NDI/death.

Characteristic		Death or NDI (N=356)	No Death or NDI (N=878)	p-value ¹
PaCO ₂ , minimum level	#	346	872	
	Mean (SD)	34.9 (13.1)	33.6 (6.6)	
	Median, IQR	33 (28-38)	33 (30-38)	0.95
PaCO ₂ , maximum level	#	346	872	
	Mean (SD)	78.7 (21.4)	64.8 (16.0)	
	Median, IQR	76 (66-88)	64 (54-74)	<.0001
PaCO ₂ , standard deviation	#	335	853	
	Mean (SD)	11.9 (6.2)	8.6 (3.4)	
	Median, IQR	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<.0001
PaCO ₂ , time-weighted	#	346	872	
	Mean (SD)	52.5 (11.6)	47.4 (6.9)	
	Median, IQR	51.7 (47.1-56)	48 (42.8-52.3)	<.0001
PaCO ₂ category:	# (%)			
	Hypocapnic	51 (14.7)	171 (19.6)	<.0001
	Hypercapnic	111 (32.1)	111 (12.7)	
	Fluctuator	49 (14.2)	44 (5.1)	
Normocapnic	135 (39.0)	546 (62.6)		
Treatment: CPAP or Surfactant group	#	356	878	
	CPAP, # (%)	173 (48.6)	448 (51.0)	0.44
Treatment: SpO ₂ group, High or Low O ₂	#	356	878	
	High O ₂ , # (%)	171 (48)	451 (51.4)	0.29
Birth Weight (g)	#	356	878	
	Mean (SD)	746 (185)	859 (187)	
	Median (IQR)	734 (621-870)	850 (710-995)	<.0001
Gender	#	356	878	
	Male, # (%)	213 (59.8)	457 (52.1)	.013

Characteristic		Death or NDI (N=356)	No Death or NDI (N=878)	p-value¹
Race:	# (%)			
NH Black		125 (35.1)	333 (37.9)	0.47
NH White		139 (39)	354 (40.3)	
Hispanic		78 (21.9)	161 (18.3)	
Other		14 (3.9)	30 (3.4)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	125 (35.1)	333 (37.9)	0.35
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	139 (39)	354 (40.3)	0.68
HTN, pregnancy induced	#	335	829	
	Yes, # (%)	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	341	863	
	Yes, # (%)	104 (30.5)	300 (34.8)	0.16
Prenatal steroids	#	355	878	
	Yes, # (%)	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	355	877	
	Yes, # (%)	130 (36.6)	181 (20.6)	<.0001
5 minute Apgar < 3	#	356	878	
	Yes, # (%)	29 (8.2)	27 (3.1)	.0001
Prophylactic indomethacin	#	330	878	
	Yes, # (%)	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	356	878	
	Yes, # (%)	114 (32)	289 (32.9)	0.76

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Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 25, 2013 6:40 AM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: SUPPORT
Attachments: RespSupport(CLEAN2-14-13).doc

Bob

This is a confidential statement (not yet released) from AAP's committee on fetus and newborn. NHLBI had contacted me about a joint press release as this change suggested in practice was prompted by the results of the NRN SUPPORT Trial.

I will try to find out a publication date. Let me know if you think we should do a press release.

Thanks
Rose

Rosemary D. Higgins, MD
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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Thursday, February 21, 2013 1:52 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT

Dear Carol and Rose:

I apologize that I did not copy Rose in this email. I was getting permission to send it to Rose also and forgot to add her name in the "To" section.

Hi Rose:

Just to get you caught up. Carol asked me for a slide on the CPAP SUPPORT trial and quoted a paper I wrote. The AAP has drafted a new statement based largely on our CPAP trial. I got permission from the AAP to share it with Carol and you confidentially. I will let you know when I hear it will be published.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

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Director, Newborn Nurseries

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From: Wally Carlo, M.D.

Sent: Tuesday, February 19, 2013 3:11 PM

To: 'Blaisdel, Carol (NIH/NHLBI) [E]'

Subject: SUPPORT

Hi Drs. Blaisdel and Higgins:

I got official permission to share with you this statement from the AAP in a confidential manner. Please be aware that not even the AAP members are aware of the contents although it is public knowledge that the AAP COFN was looking into this.

SUPPORT was instrumental in changing the AAP recommendations on early respiratory care of preterm infants from prophylactic surfactant to early CPAP as you can see from the statement. The AAP is very conservative making changes in practice so the preference was to say early CPAP is an option although the evidence is that it is superior. The statement has the facts of superiority but the wording of the recommendations is usually tuned down.

You could time a press release with the AAP publication, still several months away.

Thank you for your support.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

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From: Jim Couto [mailto:JCouto@aap.org]

Sent: Tuesday, February 19, 2013 2:43 PM

To: Wally Carlo, M.D.

Subject: Re: FW: support

yes

>>> "Wally Carlo, M.D." <WCarlo@peds.uab.edu> 2/19/2013 2:00 PM >>>

Jim:

Can I send her the draft of our Resp statement in a confidential way? She was medical officer at HLB who funded the trial.

Wally

Wally Carlo, M.D.
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From: Blaisdell, Carol (NIH/NHLBI) [E] [<mailto:blaisdellcj@nhlbi.nih.gov>]

Sent: Tuesday, February 19, 2013 10:42 AM

To: Wally Carlo, M.D.

Subject: support

Dear Dr. Carlo,

I am providing updates to NHLBI leadership about scientific advances that have occurred over the last 5 yr that might be impacting practices.

I wondered if you had a slide that summarizes the results of the CPAP arms of the SUPPORT trial (with or without image that might communicate why the study results are important and changing practice). Your recent Human Development paper gave a nice summary table of the recent CPAP trials.

If you have something readily available that you can share that would be great,

Thanks, Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

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Page 0525 of 2000

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Page 0526 of 2000

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD)
To: ["mcollins@peds.uab.edu"](mailto:mcollins@peds.uab.edu)
Subject: Re: Concerns from OHRP letter
Date: Saturday, February 23, 2013 4:15:21 PM

Monica-

I am happy to discuss. I am traveling home tomorrow from Germany and can talk to you Monday or Tuesday prior to the monthly SC call. Let me know what works for you.

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Monica Collins [<mailto:MCollins@peds.uab.edu>]
Sent: Saturday, February 23, 2013 09:39 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins <MCollins@peds.uab.edu>
Subject: Concerns from OHRP letter

Rose,

As the coordinating site for which the OHRP letter was targeted, I have had many sleepless nights over this. Shirley and I have struggled with this for a while, reviewing whether the safety of the patients was compromised in order to get the study done. After months of consideration, we are comfortable that we did not compromise the care of any patient, given the information that we had at the time.

What to do now? I understand that the Steering Committee is going to have a conference call next week and I would like to suggest a few things, some of which I have heard from other coordinators and some are generated by Shirley and me. I am sending this to you before I speak with Wally about it because I want to be sure you understand all of my concerns. I have talked with Wally about some of these things, and he tries to reassure me that they have been considered, but I want to make sure someone else is aware of these issues.

First, the letter from OHRP, regardless of the sanity of the person who wrote the original letter to OHRP, brings up points that I think we should ponder. We authored a paper on targeted saturations and the publication states that "a target range of oxygen saturation of 85-89%, as compared with a range of 91-95%, 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." The current standards for our studies may not be the same as they were when SUPPORT protocols were originally

written. For example, the TOP trial. [BB1]

Second, I would like to ask that the group look at all of the consent forms that are currently being used to make sure that we have appropriately addressed the known risks and benefits of the study in each one. [BB2] This concern stems from the OHRP letter and the publication of the saturation article that detailed that indeed, babies who were in the lower saturation group had a higher risk of mortality than those in the higher saturation group. That being said, I wonder if we have adequately addressed the risks to the babies who are kept in the restricted arm of the TOP trial. The consent form says that there is no more risk to these infants than current standard of care, as these thresholds are in the ranges of standard of care. The standard of care is what is common around nurseries in the US. What is common around the US is that different physicians take care of each baby in the nursery during their hospital stays. Many have a common threshold, but others in the same practices may have other thresholds. The infants are usually exposed to multiple philosophies during their stay. I am not sure we are not increasing their risks—we are segregating these babies to a group where they will never receive a transfusion that might have been given at a higher hematocrit by a different physician during a different day in a different month. In the restrictive arm, these babies will not receive a transfusion unless they meet the threshold requirements determined by randomization, (of course, if there is an emergency, they will exit for a time). We will be keeping them in low oxygen carrying capacity despite who the attending is or what the attending's threshold may be. This is, in my opinion, different from standard of care, as when they are taken care of by many physicians, they might receive a transfusion at a higher level with one physician versus another. We are preventing this fluctuation in the standard of care by the study algorithm. Doesn't this increase their risk, based on the NRN publication about oxygen saturation? Should this be addressed in the consent form?

Third, for the babies who are in the liberal arm, those infants may receive more transfusions; and by necessity, more IV sticks (and associated risks of infection) than those in the restrictive arm. They also may be exposed to a greater number of donors, due to greater numbers of transfusions. This is also different from standard of care. Neither of these is addressed in the protocol or sample consent.

I am requesting the re-review of consents network-wide as we do have better information than we did when some of these protocols and informed consents were written. If there are no increased risks or benefits than current standard of care, I think we can say that with confidence and not just leave the "may be unknown risks that we discover later" to cover ourselves; however, if not, I think the consents should be modified. And I don't think it should be left to the

individual site as unilateral modification of consents by the center, for risks and benefits might open a can of worms we don't want to open if we discover and publish something that one site felt was a known or suspected risk or benefit and another did not. The OHRP letter has made me realize that we should be paying more attention to our consent forms.

(And just as a matter of course, the economic questionnaire is not mentioned in the current consent for TOP.)

Thanks for your consideration

Monica

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Confidential: SUPPORT
Date: Friday, February 22, 2013 10:11:08 AM
Attachments: [A Rudczynski ltr to OHRP 9Dec11.pdf](#)
[HIC-OHRP 2007 Perinatal Guidelines 6th Ed.pdf](#)
[HIC-OHRP 2002 Perinatal Guidelines 5th Ed.pdf](#)

Wally-

See the note from Richard as well as the attachments. Please do not share the documents without permission from Rich - I had asked him to share with you. If AAP guidelines for perinatal care has 85-95 sat targets (I can't read the pdf off my BB and don't have secure internet access), this should be stated up front as the guideline for care.

Thanks for all your persistence and patience with this issue.

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, February 21, 2013 04:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose:

The information that was sent, was sent in response to a letter requesting responses. Yale's last response was on Dec 9, 2011. We have heard nothing further from OHRP. I have attached that last response. I will let our IRB-Human Research Protection Program know that they can join with from my office.

Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

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Sent: Thursday, February 21, 2013 3:43 PM
To: Ehrenkranz, Richard
Subject: Re: SUPPORT

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Let me know

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

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Sent: Thursday, February 21, 2013 01:46 PM

To: Kristi Watterberg <KWatterberg@salud.unm.edu>; nxs5@case.edu <nxs5@case.edu>; Kurt Schibler[kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Ivan Frantz <Ivan.Frantz@childrens.harvard.edu>; Michele Walsh(mcw3@cwru.edu) <mcw3@cwru.edu>; BradYoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; RogerFaix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Shahnaz' (SDuara@med.miami.edu) 'Duara <SDuara@med.miami.edu>; Beena[bsood@med.wayne.edu] Sood <bsood@med.wayne.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; M.D. Wally Carlo <WCarlo@peds.uab.edu>; Abhik Das(adas@rti.org) <adas@rti.org>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>; dstevenson@stanford.edu <dstevenson@stanford.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Brenda Morris (morrisb1@tmfhs.org) <morrisb1@tmfhs.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Wally Carlo (wacarlo@uab.edu) <wacarlo@uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Wade RIch <wrich@ucsd.edu>; Edward (Pediatrics) Bell <edward-bell@uiowa.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@URMC.Rochester.edu>; dale_phelps@urmc.rochester.edu <dale_phelps@URMC.Rochester.edu>; Nirupama Laroia <Nirupama_Laroia@URMC.Rochester.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; Abbot Laptook <Alaptook@wihri.org>

Cc: Archer, Stephanie (NIH/NICHD) [E]; Amanda (alewis@rti.org) Lewis-Evans <alewis@rti.org>; Jenna Gabrio (jgabrio@rti.org) <jgabrio@rti.org>; (kzaterka@rti.org) <kzaterka@rti.org>; (mcunningham@rti.org) <mcunningham@rti.org>; Carolyn Petrie <petrie@rti.org>

Subject: RE: SUPPORT

Wally,

I agree with Kristi-I have nothing further to add.

By the way, I have been asked by members of our IRB-Human Research Protection Program about participating in the call next week. I emailed their request to Rose; what are your thoughts? As you may remember, we were asked similar questions by OHRP; the final responses were submitted on Dec 9, 2011 and we have not heard back from them.

Richard

Richard A. Ehrenkranz, MD

Department of Pediatrics

Yale University School of Medicine

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Sent: Thursday, February 21, 2013 1:28 PM
To: nxs5@case.edu; Kurt Schibler[kurt.schibler@cchmc.org]; (Vivek.Narendran@cchmc.org); Ivan Frantz; Michele Walsh(mcw3@cwru.edu); BradYoder (Bradley.yoder@hsc.utah.edu); RogerFaix (Roger.Faix@hsc.utah.edu); bpoindex@iupui.edu; Rosemary (NIH/NICHD)[E] Higgins; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz' (SDuara@med.miami.edu) 'Duara; Beena[bsood@med.wayne.edu] Sood; Seetha Shankaran; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu); barbara_stoll@oz.ped.emory.edu; M.D. Wally Carlo; Abhik Das(adas@rti.org); mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; Krisa Van Meurs (vanmeurs@stanford.edu); Brenda Morris (morrissb1@tmfhs.org); Ambal (ambal@uab.edu); Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Wade RIch; Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; Nirupama Laroia; Jon.E.Tyson@uth.tmc.edu; Kathleen A Kennedy; Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; Abbot Laptook; Ehrenkranz, Richard
Cc: Stephanie(NIH/NICHD) [E] Archer; Amanda (alewis@rti.org) Lewis-Evans; Jenna Gabrio (jgabrio@rti.org); (kzaterka@rti.org); (mcunningham@rti.org); Carolyn Petrie
Subject: RE: SUPPORT

Very nice, Wally! - with the edits you've already received, I have nothing further to add.

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 2/21/2013 10:17 AM >>>

Wally,

Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.

Ed

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 10:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrissb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Bell, Edward (Pediatrics); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn

Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 19, 2013 8:25 AM

To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu

Cc: (mccunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn

Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

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From: Ehrenkranz, Richard
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Friday, February 22, 2013 10:05:55 AM

Yes.
Richard

Sent from my iPhone

On Feb 22, 2013, at 9:06 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

<!--[if mso 9]--> <!--[endif]-->Can this be shared with Wally? I can't read the AAP guidelines on my BB and don't have secure computer email access. If the guidelines state the 85-95 percent target range, this may address the main issue.

Thanks!

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

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Cc: Archer, Stephanie (NIH/NICHD) [E]; Amanda (alewis@rti.org) Lewis-Evans <alewis@rti.org>; Jenna Gabrio (jgabrio@rti.org) <jgabrio@rti.org>; (kzaterka@rti.org) <kzaterka@rti.org>; (mcunningham@rti.org) <mcunningham@rti.org>; Carolyn Petrie <petrie@rti.org>
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Very nice, Wally! - with the edits you've already received, I have nothing further to add.

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 2/21/2013 10:17 AM >>>

Wally,

Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.

Ed

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 10:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpointindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Bell, Edward (Pediatrics); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 19, 2013 8:25 AM
To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpointindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

Notice: This UI Health Care e-mail (including attachments) is covered by the Electronic Communications Privacy Act, 18 U.S.C. 2510-2521, is confidential and may be legally privileged. If you are not the intended recipient, you are hereby notified that any retention, dissemination, distribution, or copying of this communication is strictly prohibited. Please reply to the sender that you have received the message in error, then delete it. Thank you.

Blansfield, Earl (NIH/NICHD) [E]

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Friday, February 22, 2013 9:12 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose,
This is great news!

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, February 22, 2013 8:09 AM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: SUPPORT

Bob
The AAP is going to publish a statement regarding CPAP use (largely based on the results of our SUPPORT trial data from the NRN). See the email trail from Dr. Blaisdell from NHLBI who asked about a press release- what do you think? The CPAP results have changed clinical practice. Neonatologists are now using this less invasive form of respiratory support as opposed to inserting a breathing tube through the windpipe and giving surfactant.

Let me know - we don't have a publication date yet

Thanks
Rose

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

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Friday, February 22, 2013 08:01 AM
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Thanks Wally,
The SUPPORT trial has provided important evidence to inform NICU practice.
Appreciate your letting us know about the AAP position paper, which we recognize is under embargo.
When we learn about the date for publication, we could possibly coordinate a press release with AAP.

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 1:52 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT

Dear Carol and Rose:

I apologize that I did not copy Rose in this email. I was getting permission to send it to Rose also and forgot to add her name in the "To" section.

Hi Rose:

Just to get you caught up. Carol asked me for a slide on the CPAP SUPPORT trial and quoted a paper I wrote. The AAP has drafted a new statement based largely on our CPAP trial. I got permission from the AAP to share it with Carol and you confidentially. I will let you know when I hear it will be published.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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1700 6th Avenue South
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From: Wally Carlo, M.D.
Sent: Tuesday, February 19, 2013 3:11 PM
To: 'Blaisdell, Carol (NIH/NHLBI) [E]'
Subject: SUPPORT

Hi Drs. Blaisdel and Higgins:

I got official permission to share with you this statement from the AAP in a confidential manner. Please be aware that not even the AAP members are aware of the contents although it is public knowledge that the AAP COFN was looking into this.

SUPPORT was instrumental in changing the AAP recommendations on early respiratory care of preterm infants from prophylactic surfactant to early CPAP as you can see from the statement. The AAP is very conservative making changes in practice so the preference was to say early CPAP is an option although the evidence is that it is superior. The statement has the facts of superiority but the wording of the recommendations is usually tuned down.

You could time a press release with the AAP publication, still several months away.

Thank you for your support.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics
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From: Jim Couto [mailto:JCouto@aap.org]
Sent: Tuesday, February 19, 2013 2:43 PM
To: Wally Carlo, M.D.
Subject: Re: FW: support

yes

>>> "Wally Carlo, M.D." <WCarlo@peds.uab.edu> 2/19/2013 2:00 PM >>>

Jim:

Can I send her the draft of our Resp statement in a confidential way? She was medical officer at HLB who funded the trial.

Wally

Wally Carlo, M.D.
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From: Blaisdell, Carol (NIH/NHLBI) [E] [mailto:blaisdellcj@nhlbi.nih.gov]
Sent: Tuesday, February 19, 2013 10:42 AM
To: Wally Carlo, M.D.
Subject: support

Dear Dr. Carlo,

I am providing updates to NHLBI leadership about scientific advances that have occurred over the last 5 yr that might be impacting practices.

I wondered if you had a slide that summarizes the results of the CPAP arms of the SUPPORT trial (with or without image that might communicate why the study results are important and changing practice). Your recent Human Development paper gave a nice summary table of the recent CPAP trials.

If you have something readily available that you can share that would be great,

Thanks, Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Tyson, Jon E
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrish1@tmfhs.org); Kennedy, Kathleen A; Laroja, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT
Date: Friday, February 22, 2013 8:21:21 AM

Whoops, a typo in the last item. It should have read: "...concerns." As they note "a new ethical foundation needs to be developed that facilitates both care and research likely to benefit patients and that provides oversight that ... is commensurate with risk and burden in both realms" (Kass NE, Faden RR, Goodwin SN, Pronovost P, Tunis S, Beauchamp TL. Hastings Center Report Jan-Feb 2013. S4-S15)"

From: Tyson, Jon E
Sent: Thursday, February 21, 2013 6:38 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrish1@tmfhs.org); Kennedy, Kathleen A; Laroja, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Subject: RE: SUPPORT

For whatever they are worth, a few points that might augment an already well conceived response:

1. You quote from OHRP on page 4, "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 ... mortality."

You responded: The evidence of increased mortality with restriction of oxygen was based on a trial comparing a practice that restricted oxygen supplementation to =50% inspired oxygen concentration regardless of the condition of the preterm infants." Consider inserting here. However, in neither this trial nor in the subsequent meta-analysis was mortality significantly increased.

2. Ref the statement: "Furthermore, oxygen monitoring in the 1950s was done with intermittent blood gas

sampling whereas continuous oxygen saturation monitoring was done in SUPPORT.

With the limited technology and large volume of blood required, intermittent blood gas sampling would have been rarely if ever done in premature babies the 1950s. (I recall that Dr. Korones installed the first micro blood gas machine in Memphis in 1970 or 71.) Consider substituting something like: "In the 1950s, the technology required even to intermittently assess oxygenation by measuring blood gases in small quantities of blood had not yet been developed. In Support, oxygenation was assessed continuously by modern day oxygen saturation monitoring.

3. Ref the statement that "Restriction of oxygen using an arbitrary cut-off of inspired oxygen concentration has not been a standard clinical practice in US NICUs for years." You could substitute "decades" for "years."

4. I'd suggest you modify the Summary to say: "Risk is defined in the OHRP IRB guidebook as 'the probability of harm or injury ...occurring as a result of participation in a research study.' As emphasized above, the best available evidence indicated no discernable increased probability of death or other harms as a result of participating in this trial comparing two methods of care widely used both within and outside the NICHD Neonatal Research Network. The SUPPORT consent form was thus appropriately written for this comparative effectiveness trial based on the relevant knowledge available at the time.

If you/we are willing to go a step further, consider adding something like the following: We believe it would be particularly unfortunate to criticize the consent form on ethical grounds when little or no information has been given to parents of infants treated clinically with one of these methods and when this trial has provided knowledge important to reducing the mortality of these infants. Leading ethicists including the eminent Tom Beauchamp have recently emphasized the need to promote comparative effectiveness trials and noted that "the terms 'research' and 'practice' are poor proxies for what should be our central moral concerns." As they a new ethical foundation needs to be developed that facilitates both care and research likely to benefit patients and that provides oversight that ...is commensurate with risk and burden in both realms" (Kass NE, Faden RR, Goodwin SN, Pronovost P, Tunis S, Beauchamp TL. Hastings Center Report Jan-Feb 2013. S4-S15)"

The list of authors above on this publication includes Peter Pronovost. As you recall, OHRP received a huge storm of public criticism and rebuke after it stopped the Pronovost trial of a check list to prevent infections in ICU patients. OHRP's objection to the Pronovost trial—also a comparative effectiveness trial—involved overly stringent views about consent as in our trial. OHRP might be a little wary of going up against his position on the same kind of issue.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Thursday, February 21, 2013 10:27 AM

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I would appreciate any comments.

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Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

From: Frantz, Ivan
To: Wally Carlo, M.D.; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Subject: RE: SUPPORT
Date: Friday, February 22, 2013 6:57:23 AM

What is the group referred to in the last paragraph as "concurrent controls"? I do not recall that we had such a group. If this means eligible but not enrolled infants, we should be more specific.

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 10:05 PM
To: Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Subject: RE: SUPPORT

Thank everyone for all comments sent.

I will make these and all other changes suggested and will send a revised one tomorrow.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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176F Suite 9380R
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From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Thursday, February 21, 2013 6:39 PM

To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu

Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn

Subject: RE: SUPPORT

For whatever they are worth, a few points that might augment an already well conceived response:

1. You quote from OHRP on page 4: *"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 ...mortality."*

You responded: *The evidence of increased mortality with restriction of oxygen was based on a trial comparing a practice that restricted oxygen supplementation to =50% inspired oxygen concentration regardless of the condition of the preterm infants." Consider inserting here. However, in neither this trial nor in the subsequent meta-analysis was mortality significantly increased.*

2. Ref the statement: *"Furthermore, oxygen monitoring in the 1950s was done with intermittent blood gas sampling whereas continuous oxygen saturation monitoring was done in SUPPORT.*

With the limited technology and large volume of blood required, intermittent blood gas sampling would have been rarely if ever done in premature babies the 1950s. (I recall that Dr. Korones installed the first micro blood gas machine in Memphis in 1970 or 71.) Consider substituting something like: *"In the 1950s, the technology required even to intermittently assess oxygenation by measuring blood gases in small quantities of blood had not yet been developed. In Support, oxygenation was assessed continuously by modern day oxygen saturation monitoring.*

3. Ref the statement that *"Restriction of oxygen using an arbitrary cut-off of inspired oxygen concentration has not been a standard clinical practice in US NICUs for years."* You could substitute *"decades"* for *"years."*
4. I'd suggest you modify the Summary to say: *"Risk is defined in the OHRP IRB guidebook as 'the probability of harm or injuryoccurring as a result of participation in a research study.' As emphasized above, the best available evidence indicated no discernable increased*

probability of death or other harms as a result of participating in this trial comparing two methods of care widely used both within and outside the NICHD Neonatal Research Network. The SUPPORT consent form was thus appropriately written for this comparative effectiveness trial based on the relevant knowledge available at the time.

If you/we are willing to go a step further, consider adding something like the following: We believe it would be particularly unfortunate to criticize the consent form on ethical grounds when little or no information has been given to parents of infants treated clinically with one of these methods and when this trial has provided knowledge important to reducing the mortality of these infants. Leading ethicists including the eminent Tom Beauchamp have recently emphasized the need to promote comparative effectiveness trials and noted that "the terms 'research' and 'practice' are poor proxies for what should be our central moral concerns." As they a new ethical foundation needs to be developed that facilitates both care and research likely to benefit patients and that provides oversight that ...is commensurate with risk and burden in both realms" (Kass NE , Faden RR, Goodwin SN, Pronovost P, Tunis S, Beauchamp TL. Hastings Center Report Jan-Feb 2013. S4-S15)"

The list of authors above on this publication includes Peter Pronovost. As you recall, OHRP received a huge storm of public criticism and rebuke after it stopped the Pronovost trial of a check list to prevent infections in ICU patients. OHRPs objection to the Pronovost trial—also a comparative effectiveness trial—involved overly stringent views about consent as in our trial. OHRP might be a little wary of going up against his position on the same kind of issue.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Thursday, February 21, 2013 10:27 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Tyson, Jon E; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu

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Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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1700 6th Avenue South
176F Suite 9380R
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 19, 2013 8:25 AM
To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrish1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6)

with pass code (b)(6)

Rose

From: Phelps, Dale
To: "Wally Carlo, M.D."
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 11:46:50 PM
Attachments: OHRP RESPONSE LETTER 2-21-13.Ver1.DLPtracked.docx

Hi Wally,

Nice work.

whew! lots of e-mail -- I'm not sure I've even read it all.

I drafted a number of mainly small edits which I put in with track changes (attached) for you to consider.

I think many of us probably picked out similar things.

Acknowledging the OHRP efforts to be fair and just is important. They are trying to do the best they can with the information they have. You have provided more information.

Offering to do 'something' I think may be important. I've put one in at the end... you'll probably think of a better one.

but I think their office is going to have to be able to say they have "done something about it", and what.

If we offer something we can live with, it is likely to be better than something they will come up with.

You may not like my offer, and I'm not wedded to it.. just trying to come up with something they can point to.

Dale

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 11:32 AM
To: Phelps, Dale
Subject: RE: SUPPORT

THX, I just did.

wally

Wally Carlo, M.D.
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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, February 20, 2013 7:52 PM
To: Wally Carlo, M.D.
Subject: RE: SUPPORT

sure, I'd be glad to.... please forward by e-mail.
Dale

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, February 20, 2013 8:03 PM
To: Phelps, Dale
Subject: RE: SUPPORT

Dale.

Could you take a look at the draft we wrote?

Wally

In response to the letter dated February 8, 2013 sent to Dr. Marchase (UAB) and Mr. Saz (RTI) we would like to respectfully submit ~~a rebuttal several~~ some additional information regarding its contents and interpretations.

Historical Background

The summary statement on page 4 of the review of the literature states that, "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 preterm infant developing ROP and other aspects of morbidity and mortality."

The evidence of increased mortality with restriction of oxygen was based on a trial comparing a practice that restricted oxygen supplementation to $\leq 50\%$ inspired oxygen concentration regardless of the condition of the preterm infants. The unrestricted oxygen policy provided oxygen routinely for 28 days at over 50% concentration. This was tested in the 1950s in a trial that included few extremely preterm infants (since this occurred before ventilators were available, or any means of measuring blood gases, and before intravenous fluids were used), whereas the SUPPORT trial only enrolled extremely preterm infants. Restriction of oxygen using an arbitrary cut-off of inspired oxygen concentration has not been a standard clinical practice in US NICUs for decades years, and was not a practice tested in the SUPPORT trial. Furthermore, in oxygen "monitoring" in the 1950s was only monitoring of the inspired oxygen, not done with intermittent blood gas sampling, whereas continuous oxygen saturation monitoring of the infant was done in SUPPORT. In addition, most NICU practices have changed substantially since the 1950s. Notice that the references used in the "Background" in the OHRP letter are for 1956 (ref. 4), 1973 (ref. 5), and 1984 (ref. 6). The newer reference 8 states, "marked variability in opinion exists." but does not include references to support the statement.

The appropriate prior evidence used for the design of the SUPPORT trial are the following cohort studies:

The study by Tin et al.¹ was the highest level of evidence study testing targets less than 95% before SUPPORT was performed. The Tin study was a multicenter population-based prospective retrospective study of infants <28 weeks (just like SUPPORT). The Tin study was the only one with follow-up assessments which included at least 10 months of age.

The policy for saturation alarm limits and targets varied between the centers examined by Tin and colleagues. ROP was lowest decreased in the center using 70-90% saturation targets and there was patients without any difference in survival (51.6% survival in the 70-90% O₂ saturation target group vs. 51.7% in 84-95% group, Table 1).

Comment [01]: Wally, Tin actually had data from more centers in one region. All collected retrospectively. An observational study started by ophthalmologists who noticed the difference! But the 3 centers you refer to were the largest centers with the most babies. The other smaller centers fell inbetween on everything.

Table 1.

Saturation Alarm Targets	N	Survival	Survival with ROP	Survival with Cerebral Palsy
70-90%	126	51.6%	6.2%	15.4%
84-95%	319	51.7%	15.8%	15.5%

88-98%	123	52.8%	27.7%	16.9%
--------	-----	-------	-------	-------

It should be noted that impaired neurodevelopmental outcome was not higher with saturation targets as low as 70-90%. Furthermore, not a single case of blindness was reported in infants at targets up to 95% despite the difference in ROP.

The Chow et al. study² was a single center prospective study to assess the impact of implementation of an oxygen monitoring and administration policy for very low birth weight infants. Lowering saturation targets to 83-93% compared to a previous period with targets 90-98% decreased severe ROP from 12.5% to 2.5% and decreased the need for ROP laser treatment from 4.5% to 0%. In addition, great efforts were exerted to avoid turning up oxygen concentrations to high levels (100%) for all the daily procedures and apenic events. Over the years of the study, there was a trend for **increased survival following implementation of the restriction of oxygen policy** (contrary to what we found in SUPPORT). Survival improved from 48% to 75% in the infants 500-749 g and for 74 to 81% in the infants 750-999 g from 1997 to 2001. The policy was changed in the middle of 1998 (Table 2).

Table 2.

Birth Weight (g)	1997		1998		1999		2000		2001		Total	
	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival
500-749	14	48	15	40	18	73	15	87	12	75	74	58
750-999	25	74	27	78	18	78	21	82	17	81	108	83
1000-1249	24	88	20	100	26	96	28	100	21	94	119	95
1250-1500	29	97	27	100	26	100	28	100	36	97	146	99
Total	92	81	89	83	88	85	92	93	86	90	447	86

Other studies that assessed BPD and growth suggested benefits from lower oxygen saturation targets (ref). It should be noted that these studies targeted saturations above 95% which was not the goal of the study.

Thus, the highest level of evidence studies when SUPPORT was designed and conducted suggested that lower oxygen saturation targets would lead to a decrease in ROP, decreased BPD, and decreased poor growth. Furthermore, there was not even suggestive evidence from relevant prior literature that would suggest an increase in death, blindness, or other serious morbidity with either set of oxygen saturation targets used in SUPPORT.

Based on these and other studies, many clinicians started to recommend lower oxygen saturation targets and developed educational programs promoting the same. The most prominent program was developed by Dr. Jay Goldsmith from Oschner Clinic (not published in the peer-reviewed literature). In this program, saturation targets of 85 to 93% were recommended. The benefits stated were decreased ROP, decreased days on a ventilator and on oxygen, and decreased hospitalization duration. Risk for adverse effects or increased mortality were not included in the materials.

Four other multicenter trials were designed after the SUPPORT trial was conceived. These trials were led by investigators based in the United Kingdom, Australia, New Zealand, and

Comment [O2]: Wally, are you thinking about STOP-ROP and the BOOST studies here? I don't think I would use them because they only started much later in the hospitalization.

Canada/US. These protocols were also designed without the expectation of increased mortality in the lower oxygen saturation group.

Summary

In summary, the existing published data that is pertinent when the SUPPORT Trial was designed and conducted did not indicate any evidence to support an adverse effect on mortality or blindness in either treatment group. Other morbidities had not been reported in the published studies. Since the evidence for a possible benefit in the lower saturation group was only observational, we did not want to overemphasize the potential benefit, and worked to give parents a balanced perspective.

The SUPPORT consent form was appropriately written based on the relevant knowledge available at the time. Furthermore, throughout the trial, survival was better than the historical reference group used prospectively to monitor the trial by the independent Neonatal Research Network (NRN) DSMC and the NRN Steering Committee. Rates of morbidities and mortality compared to historic controls were reviewed during each quarterly NRN Steering Committee meeting and found to be lower than the historical reference group. Concurrent controls had a mortality rate of 24.1% compared to infants in the higher saturation group (16.2%) and infants in the lower oxygen saturation group (19.9%) although these differences were not statistically significant in adjusted regression analyses.

Comment [03]: Wally, here you say 'concurrent', but within the paragraph you say compared to historical controls. This is confusing. DLP

Nonetheless, your office points out a very important issue. We must remain very careful to help the families of our minor subjects to understand as much as possible the known and unknown risks that they take when participating in research. We truly did not believe there was an increased risk of death and therefore had not pointed it out. We did think that controlling saturations carefully in the lower end of the acceptable range might reduce ROP, but suspected that if so, it would actually be the reduction in inadvertent over-oxygenation that would be the reason, not the reduction in 'mean saturation' while on the pulse oximeter. The only concern was for long term consequences of mild hypoxia, and that is why the developmental follow up was planned so carefully. That aspect of concern is one that would have appropriately been included in the consent form, even though the Tin studies saw no evidence for it.

As a general principle, we should probably always force ourselves to list at least one potential risk for every study arm in a RCT, even if it is very low. This may help us.

REFERENCES

1. 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:F106-10.

2. Chow LC, Wright KW, Sola A, CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics*. 2003;111:339-45.

From: Brenda Morris
To: nxs5@case.edu; Kurt Schibler [kurt.schibler@cchmc.org]; (Vivek.Narendran@cchmc.org); Ivan Frantz; Michele Walsh (mcw3@cwru.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); bpoindex@iupui.edu; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz" (SDuara@med.miami.edu) "Duara; Beena [bsood@med.wayne.edu] Sood; Seetha Shankaran; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); barbara_stoll@oz.ped.emory.edu; M.D. Wally Carlo; Abhik Das (adas@rti.org); mgantz@rti.org; poo@rti.org; Kristi Watterberg (kwatterberg@salud.unm.edu); dstevenson@stanford.edu; Krisa Van Meurs (vanmeurs@stanford.edu); Ambal (ambal@uab.edu); Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Wade Rich; Ed Bell (edward-bell@uiowa.edu); carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; Nirupama Laroia; Jon.E.Tyson@uth.tmc.edu; Kathleen A Kennedy; Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; Abbot Laptook; richard.ehrenkranz@yale.edu
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Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 5:28:19 PM

Wally, Your response is excellent. I was wondering if it would be important to emphasize more emphatically that almost all the NRN NICUs were using 85-95% as the limits prior to the study and during this study for infants not enrolled and that were some NICUs (in the NRN and across the country) using even lower limits. Then, at least make one comment that the results have better informed us about how to manage these very vulnerable infants. I will try and be on the call. Thanks, Brenda Morris

>>> "Wally Carlo, M.D." <WCarlo@peds.uab.edu> 2/21/2013 10:27 AM >>>
Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Sent: Tuesday, February 19, 2013 8:25 AM
To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrish1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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The call in number is:

(b)(6)

with pass code

(b)(6)

Rose

Follow Trinity Mother Frances Hospitals and Clinics on Facebook and Twitter

From: Ehrenkranz, Richard
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 4:38:49 PM
Attachments: [A Rudczynski ltr to OHRP 9Dec11.pdf](#)
[HIC-OHRP 2007 Perinatal Guidelines 6th Ed.pdf](#)
[HIC-OHRP 2002 Perinatal Guidelines 5th Ed.pdf](#)

Rose:

The information that was sent, was sent in response to a letter requesting responses. Yale's last response was on Dec 9, 2011. We have heard nothing further from OHRP. I have attached that last response. I will let our IRB-Human Research Protection Program know that they can join with from my office.

Richard

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The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 21, 2013 3:43 PM
To: Ehrenkranz, Richard
Subject: Re: SUPPORT

I am trying to balance those who need to be on the call with being open to sites- could they join from your office? Otherwise I will need a different call in or a different phone line to allow participation. Have you received any official correspondence from OHRP or was the information you sent in 11/2011 provided after their visit to Yale?

Let me know

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, February 21, 2013 01:46 PM
To: Kristi Watterberg <KWatterberg@salud.unm.edu>; nxs5@case.edu <nxs5@case.edu>; Kurt Schibler[kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Ivan Frantz <Ivan.Frantz@childrens.harvard.edu>; Michele Walsh(mcw3@cwru.edu) <mcw3@cwru.edu>; BradYoder (Bradley.yoder@hsc.utah.edu)

<Bradley.yoder@hsc.utah.edu>; RogerFaix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Shahnaz' (SDuara@med.miami.edu) 'Duara' <SDuara@med.miami.edu>; Beena[bsood@med.wayne.edu] Sood <bsood@med.wayne.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; M.D. Wally Carlo <WCarlo@peds.uab.edu>; Abhik Das(adas@rti.org) <adas@rti.org>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>; dstevenson@stanford.edu <dstevenson@stanford.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Brenda Morris (morrisb1@tmfhs.org) <morrisb1@tmfhs.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Wally Carlo (wacarlo@uab.edu) <wacarlo@uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Wade RIch <wrich@ucsd.edu>; Edward (Pediatrics) Bell <edward-bell@uiowa.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@URMC.Rochester.edu>; dale_phelps@urmc.rochester.edu <dale_phelps@URMC.Rochester.edu>; Nirupama Laroia <Nirupama_Laroia@URMC.Rochester.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; Abbot Laptook <Alaptook@wihri.org>
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Subject: RE: SUPPORT

Wally,

I agree with Kristi-I have nothing further to add.

By the way, I have been asked by members of our IRB-Human Research Protection Program about participating in the call next week. I emailed their request to Rose; what are your thoughts? As you may remember, we were asked similar questions by OHRP; the final responses were submitted on Dec 9, 2011 and we have not heard back from them.

Richard

Richard A. Ehrenkranz, MD
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Cc: Stephanie(NIH/NICHD) [E] Archer; Amanda (alewis@rti.org) Lewis-Evans; Jenna Gabrio (jgabrio@rti.org); (kzaterka@rti.org); (mcunningham@rti.org); Carolyn Petrie
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Very nice, Wally! - with the edits you've already received, I have nothing further to add.

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 2/21/2013 10:17 AM >>>

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Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.

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Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

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Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

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Rose

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From: Kennedy, Kathleen A
To: [Laptook, Abbot](mailto:Laptook.Abbot); [Kristi Watterberg](mailto:Kristi.Watterberg); nxs5@case.edu; [Kurt Schibler](mailto:Kurt.Schibler@cchmc.org) [kurt.schibler@cchmc.org]; [Vivek Narendran](mailto:Vivek.Narendran@cchmc.org) [cchmc.org]; [Ivan Frantz](mailto:Ivan.Frantz); [Michele Walsh](mailto:Michele.Walsh@cwru.edu) [mcw3@cwru.edu]; [Brad Yoder](mailto:BradYoder) [Bradley.yoder@hsc.utah.edu]; [Roger Faix](mailto:RogerFaix) [Roger.Faix@hsc.utah.edu]; bpoindex@iupui.edu; [Higgins, Rosemary](mailto:Higgins.Rosemary) [NIH/NICHD] [E]; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz" [SDuara@med.miami.edu] "Duara"; [Beena\[bsood@med.wayne.edu\]](mailto:Beena[bsood@med.wayne.edu) Sood; [Seetha Shankaran](mailto:Seetha.Shankaran); [Anthony Piazza](mailto:Anthony.Piazza) [Anthony.Piazza@oz.ped.emory.edu]; barbara_stoll@oz.ped.emory.edu; [M.D. Wally Carlo](mailto:M.D.WallyCarlo); [Abhik Das](mailto:Abhik.Das@rti.org) [adas@rti.org]; mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; [Krisa Van Meurs](mailto:Krisa.Van.Meurs) [vanmeurs@stanford.edu]; [Brenda Morris](mailto:Brenda.Morris) [morrisb1@tmfhs.org]; Ambal [ambal@uab.edu]; [Wally Carlo](mailto:WallyCarlo) [wacarlo@uab.edu]; nfiner@ucsd.edu; [Wade Rich](mailto:Wade.Rich); Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; [Nirupama Laroia](mailto:Nirupama.Laroia); [Tyson, Jon E](mailto:Tyson,JonE); Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu
Cc: [Archer, Stephanie](mailto:Archer) [NIH/NICHD] [E]; Amanda [alewis@rti.org] Lewis-Evans; [Jenna Gabrio](mailto:Jenna.Gabrio) [jgabrio@rti.org]; kzaterka@rti.org; [mcunningham@rti.org]; [Carolyn Petrie](mailto:Carolyn.Petrie)
Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 2:46:54 PM

I agree with the points made by others. We very commonly use death as a competing outcome for the outcome that's our primary target. I think it's important to make it clear that including death as a potential competing outcome does not mean that we think or have any evidence that the risk of death will be increased by study participation.

About the IRB members, I think it would be chaos to include them on an otherwise very large conference call. What about a follow-up call with interested IRB members and Wally and Rose?

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Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Laptook, Abbot [<mailto:ALaptook@Wihri.org>]
Sent: Thursday, February 21, 2013 1:07 PM
To: [Kristi Watterberg](mailto:Kristi.Watterberg); nxs5@case.edu; [Kurt Schibler](mailto:Kurt.Schibler@cchmc.org) [kurt.schibler@cchmc.org]; [Vivek Narendran](mailto:Vivek.Narendran@cchmc.org) [cchmc.org]; [Ivan Frantz](mailto:Ivan.Frantz); [Michele Walsh](mailto:Michele.Walsh@cwru.edu) [mcw3@cwru.edu]; [Brad Yoder](mailto:BradYoder) [Bradley.yoder@hsc.utah.edu]; [Roger Faix](mailto:RogerFaix) [Roger.Faix@hsc.utah.edu]; bpoindex@iupui.edu; Rosemary [NIH/NICHD] [E] Higgins; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz" [SDuara@med.miami.edu] "Duara"; [Beena\[bsood@med.wayne.edu\]](mailto:Beena[bsood@med.wayne.edu) Sood; [Seetha Shankaran](mailto:Seetha.Shankaran); [Anthony Piazza](mailto:Anthony.Piazza) [Anthony.Piazza@oz.ped.emory.edu]; barbara_stoll@oz.ped.emory.edu; [M.D. Wally Carlo](mailto:M.D.WallyCarlo); [Abhik Das](mailto:Abhik.Das@rti.org) [adas@rti.org]; mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; [Krisa Van Meurs](mailto:Krisa.Van.Meurs) [vanmeurs@stanford.edu]; [Brenda Morris](mailto:Brenda.Morris) [morrisb1@tmfhs.org]; Ambal [ambal@uab.edu]; [Wally Carlo](mailto:WallyCarlo) [wacarlo@uab.edu]; nfiner@ucsd.edu; [Wade Rich](mailto:Wade.Rich); Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; [Nirupama Laroia](mailto:Nirupama.Laroia); [Tyson, Jon E](mailto:Tyson,JonE); [Kennedy, Kathleen A](mailto:Kennedy,KathleenA); Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu
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Subject: RE: SUPPORT

Wally

Nice job. My only addition would be to briefly explain the rationale for the use of a composite primary outcome of death or.... We could acknowledge the absence of this statement as Neil suggested and agree that incorporation of the primary outcome in lay language for future consents will be adhered to. Tx, AL

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Kristi

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Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology

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Rose

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delete this message and any attachment(s) immediately. Thank you for your consideration in this matter.

From: Schibler, Kurt
To: Laptook, Abbot; Kristi Watterberg; nxs5@case.edu; Narendran, Vivek; Ivan Frantz; Michele Walsh(mcw3@cwru.edu); BradYoder (Bradley.yoder@hsc.utah.edu); RogerFaix (Roger.Faix@hsc.utah.edu); bpoindex@iupui.edu; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz' (SDuara@med.miami.edu) 'Duara; Beena[bsood@med.wayne.edu] Sood; Seetha Shankaran; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu); barbara_stoll@oz.ped.emory.edu; M.D. Wally Carlo; Abhik Das(adas@rti.org); mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; Krisa Van Meurs (vanmeurs@stanford.edu); Brenda Morris (morrish1@tmfhs.org); Ambal (ambal@uab.edu); Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Wade Rich; Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; Nirupama Laroia; Jon.E.Tyson@uth.tmc.edu; Kathleen A Kennedy; Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu
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Subject: Re: SUPPORT
Date: Thursday, February 21, 2013 2:39:06 PM

Wally, I think the point is well made by your statement with added diplomatic edits already proposed. Kurt

From: <Laptook>, "ALaptook@WIHRI.org" <ALaptook@WIHRI.org>
Date: Thursday, February 21, 2013 2:07 PM
To: Kristi Watterberg <KWatterberg@salud.unm.edu>, "nxs5@case.edu" <nxs5@case.edu>, CCHMC <kurt.schibler@cchmc.org>, Vivek Narendran <Vivek.Narendran@cchmc.org>, Ivan Frantz <ivan.frantz@childrens.harvard.edu>, "Michele Walsh(mcw3@cwru.edu)" <mcw3@cwru.edu>, "Bradley.Yoder@hsc.utah.edu" <Bradley.Yoder@hsc.utah.edu>, "Roger.Faix@hsc.utah.edu" <Roger.Faix@hsc.utah.edu>, Brenda B Poindexter <bpoindex@iupui.edu>, "higginsr@mail.nih.gov" <higginsr@mail.nih.gov>, Michael Cotten <cotte010@mc.duke.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "Shahnaz' (SDuara@med.miami.edu) 'Duara" <SDuara@med.miami.edu>, "Beena[bsood@med.wayne.edu] Sood" <bsood@med.wayne.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, "Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, "barbara_stoll@oz.ped.emory.edu" <barbara_stoll@oz.ped.emory.edu>, Wally Carlo <WCarlo@peds.uab.edu>, "adas@rti.org" <adas@rti.org>, "mgantz@rti.org" <mgantz@rti.org>, "poo@rti.org" <poo@rti.org>, "dstevenson@stanford.edu" <dstevenson@stanford.edu>, "Krisa Van Meurs (vanmeurs@stanford.edu)" <vanmeurs@stanford.edu>, "Brenda Morris (morrish1@tmfhs.org)" <morrish1@tmfhs.org>, "ambal@uab.edu" <ambal@uab.edu>, "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "wrich@ucsd.edu" <wrich@ucsd.edu>, Edward Bell <edward-bell@uiowa.edu>, "Carl_Dangio@URMC.Rochester.edu" <Carl_Dangio@URMC.Rochester.edu>, "dale_phelps@urmc.rochester.edu" <dale_phelps@URMC.Rochester.edu>, Nirupama Laroia <Nirupama_Laroia@URMC.Rochester.edu>, "Jon.E.Tyson@uth.tmc.edu" <Jon.E.Tyson@uth.tmc.edu>, "Kathleen.A.Kennedy@uth.tmc.edu" <Kathleen.A.Kennedy@uth.tmc.edu>, "Pablo.Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "moshea@wfubmc.edu" <moshea@wfubmc.edu>, "richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>
Cc: "Stephanie (NIH/NICHD) [E] Archer" <archerst@mail.nih.gov>, "Amanda (alewis@rti.org) Lewis-Evans" <alewis@rti.org>, "jgabrio@rti.org" <jgabrio@rti.org>, "kzaterka@rti.org" <kzaterka@rti.org>, Meg Cunningham <mcunningham@rti.org>, Carolyn Petrie <petrie@rti.org>
Subject: RE: SUPPORT

<!--[if mso 9]--> <!--[endif]-->

Wally

Nice job. My only addition would be to briefly explain the rationale for the use of a composite primary outcome of death or.... We could acknowledge the absence of this statement as Neil suggested and agree that incorporation of the primary outcome in lay language for future consents will be adhered to. Tx, AL

From: Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]
Sent: Thursday, February 21, 2013 1:28 PM
To: nxs5@case.edu; Kurt Schibler [kurt.schibler@cchmc.org]; (Vivek.Narendran@cchmc.org); Ivan Frantz; Michele Walsh (mcw3@cwru.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); bpoindex@iupui.edu; Rosemary (NIH/NICHD) [E] Higgins; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Shahnaz' (SDuara@med.miami.edu) 'Duara; Beena [bsood@med.wayne.edu] Sood; Seetha Shankaran; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); barbara_stoll@oz.ped.emory.edu; M.D. Wally Carlo; Abhik Das (adas@rti.org); mgantz@rti.org; poo@rti.org; dstevenson@stanford.edu; Krisa Van Meurs (vanmeurs@stanford.edu); Brenda Morris (morrisb1@tmfhs.org); Ambal (ambal@uab.edu); Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Wade RIch; Edward (Pediatrics) Bell; carl_dangio@urmc.rochester.edu; dale_phelps@urmc.rochester.edu; Nirupama Laroia; Jon.E.Tyson@uth.tmc.edu; Kathleen A Kennedy; Pablo.Sanchez@UTSouthwestern.edu; moshea@wfubmc.edu; Laptook, Abbot; richard.ehrenkranz@yale.edu
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Subject: RE: SUPPORT

Very nice, Wally! - with the edits you've already received, I have nothing further to add.

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 2/21/2013 10:17 AM >>>

Wally,

Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.

Ed

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Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

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Phone: 205 934 4680

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Cell: 205 (b)(6)

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Sent: Tuesday, February 19, 2013 8:25 AM

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Subject: SUPPORT

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The call in number is:

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Rose

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delete this message and any attachment(s) immediately. Thank you for your consideration in this matter.

From: [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 1:24:48 PM

These are IRB folks right? If they can add something -sure.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, February 21, 2013 12:32 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: SUPPORT

Marian-

See the note from Dr. Ehrenkranz- my take is to allow his folks to listen in as this is a network issue - what is your take?

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Ehrenkranz, Richard [<mailto:richard.ehrenkranz@yale.edu>]
Sent: Thursday, February 21, 2013 12:29 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Rose:

Can members of IRB Human Research Protection Program participate in this call on Tuesday? Yale responded to OHRP on Dec 9, 2011 and has not heard back from them. Please let me know.

Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

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To: Bell, Edward (Pediatrics); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler (kurt.schibler@cchmc.org); nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; Ronald Goldberg, M.D.; Krisa Van Meurs (vanmeurs@stanford.edu); "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 1:20:59 PM
Attachments: OHRRESPONSELETTER2-21-13-efbmc11.doc

Hi Ed and Wally.....I agree w/ Carl's points to be cautious (from the Duke perspective w/ OHRP shutting down clinical research here for a week in 1999).....I think Wally's letter addresses the main points...I've added suggestions to the letter after Ed's....including mention of the BOOST trial, where mortality was higher in the higher o2 target group than lower....(mentioning this study may not be entirely ok as the study population and timing of intervention is much different)

mc

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2424 Erwin Road Suite 504
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Wally Carlo, M.D.

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In response to the letter dated February 8, 2013 sent to Dr. Marchase (UAB) and Mr. Saz (RTT) we would like to respectfully submit a rebuttal of several of its contents-assertions and interpretations.

Historical Background

The summary statement on page 4 of the review of the literature states that, "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 preterm infant developing ROP and other aspects of morbidity and mortality."

The evidence of increased mortality with restriction of oxygen was based on uncontrolled observations of temporal trends and on a trial comparing a practice that restricted oxygen supplementation to ≤50% inspired oxygen concentration regardless of the condition of the preterm infants (ref). The unrestricted oxygen policy provided oxygen routinely for 28 days at over 50% concentration. This was tested in the 1950s in a trial that included few extremely preterm infants, whereas the SUPPORT trial only enrolled only extremely preterm infants.

Comment [reviewer1]: Should you provide a gestational age range to define "extreme premature"?

Restriction of oxygen using an arbitrary cut-off of inspired oxygen concentration has not been a standard clinical practice in US NICUs for years, and this was not a practice tested in the SUPPORT trial. Furthermore, in-oxygen monitoring in the 1950s was done by monitoring infant skin color or with intermittent blood gas sampling, whereas continuous oxygen saturation monitoring, not available in the 1950's, was done in SUPPORT. In addition, most NICU practices have changed substantially since the 1950s. Notice that the references used in the "Background" in the OHRP letter are for from 1956 (ref. 4), 1973 (ref. 5), and 1984 (ref. 6). The newer reference 8, published in 2006, states, "marked variability in opinion exists [with respect to oxygen saturation targets]." but the authors did does not include provide references to support the statement.

Comment [EB2]: Consider omitting this sentence. It doesn't contribute much to our message.

The appropriate prior evidence used for the design of the SUPPORT trial included are the following cohort studies:

The study by Tin et al.¹ was the highest level of evidence most rigorous study testing oxygen saturation targets less than 95% before SUPPORT was performed. The Tin study was a multicenter population-based prospective cohort study of infants <28 weeks (just like SUPPORT). The Tin study was the only one study reported at that time with follow-up assessments which included to at least 10 months of age.

The policy for oxygen saturation targets and alarm limits and targets varied between among the centers. ROP was decreased in the 70-90% saturation target patients **without a difference in survival (51.6% survival in the 70-90% O₂ saturation target group vs. 51.7% in 84-95% group, Table 1).**

Table 1.

Saturation Alarm Targets	N	Survival	Survival with ROP	Survival with Cerebral Palsy
70-90%	126	51.6%	6.2%	15.4%

84-95%	319	51.7%	15.8%	15.5%
88-98%	123	52.8%	27.7%	16.9%

It should be noted that impaired neurodevelopmental outcome was not higher with oxygen saturation targets as low as 70-90%. Furthermore, not a single case of blindness was reported in infants at targets up to 95% despite the difference in ROP.

The Chow et al. study² was a single center prospective cohort study to assess the impact of implementation of an oxygen monitoring and administration policy for very low birth weight infants. Outcomes for very-low-birth-weight infants after lowering the oxygen saturation targets to 83-93% were compared to outcomes during a previous period when the saturation with target was 90-98%. With lower saturation targets, severe ROP decreased from 12.5% to 2.5% and decreased the need for ROP laser treatment from 4.5% to 0%. Over the years of the study, there was a trend for increased survival following implementation of the restrictive oxygen policy (contrary to what we found in SUPPORT). Survival improved from 48 to 75% in the infants 500-749 g and from 74 to 81% in the infants 750-999 g from 1997 to 2001. The policy was changed in the middle of 1998 (Table 2).

Table 2.

Birth Weight (g)	1997		1998		1999		2000		2001		Total	
	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival
500-749	14	48	15	40	18	73	15	87	12	75	74	58
750-999	25	74	27	78	18	78	21	82	17	81	108	83
1000-1249	24	88	20	100	26	96	28	100	21	94	119	95
1250-1500	29	97	27	100	26	100	28	100	36	97	146	99
Total	92	81	89	83	88	85	92	93	86	90	447	86

Other studies that assessed BPD and growth suggested benefits from lower oxygen saturation targets (ref Askie 2003). In this study, which targeted lower vs. higher oxygen saturations after 32 postnatal weeks, mortality was higher among infants in the high oxygen saturation target group (5%) than the lower saturation target group (3%), but the difference was not statistically significant (p = 0.41). It should be noted that these studies targeted saturations above 95%, which was not the goal of the study.

Comment [EB3]: Did you mean "higher"?

Comment [reviewer4]: Boost? Stopprop?

Thus, the best available studies, those conducted with the highest level of evidence, studies when SUPPORT was designed and conducted suggested that lower oxygen saturation targets would lead to a decrease in ROP, decreased BPD, and decreased poor growth. Furthermore, there was not even suggestive evidence from relevant prior literature that would suggest an increase in death, blindness, or other serious morbidity with either set of oxygen saturation targets used in SUPPORT.

Comment [EB5]: ?

Based on these and other studies, many clinicians started to recommend lower oxygen saturation targets and developed educational programs promoting the same. The most prominent program was developed by Dr. Jay Goldsmith from Ochsner-Ochsner Clinic (not published in the peer-reviewed literature, but presented at international Neonatology conferences including Hot Topics in Neonatology, in 2008(?)). In this program, Dr. Goldsmith and his colleagues recommended oxygen saturation targets of 85 to 93% were recommended. The benefits stated were decreased

ROP, decreased days on a ventilator and on oxygen, and decreased hospitalization duration.
Risk for adverse effects or increased mortality ~~was~~ were not included in the ~~materials~~ discussion.

Four other multicenter trials were designed after the SUPPORT trial was conceived. These trials were led by investigators based in the United Kingdom, Australia, New Zealand, and Canada/US. These protocols were also designed without the expectation of increased mortality in the lower oxygen saturation group.

Summary

In summary, the existing published data that ~~were~~ is pertinent when the SUPPORT Trial was designed and conducted did not indicate any evidence to support an effect ~~portend an increase in~~ on mortality or blindness in either treatment group. Other morbidities had not been reported in the published studies.

The SUPPORT consent ~~template, the UAB consent form, and those at the other participating clinical centers~~ were/was appropriately written based on the relevant knowledge available at the time. Furthermore, throughout the trial, survival was better than the historical reference group used prospectively to monitor the trial by the independent Neonatal Research Network (NRN) DSMC and the NRN Steering Committee. Rates of morbidities and mortality compared to historic controls were reviewed during each quarterly NRN Steering Committee meeting and found to be lower than the historical reference group. Concurrent controls had a mortality rate of 24.1% compared to infants in the higher saturation group (16.2%) and infants in the lower oxygen saturation group (19.9%) although these differences were not statistically significant in adjusted regression analyses.

REFERENCES

1. Tin W, Milligan DW, Pennfather P, Hey E. Pulse ~~oximetry~~ oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001;84:F106-10.
2. Chow LC, Wright KW, Sola A, CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003;111:339-45.
3. Askie L, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-Saturation Targets and Outcomes in Extremely Preterm Infants N Engl J Med 2003;349:959-67.

From: Bell, Edward (Pediatrics)
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarfo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morriss1@trmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi.Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mccunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 12:17:59 PM
Attachments: OHRP RESPONSE LETTER 2-21-13-efb.doc

Wally,

Your draft letter makes the important points. It should conclude with a statement that we see no need for corrective actions. SUPPORT was conducted with the highest standards of science, ethics, and patient protection. I have made some editing suggestions and comments in the attached copy.

Ed

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]

Sent: Thursday, February 21, 2013 10:27 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarfo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morriss1@trmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; Bell, Edward (Pediatrics); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu

Cc: (mccunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn

Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 19, 2013 8:25 AM

To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu

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Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

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From: Michael O'Shea
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrissb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Subject: RE: SUPPORT
Date: Thursday, February 21, 2013 12:10:27 PM
Attachments: OHRP RESPONSE LETTER 2-21-13-mos.doc

Wally,
This looks very good to me.
In yellow highlighting I have offered a few edits.
Thank you,
Mike

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 11:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrissb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; Michael O'Shea; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
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Subject: RE: SUPPORT

Enclosed is a draft response to the OHRP letter.

I would appreciate any comments.

Wally

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Subject: SUPPORT

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For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

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Rose

In response to the letter dated February 8, 2013 sent to Dr. Marchase (UAB) and Mr. Saz (RTI) we would like to respectfully submit a rebuttal several of its contents and interpretations.

Historical Background

The summary statement on page 4 of the review of the literature states that, "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 preterm infant developing ROP and other aspects of morbidity and mortality."

The evidence of increased mortality with restriction of oxygen was based on a trial comparing a practice that restricted oxygen supplementation to $\leq 50\%$ inspired oxygen concentration regardless of the condition of the preterm infants. The unrestricted oxygen policy provided oxygen routinely for 28 days at over 50% concentration. This was tested in the 1950s in a trial that included few extremely preterm infants, whereas the SUPPORT trial only enrolled extremely preterm infants. Restriction of oxygen using an arbitrary cut-off of inspired oxygen concentration has not been a standard clinical practice in US NICUs for years, and was not a practice tested in the SUPPORT trial. Furthermore, ~~in~~ oxygen monitoring in the 1950s consisted of ~~was done with~~ intermittent blood gas sampling whereas continuous oxygen saturation monitoring was used ~~done~~ in SUPPORT. In addition, most NICU practices have changed substantially since the 1950s. Notice that the references used in the "Background" in the OHRP letter are for 1956 (ref. 4), 1973 (ref. 5), and 1984 (ref. 6). The newer reference 8 states, "marked variability in opinion exists." but does not include references to support the statement.

The appropriate prior evidence used for the design of the SUPPORT trial are the following cohort studies:

The study by Tin et al.¹ was the highest level of evidence study testing targets less than 95% before SUPPORT was performed. The Tin study was a multicenter population-based prospective study of infants <28 weeks (just like SUPPORT). The Tin study was the only one with follow-up assessments which included at least 10 months of age.

The policy for saturation alarm limits and targets varied between the centers. ROP was decreased in the 70-90% saturation target patients **without a difference in survival (51.6% survival in the 70-90% O₂ saturation target group vs. 51.7% in 84-95% group, Table 1).**

Table 1.

Saturation Alarm Targets	N	Survival	Survival with ROP	Survival with Cerebral Palsy
70-90%	126	51.6%	6.2%	15.4%
84-95%	319	51.7%	15.8%	15.5%
88-98%	123	52.8%	27.7%	16.9%

It should be noted that impaired neurodevelopmental outcome was not higher with saturation targets as low as 70-90%. Furthermore, not a single case of blindness was reported in infants at targets up to 95% despite the difference in ROP.

The Chow et al. study² was a single center prospective study to assess the impact of implementation of an oxygen monitoring and administration policy for very low birth weight infants. Lowering saturation targets to 83-93% compared to a previous period with targets 90-98% decreased severe ROP from 12.5% to 2.5% and decreased the need for ROP laser treatment from 4.5% to 0%. Over the years of the study, there was a trend **for increased survival following implementation of the restriction of oxygen policy** (contrary to what we found in SUPPORT). Survival improved from 48 to 75% in the infants 500-749 g and for 74 to 81% in the infants 750-999 g from 1997 to 2001. The policy was changed in the middle of 1998 (Table 2).

Table 2.

Birth Weight (g)	1997		1998		1999		2000		2001		Total	
	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival
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750-999	25	74	27	78	18	78	21	82	17	81	108	83
1000-1249	24	88	20	100	26	96	28	100	21	94	119	95
1250-1500	29	97	27	100	26	100	28	100	36	97	146	99
Total	92	81	89	83	88	85	92	93	86	90	447	86

Other studies that assessed BPD and growth suggested benefits from lower oxygen saturation targets (ref). It should be noted that these studies targeted saturations above 95% which was not the goal of the study.

Thus, the highest level of evidence studies when SUPPORT was designed and conducted suggested that lower oxygen saturation targets would lead to a decrease in ROP, decreased BPD, and decreased poor growth. Furthermore, there was not even suggestive evidence from relevant prior literature that would suggest an increase in death, blindness, or other serious morbidity with either set of oxygen saturation targets used in SUPPORT.

Based on these and other studies, many clinicians started to recommend lower oxygen saturation targets and developed educational programs promoting the same. The most prominent program was developed by Dr. Jay Goldsmith from Oschner Clinic (not published in the peer-reviewed literature). In this program, saturation targets of 85 to 93% were recommended. The benefits stated were decreased ROP, decreased days on a ventilator and on oxygen, and decreased hospitalization duration. Risk for adverse effects or increased mortality were not included in the materials.

Four other multicenter trials were designed after the SUPPORT trial was conceived. These trials were led by investigators based in the United Kingdom, Australia, New Zealand, and Canada/US. These protocols were also designed without the expectation of increased mortality in the lower oxygen saturation group.

Summary

In summary, the existing published data that is pertinent when the SUPPORT Trial was designed and conducted did not indicate any evidence to support an effect on mortality or blindness in either treatment group. Other morbidities had not been reported in the published studies.

The SUPPORT consent form was appropriately written based on the relevant knowledge available at the time. Furthermore, throughout the trial, survival was better than the historical reference group used prospectively to monitor the trial by the independent Neonatal Research Network (NRN) DSMC and the NRN Steering Committee. Rates of morbidities and mortality compared to historic controls were reviewed during each quarterly NRN Steering Committee meeting and found to be lower than the historical reference group. Concurrent controls had a mortality rate of 24.1% compared to infants in the higher saturation group (16.2%) and infants in the lower oxygen saturation group (19.9%) although these differences were not statistically significant in adjusted regression analyses.

REFERENCES

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2. Chow LC, Wright KW, Sola A, CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics.* 2003;111:339-45.

From: [Finer, Neil](#)
To: [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally Carlo \(wacarlo@uab.edu\)](#); [Michele Walsh \(mcw3@cwru.edu\)](#); [Rich, Wade \(mgantz@rti.org\)](#); [Abbot Laptook](#); [Brad Yoder \(Bradley.yoder@hsc.utah.edu\)](#); [Roger Faix \(Roger.Faix@hsc.utah.edu\)](#); [Abhik Das \(adas@rti.org\)](#); [poo@rti.org](#); [Kurt Schibler \(kurt.schibler@cchmc.org\)](#); [nxs5@case.edu](#); [Ambal \(ambal@uab.edu\)](#); [Frantz, Ivan; barbara_stoll@oz.ped.emory.edu](#); [Anthony Piazza \(Anthony.Piazza@oz.ped.emory.edu\)](#); [Pablo Sanchez@UTSouthwestern.edu](#); [Brenda Morris \(morrisb1@tmfhs.org\)](#); [Kennedy, Kathleen A; Jon E.Tyson@uth.tmc.edu](#); [Laroya, Nirupama; dale_phelps@umc.rochester.edu](#); [bpoindex@iupui.edu](#); [cotte010@mc.duke.edu](#); [goldb008@mc.duke.edu](#); [Krisa Van Meurs \(vanmeurs@stanford.edu\)](#); ["Duara, Shahnaz" \(SDuara@med.miami.edu\)](#); [dstevenson@stanford.edu](#); [\(Vivek.Narendran@cchmc.org\)](#); [Spod, Beena \(bsood@med.wayne.edu\)](#); [Seetha Shankaran; moshea@wfubmc.edu](#); [Ed Bell \(edward-bell@uiowa.edu\)](#); [richard.ehrenkranz@yale.edu](#); [Kristi Watterberg \(kwatterberg@salud.unm.edu\)](#); [carl_dangio@umc.rochester.edu](#)
Cc: [\(mcunningham@rti.org\)](#); [\(kzaterka@rti.org\)](#); [Jenna Gabrio \(jgabrio@rti.org\)](#); [Lewis-Evans, Amanda \(alewis@rti.org\)](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Petrie, Carolyn](#)
Subject: Re: SUPPORT
Date: Thursday, February 21, 2013 11:59:21 AM

Wally

This reads well and states the detailed evidence

My view is that in the future under other risks, we will include the possibility of increased death

Our SUPPORT consent did not detail the primary outcome - i.e. Death or survival with ROP etc

Even saying that would have been informative about the possibility of increased death in an arm

I now believe that there should be a statement of the primary outcome in plain language

That all being said, I totally support your response

Be well

Neil

From: "<Wally Carlo>", Wally Carlo <wacarlo@peds.uab.edu<<mailto:wacarlo@peds.uab.edu>>>

Date: Thursday, February 21, 2013 8:27 AM

To: Rosemary Higgins <higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>>, "Wally Carlo (wacarlo@uab.edu<<mailto:wacarlo@uab.edu>>>)" <wacarlo@uab.edu<<mailto:wacarlo@uab.edu>>>, Neil Finer <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>, "Michele Walsh (mcw3@cwru.edu<<mailto:mcw3@cwru.edu>>>)" <mcw3@cwru.edu<<mailto:mcw3@cwru.edu>>>, Wade Rich <wrich@ucsd.edu<<mailto:wrich@ucsd.edu>>>, Marie Gantz <mgantz@rti.org<<mailto:mgantz@rti.org>>>, Abbot Laptook <ALaptook@WHIRL.org<<mailto:ALaptook@WHIRL.org>>>, "Bradley.yoder@hsc.utah.edu<<mailto:Bradley.yoder@hsc.utah.edu>>>" <Bradley.yoder@hsc.utah.edu<<mailto:Bradley.yoder@hsc.utah.edu>>>, Roger Faix <Roger.Faix@hsc.utah.edu<<mailto:Roger.Faix@hsc.utah.edu>>>, Abhik Das <adas@rti.org<<mailto:adas@rti.org>>>, Ken Poole <poo@rti.org<<mailto:poo@rti.org>>>, "kurt.schibler@cchmc.org<<mailto:kurt.schibler@cchmc.org>>>" <kurt.schibler@cchmc.org<<mailto:kurt.schibler@cchmc.org>>>, nancy newman <nxs5@case.edu<<mailto:nxs5@case.edu>>>, Ambal <ambal@uab.edu<<mailto:ambal@uab.edu>>>, "Frantz, Ivan" <Ivan.Frantz@childrens.harvard.edu<<mailto:Ivan.Frantz@childrens.harvard.edu>>>, Stoll Barbara <barbara_stoll@oz.ped.emory.edu<mailto:barbara_stoll@oz.ped.emory.edu>>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu<<mailto:Anthony.Piazza@oz.ped.emory.edu>>>)" <Anthony.Piazza@oz.ped.emory.edu<<mailto:Anthony.Piazza@oz.ped.emory.edu>>>, Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu<<mailto:Pablo.Sanchez@UTSouthwestern.edu>>>, "Brenda Morris (morrisb1@tmfhs.org<<mailto:morrisb1@tmfhs.org>>>)" <morrisb1@tmfhs.org<<mailto:morrisb1@tmfhs.org>>>, "kathleen.a.kennedy@uth.tmc.edu<<mailto:kathleen.a.kennedy@uth.tmc.edu>>>" <kathleen.a.kennedy@uth.tmc.edu<<mailto:kathleen.a.kennedy@uth.tmc.edu>>>, Jon Tyson <Jon.E.Tyson@uth.tmc.edu<<mailto:Jon.E.Tyson@uth.tmc.edu>>>, "Laroya, Nirupama" <Nirupama_Laroya@URMC.Rochester.edu<mailto:Nirupama_Laroya@URMC.Rochester.edu>>, Dale Phelps <Dale_Phelps@URMC.Rochester.edu<mailto:Dale_Phelps@URMC.Rochester.edu>>, Brenda Poindexter <bpoindex@iupui.edu<<mailto:bpoindex@iupui.edu>>>, Michael Cotten <cotte010@mc.duke.edu<<mailto:cotte010@mc.duke.edu>>>, "Duke, Edu>:" <goldb008@mc.duke.edu<<mailto:goldb008@mc.duke.edu>>>, Krisa Van Meurs <vanmeurs@stanford.edu<<mailto:vanmeurs@stanford.edu>>>, "'Duara, Shahnaz'

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<Vivek.Narendran@cchmc.org<mailto:Vivek.Narendran@cchmc.org>>, "Sood, Beena
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Cc: "mcunningham@rti.org<mailto:mcunningham@rti.org>"
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Evans, Amanda (alewis@rti.org<mailto:alewis@rti.org>)" <alewis@rti.org<mailto:alewis@rti.org>>, Stephanie
Archer <archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>>, Carolyn Petrie
<petrie@rti.org<mailto:petrie@rti.org>>
Subject: RE: SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Re: SUPPORT
Date: Thursday, February 21, 2013 9:54:36 AM

Yes

I can't get internet access currently, so please send.

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, February 21, 2013 09:15 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT

Hi Rose.

Can I send the draft of our response as edited by Abhik to the group you sent the OHRP letter?

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo (wcarlo@uab.edu)" <wcarlo@uab.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "Michele Walsh (mcw3@cwru.edu)" <mcw3@cwru.edu>, Wade Rich <wrich@ucsd.edu>, "mgantz@rti.org" <mgantz@rti.org>, Abbot Laptook <Alaptook@wihri.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, "Roger Faix (Roger.Faix@hsc.utah.edu)" <Roger.Faix@hsc.utah.edu>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "poo@rti.org" <poo@rti.org>, "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>, "nxs5@case.edu" <nxs5@case.edu>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Frantz, Ivan" <Ivan.Frantz@childrens.harvard.edu>, "barbara_stoll@oz.ped.emory.edu" <barbara_stoll@oz.ped.emory.edu>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, "Pablo.Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "Brenda Morris (morrisb1@tmfhs.org)" <morrisb1@tmfhs.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Jon.E.Tyson@uth.tmc.edu" <Jon.E.Tyson@uth.tmc.edu>, "Laroia, Nirupama" <Nirupama_Laroia@URMC.Rochester.edu>, "dale_phelps@urmc.rochester.edu" <dale_phelps@URMC.Rochester.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "Krisa Van Meurs (vanmeurs@stanford.edu)" <vanmeurs@stanford.edu>, "'Duara, Shahnaz'" (SDuara@med.miami.edu) <SDuara@med.miami.edu>, "dstevenson@stanford.edu" <dstevenson@stanford.edu>, "Vivek.Narendran@cchmc.org" <Vivek.Narendran@cchmc.org>, "Sood, Beena [bsood@med.wayne.edu]" <bsood@med.wayne.edu>, Seetha Shankaran

<sshankar@med.wayne.edu>, "moshea@wfubmc.edu" <moshea@wfubmc.edu>, "Ed Bell (edward-bell@uiowa.edu)" <edward-bell@uiowa.edu>, "richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>, "Kristi Watterberg (kwatterberg@salud.unm.edu)" <kwatterberg@salud.unm.edu>, "carl_dangio@urmc.rochester.edu" <carl_dangio@URMC.Rochester.edu>
Cc: " (mcunningham@rti.org)" <mcunningham@rti.org>, " (kzaterka@rti.org)" <kzaterka@rti.org>, "Jenna Gabrio (jgabrio@rti.org)" <jgabrio@rti.org>, "Lewis-Evans, Amanda (alewis@rti.org)" <alewis@rti.org>, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Petrie, Carolyn" <petrie@rti.org>
Sent: Tue, Feb 19, 2013 14:26:00 GMT+00:00
Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

From: D'Angio, Carl
To: "Roger Faix"; Bell, Edward (Pediatrics); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Bradley Yoder; Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler (kurt.schibler@cchmc.org); nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Larola, Nirupama; Phelops, Dale; hnoindex@iunui.edu; cottle01@mc.duke.edu; goldh008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena (bsood@med.wayne.edu); Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu)
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT
Date: Wednesday, February 20, 2013 4:53:09 PM

All,

I'll take what may be an unpopular stance. Although the basis of the allegations is clearly hyperbolic and the OHRP conclusions are overreaching (particularly regarding the low sat group), there may be a kernel of important information buried somewhere in the OHRP letter.

A consent form for an RCT that lists the only risk of the high vs. low sat groups as "skin breakdown" might be difficult to defend as fully communicating potential risks. OHRP's contention is further supported by the suggested benefit language in the form, which lists lower ROP as a benefit of the low sat group (implying a risk of higher ROP in the high sat group).

I find no convincing evidence that there was any clear suggestion of which way mortality risks might cut, so I think it would have been hard to frame consent language about mortality any more clearly than it was.

I'm not suggesting that individual families were misled and I'm certainly not suggesting that every conceivable risk be listed in consent forms. (The literature is pretty clear that more information produces poorer comprehension, not better comprehension.) I am suggesting that, even placing oneself back at the beginning of the study, it might be hard to characterize the risk language in the model consent as perfect.

On the other hand, the opinions of 16+ IRBs, several experts and a whole bunch of smart investigators suggest the language was appropriate.

Carl

Carl T. D'Angio, MD
Professor of Pediatrics and Medical Humanities & Bioethics
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Director, Pediatric Clinical Research Office
Division of Neonatology
Golisano Children's Hospital
University of Rochester Medical Center
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Roger Faix [mailto:Roger.Faix@hsc.utah.edu]
Sent: Wednesday, February 20, 2013 4:23 PM
To: Bell, Edward (Pediatrics); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Bradley Yoder; Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler

[kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrissb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; Phelps, Dale; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); D'Angio, Carl
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT

Most interesting and very disturbing. Totally baseless allegations. **Very strong pushback** definitely warranted!!

Roger

From: Bell, Edward (Pediatrics) [edward-bell@uiowa.edu]
Sent: Wednesday, February 20, 2013 2:17 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Bradley Yoder; Roger Faix; Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrissb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT

Barbara Schmidt showed me the Aleff website.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, February 20, 2013 3:10 PM
To: Bell, Edward (Pediatrics); Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade RIch; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrissb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT

Ed.

Thanks for identifying this. I agree that we need to have a strong response and reject the

OHRP conclusions.

Wally

-----Original message-----

From: "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu>
To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "Michele Walsh (mcw3@cwru.edu)" <mcw3@cwru.edu>, Wade Rich <wrich@ucsd.edu>, "mgantz@rti.org" <mgantz@rti.org>, Abbot Laptook <Alaptook@wihri.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, "Roger Faix (Roger.Faix@hsc.utah.edu)" <Roger.Faix@hsc.utah.edu>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "poo@rti.org" <poo@rti.org>, "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>, "nxs5@case.edu" <nxs5@case.edu>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Frantz, Ivan" <Ivan.Frantz@childrens.harvard.edu>, "barbara_stoll@oz.ped.emory.edu" <barbara_stoll@oz.ped.emory.edu>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, "Pablo.Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "Brenda Morris (morrisb1@tmfhs.org)" <morrisb1@tmfhs.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Jon.E.Tyson@uth.tmc.edu" <Jon.E.Tyson@uth.tmc.edu>, "Laroia, Nirupama" <Nirupama_Laroia@URMC.Rochester.edu>, "dale_phelps@urmc.rochester.edu" <dale_phelps@URMC.Rochester.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "Krisa Van Meurs (vanmeurs@stanford.edu)" <vanmeurs@stanford.edu>, "'Duara, Shahnaz' (SDuara@med.miami.edu)" <SDuara@med.miami.edu>, "dstevenson@stanford.edu" <dstevenson@stanford.edu>, "(Vivek.Narendran@cchmc.org)" <Vivek.Narendran@cchmc.org>, "Sood, Beena [bsood@med.wayne.edu]" <bsood@med.wayne.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, "moshea@wfubmc.edu" <moshea@wfubmc.edu>, "richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>, "Kristi Watterberg (kwatterberg@salud.unm.edu)" <kwatterberg@salud.unm.edu>, "carl_dangio@urmc.rochester.edu" <carl_dangio@URMC.Rochester.edu>
Cc: "(mcunningham@rti.org)" <mcunningham@rti.org>, "(kzaterka@rti.org)" <kzaterka@rti.org>, "Jenna Gabrio (jgabrio@rti.org)" <jgabrio@rti.org>, "Lewis-Evans, Amanda (alewis@rti.org)" <alewis@rti.org>, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Petrie, Carolyn" <petrie@rti.org>
Sent: Wed, Feb 20, 2013 16:53:07 GMT+00:00
Subject: RE: SUPPORT

I suspect this was triggered by a complaint to OHRP by Peter Aleff (<http://retinopathyofprematurity.org/BioethicsConsent.htm>). I think we need to push back hard against OHRP's interpretation that we were not in compliance with federal regulations.

Ed

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 19, 2013 8:25 AM
To: Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler

[kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran ; moshea@wfubmc.edu; Bell, Edward (Pediatrics); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

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From: Roger Faix
To: Phelps, Dale; Bell, Edward (Pediatrics); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Bradley Yoder; Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler (kurt.schibler@cchmc.org); nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kathleen.A.Kennedy@uth.tmc.edu; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; vanmeurs@stanford.edu; "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); bsood@med.wayne.edu; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); D'Angio, Carl
Cc: mcunningham@rti.org; (kzaterka@rti.org); jgabrio@rti.org; Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; petrie@rti.org
Subject: RE: SUPPORT
Date: Wednesday, February 20, 2013 4:50:14 PM

Seems more in keeping with the ambience of the Network in any event.

Roger

From: Phelps, Dale [Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, February 20, 2013 2:39 PM
To: Roger Faix; Bell, Edward (Pediatrics); Wally Carlo, M.D.; higginsr@mail.nih.gov; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Bradley Yoder; Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler (kurt.schibler@cchmc.org); nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kathleen.A.Kennedy@uth.tmc.edu; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; vanmeurs@stanford.edu; "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); bsood@med.wayne.edu; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); D'Angio, Carl
Cc: mcunningham@rti.org; (kzaterka@rti.org); jgabrio@rti.org; Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; petrie@rti.org
Subject: RE: SUPPORT

I would urge thoughtful caution before too strong a response. (I have had experience with Mr. Aleff before when he knew that fluroescent lights caused ROP and so informed every member of congress in writing, including his thesis on it.)

National Eye Institute has had experience with him and might add insight.

Carl D'Angio has some really well thought out ideas. (We were discussing today)

A thoughtful, science based response is going to go a lot further than a strong defensive reaction.

Dale Phelps
From my Droid

-----Original message-----

From: Roger Faix <Roger.Faix@hsc.utah.edu>
To: "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "Michele Walsh (mcw3@cwru.edu)"

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<Ivan.Frantz@childrens.harvard.edu>, "barbara_stoll@oz.ped.emory.edu"
<barbara_stoll@oz.ped.emory.edu>, "Anthony Piazza
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"richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>, "Kristi Watterberg
(kwatterberg@salud.unm.edu)" <kwatterberg@salud.unm.edu>, "D'Angio, Carl"
<Carl_Dangio@URMC.Rochester.edu>
Cc: " (mcunningham@rti.org)" <mcunningham@rti.org>, " (kzaterka@rti.org)"
<kzaterka@rti.org>, "Jenna Gabrio (jgabrio@rti.org)" <jgabrio@rti.org>, "Lewis-Evans,
Amanda (alewis@rti.org)" <alewis@rti.org>, "Archer, Stephanie (NIH/NICHD) [E]"
<archerst@mail.nih.gov>, "Petrie, Carolyn" <petrie@rti.org>
Sent: Wed, Feb 20, 2013 21:21:59 GMT+00:00
Subject: RE: SUPPORT

Most interesting and very disturbing. Totally baseless allegations. **Very strong pushback**
_definitely warranted!!

Roger

From: Bell, Edward (Pediatrics) [edward-bell@uiowa.edu]
Sent: Wednesday, February 20, 2013 2:17 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu);
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Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen
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bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs
(vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu);
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[bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu;
richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu);
carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans,
Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT

Barbara Schmidt showed me the Aleff website.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, February 20, 2013 3:10 PM
To: Bell, Edward (Pediatrics); Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); nfiner@ucsd.edu; Michele Walsh (mcw3@cwru.edu); Wade Rich; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler [kurt.schibler@cchmc.org]; nxs5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ped.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Pablo.Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@tmfhs.org); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; Laroia, Nirupama; dale_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; goldb008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena [bsood@med.wayne.edu]; Seetha Shankaran; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: SUPPORT

Ed.

Thanks for identifying this. I agree that we need to have a strong response and reject the OHRP conclusions.

Wally

-----Original message-----

From: "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu>
To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "Michele Walsh (mcw3@cwru.edu)" <mcw3@cwru.edu>, Wade Rich <wrich@ucsd.edu>, "mgantz@rti.org" <mgantz@rti.org>, Abbot Laptook <Alaptook@wihri.org>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, "Roger Faix (Roger.Faix@hsc.utah.edu)" <Roger.Faix@hsc.utah.edu>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "poo@rti.org" <poo@rti.org>, "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>, "nxs5@case.edu" <nxs5@case.edu>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Frantz, Ivan" <ivan.Frantz@childrens.harvard.edu>, "barbara_stoll@oz.ped.emory.edu" <barbara_stoll@oz.ped.emory.edu>, "Anthony Piazza (

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); Michele Walsh (mcw3@cwru.edu); Rich. Wade; mgantz@rti.org; Abbot Lantook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); poo@rti.org; Kurt Schibler (kurt.schibler@cchmc.org); nys5@case.edu; Ambal (ambal@uab.edu); Frantz, Ivan; barbara_stoll@oz.ned.emory.edu; Anthony Piazza (Anthony.Piazza@oz.ned.emory.edu); Pablo Sanchez@UTSouthwestern.edu; Brenda Morris (morrisb1@trmhs.org); Kennedy, Kathleen A; Jon E. Tyson@uth.tmc.edu; Laroia, Nirupama; dale_nhelps@urmc.rochester.edu; hpoindex@iupui.edu; cotte010@mc.duke.edu; gndh008@mc.duke.edu; Krisa Van Meurs (vanmeurs@stanford.edu); "Duara, Shahnaz" (SDuara@med.miami.edu); dstevenson@stanford.edu; (Vivek.Narendran@cchmc.org); Sood, Beena (hsood@med.wayne.edu); Seetha Shankaran; moshea@wfubmc.edu; Ed Bell (edward-bell@uiowa.edu); richard.ehrenkranz@yale.edu; Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu
Cc: (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn
Subject: Re: SUPPORT
Date: Tuesday, February 19, 2013 3:33:55 PM
Attachments: 51D48006-FC71-4F0A-B3F9-0D0B197771BA.tiff

Hi Rose

Thank you for sharing this

I will try to be on the call[cid:51D48006-FC71-4F0A-B3F9-0D0B197771BA]

I wanted to put some thoughts on paper about this issue

The key paragraph as I read the document was middle paragraph of page 11

This says that there was significant data from past studies about oxygen toxicity regarding outcomes including death

Secondly many studies – such as the study from Cedars – Chow et al relating their experience with lowering the SpO2 level – did NOT report any toxicity including death, with SpO2 limits as low as 83% and nor did the review by Win Tin using SpO2 limits as low as 70%

We did base the known risks based on the actual risks available from then current literature which did not include increased death.

Indeed the studies of death where before the clinical measurements of SpO2 in neonatal practice. I am not even sure if there where studies evaluating mortality using transcutaneous measurements of PaO2

The stimulus for the trial was that many units where moving to use lower SpO2 limits as noted above, without any data about the longer term outcomes, and that this was becoming an accepted standard of care

It is interesting that the increased death rate in the smaller strata associated with the surfactant arm, was not commented upon

There was no preceding data which had indicated that surfactant use was associated with more death than CPAP before SUPPORT.

My take on their final comments is that the wording on all of our consents moving forward is that under general risks where we state that " Some unknown risks may be learned during the study "– should be modified to say that "some unknown risks including death may be learned during the study"

Indeed we learned this both for the oxygen arm and the CPAP arm.

We based our discussion of risks on the available current literature and current clinical practice– The only data regarding death and altered oxygen levels was from the 1950s and at that time there was no understanding of the concept of measuring continuous SpO2, nor was there data about such risks and SpO2 values

I would argue that we met the requirements of CFR#45 for consent – death was not a known risk for differing SpO2 levels which we where investigating, and we did indicate that there where possibly unknown risks

The completed trial, as planned, has now described these risks for future studies

I regret that UAB was singled out – as we where all involved

I trust that they will provide an adequate response

Regards

Neil

rom: <Higgins>, Rosemary Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>
Date: Tuesday, February 19, 2013 6:25 AM
To: "Wally Carlo (wacarlo@uab.edu<mailto:wacarlo@uab.edu>)" <wacarlo@uab.edu<mailto:wacarlo@uab.edu>>, UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>, "Michele Walsh (mcw3@cwru.edu<mailto:mcw3@cwru.edu>)" <mcw3@cwru.edu<mailto:mcw3@cwru.edu>>, Wade Rich <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>, Marie Gantz <mgantz@rti.org<mailto:mgantz@rti.org>>, Abbot Laptook <ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>>, "Bradley.yoder@hsc.utah.edu<mailto:Bradley.yoder@hsc.utah.edu>" <Bradley.yoder@hsc.utah.edu<mailto:Bradley.yoder@hsc.utah.edu>>, Roger Faix <Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>>, Abhik Das <adas@rti.org<mailto:adas@rti.org>>, Ken Poole <poo@rti.org<mailto:poo@rti.org>>, "kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>" <kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>>, nancy newman <nxs5@case.edu<mailto:nxs5@case.edu>>, Ambal <ambal@uab.edu<mailto:ambal@uab.edu>>, "Frantz, Ivan" <Ivan.Frantz@childrens.harvard.edu<mailto:Ivan.Frantz@childrens.harvard.edu>>, Stoll Barbara <barbara_stoll@oz.ped.emory.edu<mailto:barbara_stoll@oz.ped.emory.edu>>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu<mailto:Anthony.Piazza@oz.ped.emory.edu>)" <Anthony.Piazza@oz.ped.emory.edu<mailto:Anthony.Piazza@oz.ped.emory.edu>>, Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>>, "Brenda Morris (morrish1@tmfhs.org<mailto:morrish1@tmfhs.org>)" <morrish1@tmfhs.org<mailto:morrish1@tmfhs.org>>, "kathleen.a.kennedy@uth.tmc.edu<mailto:kathleen.a.kennedy@uth.tmc.edu>" <kathleen.a.kennedy@uth.tmc.edu<mailto:kathleen.a.kennedy@uth.tmc.edu>>, Jon Tyson <Jon.E.Tyson@uth.tmc.edu<mailto:Jon.E.Tyson@uth.tmc.edu>>, "Laroia, Nirupama" <Nirupama_Laroia@URMC.Rochester.edu<mailto:Nirupama_Laroia@URMC.Rochester.edu>>, Dale Phelps <Dale_Phelps@URMC.Rochester.edu<mailto:Dale_Phelps@URMC.Rochester.edu>>, Brenda Poindexter <bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>>, Michael Cotten <cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>>, "Duke. Edu;" <goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>>, Krisa Van Meurs <vanmeurs@stanford.edu<mailto:vanmeurs@stanford.edu>>, "Duara, Shahnaz (SDuara@med.miami.edu<mailto:SDuara@med.miami.edu>)" <SDuara@med.miami.edu<mailto:SDuara@med.miami.edu>>, Stevenson David <dstevenson@stanford.edu<mailto:dstevenson@stanford.edu>>, " (Vivek.Narendran@cchmc.org<mailto:Vivek.Narendran@cchmc.org>)" <Vivek.Narendran@cchmc.org<mailto:Vivek.Narendran@cchmc.org>>, "Sood, Beena [bsood@med.wayne.edu<mailto:bsood@med.wayne.edu>]" <bsood@med.wayne.edu<mailto:bsood@med.wayne.edu>>, Seetha Shankaran <sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>>, "moshea@wfubmc.edu<mailto:moshea@wfubmc.edu>" <moshea@wfubmc.edu<mailto:moshea@wfubmc.edu>>, Edward Bell <edward-bell@uiowa.edu<mailto:edward-bell@uiowa.edu>>, "Ehrenkranz@Yale. Edu" <richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>>, "kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>" <kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>>, "carl_dangio@urmc.rochester.edu<mailto:carl_dangio@urmc.rochester.edu>" <carl_dangio@urmc.rochester.edu<mailto:carl_dangio@urmc.rochester.edu>>
Cc: "mcunningham@rti.org<mailto:mcunningham@rti.org>" <mcunningham@rti.org<mailto:mcunningham@rti.org>>, Kristin Zaterka-Baxter <kzaterka@rti.org<mailto:kzaterka@rti.org>>, Jenna Gabrio <jgabrio@rti.org<mailto:jgabrio@rti.org>>, "Lewis-Evans, Amanda (alewis@rti.org<mailto:alewis@rti.org>)" <alewis@rti.org<mailto:alewis@rti.org>>, Stephanie Archer <archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>>, Carolyn Petrie <petrie@rti.org<mailto:petrie@rti.org>>
Subject: SUPPORT

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose

From: Das, Abhik
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wallace, Dennis; Zaterka-Baxter, Kristin
Subject: RE: Response Letter
Date: Tuesday, February 19, 2013 1:20:39 PM
Attachments: RESPONSE LETTER dated 2-18-13 AD.doc

Wally:

This is a great draft. Here are some comments and suggested changes.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, February 18, 2013 4:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: FW: Response Letter

Hi Rose and Abhik:

I have reviewed the letter from OHRP and read again many related papers.

Enclosed is the draft of my response.

I think we should improve this document and send it to the SC members for revision/approval. I think it should be supported also by the DSMB and the NICHD leadership as well as RTI and UAB officials.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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From: Kathryn Fallon
Sent: Monday, February 18, 2013 3:26 PM
To: Wally Carlo, M.D.
Subject: Response Letter

In response to the letter dated February 8, 2013 sent to Dr. Marchase (UAB) and Mr. Saz (RTI) we would like to respectfully submit a rebuttal several of its contents and interpretations.

Historical Background

The summary statement on page 4 of the review of the literature states that, "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 affects the likelihood of a preterm infant developing ROP and other aspects of morbidity and mortality."

The evidence of increased mortality with restriction of oxygen was based on a practice that restricted oxygen supplementation to $\leq 50\%$ FiO_2 regardless of the condition of the preterm infants. This was tested in the 1950s which in a study that included few extremely preterm infants, which were those enrolled in whereas the SUPPORT trial only enrolled extremely preterm infants. The unrestricted oxygen policy provided oxygen routinely for 28 days at over 50% concentration. This is no longer standard clinical practice in US NICUs, and was not a practice tested in the SUPPORT trial. Notice that the references used in the "Historical Background" are for 1956 (ref. 4), 1973 (ref. 5), and 1984 (ref. 6). Reference 8 states, "marked variability in opinion exists." but does not include references to support the statement.

Comment [AD1]: Can we use less technical phrasing?

Comment [AD2]: Perhaps also add a couple of sentences to summarize the vast changes in neonatal practice and results since the 1950s, and why old results are no longer relevant?

The appropriate prior evidence used for the design of the SUPPORT trial are the following cohort studies:

The study by Tin et al. was the highest level of evidence study testing targets less than 95% before SUPPORT was performed (ref.). The Tin study was a multicenter population-based prospective study of infants <28 weeks (just like SUPPORT). The Tin study was the only one with follow-up assessments which included at least 10 months of age.

The policy for saturation alarm limits and targets varied between the centers. ROP was decreased in the 70-90% saturation target patients **without a difference in survival (51.6% survival in the 70-90% O_2 saturation target group vs. 51.7% in 84-95% group, Table 1).**

Table 1.

Saturation Alarm Targets	N	Survival	Survival with ROP	Survival with Cerebral Palsy
70-90%	126	51.6%	6.2%	15.4%
84-95%	319	51.7%	15.8%	15.5%
88-98%	123	52.8%	27.7%	16.9%

It should be noted that impaired neurodevelopmental outcome was not higher with saturation targets as low as 70-90%. Furthermore, not a single case of blindness was reported in infants at targets up to 95% despite the difference in ROP.

The Chow et al. study (ref.) was a single center prospective study to assess the impact of implementation of an oxygen monitoring and administration policy for VLBW infants. Lowering saturation targets to 83-93% compared to a previous period with targets 90-98%

Comment [AD3]: Do we need to spell out?

decreased severe ROP from 12.5% to 2.5% and decreased the need for ROP laser treatment from 4.5% to 0%. Over the years of the study, there was a trend for **increased survival following implementation of the restriction of oxygen policy** (contrary to what we found in SUPPORT). Survival improved from 48 to 75% in the infants 500-749 g and for 74 to 81% in the infants 750-999 g from 1997 to 2001. The policy was changed in the middle of 1998 (Table 2).

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Table 2.

Birth Weight (g)	1997		1998		1999		2000		2001		Total	
	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival	n	%Survival
500-749	14	48	15	40	18	73	15	87	12	75	74	58
750-999	25	74	27	78	18	78	21	82	17	81	108	83
1000-1249	24	88	20	100	26	96	28	100	21	94	119	95
1250-1500	29	97	27	100	26	100	28	100	36	97	146	99
Total	92	81	89	83	88	85	92	93	86	90	447	86

Other studies that assessed BPD and growth suggested benefits from lower oxygen saturation targets (ref). It should be noted that these studies targeted saturations above 95% which was not the goal of the study.

These studies suggested that lower oxygen saturation targets would lead to a decrease in ROP, decreased BPD, and decreased poor growth, and there was no conclusive evidence from relevant prior literature without that we could see an increase in death or other serious morbidity.

Based on these and other studies, many clinicians started to recommend lower oxygen saturation targets and developed educational programs promoting the same. The most prominent program was developed by Dr. Jay Goldsmith from Oschner Clinic (ref?). In this program, saturation targets of 85 to 93% were recommended. The benefits stated were decreased ROP, decreased days on a ventilator and on oxygen, and decreased hospitalization duration. Risk for adverse effects or increased mortality were not included in the materials.

Summary

Thus, in summary, the existing published data that is pertinent when the SUPPORT Trial was designed and conducted did not indicate any evidence to support an effect on mortality or blindness in either treatment group. Other morbidities had not been reported in the published studies.

Four other multicenter trials were designed after the SUPPORT trial was conceived. These trials were led by investigators based in the United Kingdom, Australia, New Zealand, and Canada/US. These protocols were also designed without the expectation of increased mortality in the lower oxygen saturation group.

Thus, the SUPPORT consent form was appropriately written based on the relevant knowledge available at the time. Furthermore, throughout the trial, survival was better than the historical reference group used prospectively to monitor the trial by the independent Neonatal Research Network (NRN) DSMC and the Global Network NRN Steering Committee. Rates of morbidities and mortality compared to historic controls were reviewed during each quarterly meeting and

Comment [AD4]: Are we referring to DSMC or subcommittee meetings?

found to be lower than the historical reference group. Concurrent controls had a mortality rate of 24.1% compared to infants in the higher saturation group (16.2%) and infants in the lower oxygen saturation group (19.9%) although these differences ~~became not significant in a logistic regression model~~ were not statistically significant in adjusted regression analyses.

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Subject: SUPPORT
Date: Tuesday, February 19, 2013 9:25:00 AM
Attachments: DHHS_FWA_5960_SUPPORT11.pdf

Hi

The attached letter was sent to UAB and RTI. We will discuss on Tuesday February 26 at 3 PM ET on the Standing Steering Committee call as the first agenda item.

For co-authors who are no longer full NRN sites, we invite you to the discussion.

The call in number is:

(b)(6) with pass code (b)(6)

Rose



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of the Assistant Secretary for Health

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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 Mr Sax:

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)

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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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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>.

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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-Smith, 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.”).

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

E. Ward Sax, M.B.A. -- Research Triangle Institute

February 8, 2013

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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Richard B. Marchase, Ph.D. -- University of Alabama at Birmingham
E. Ward Sax, M.B.A. -- Research Triangle Institute
February 8, 2013

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

E. Ward Sax, M.B.A. -- Research Triangle Institute

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: Das, Abhik
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Response Letter
Date: Monday, February 18, 2013 5:20:41 PM

Have you shared this with your IRB?

Thanks
Abhik

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

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Monday, February 18, 2013 04:34 PM Eastern Standard Time
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: FW: Response Letter

Hi Rose and Abhik:

I have reviewed the letter from OHRP and read again many related papers.

Enclosed is the draft of my response.

I think we should improve this document and send it to the SC members for revision/approval. I think it should be supported also by the DSMB and the NICHD leadership as well as RTI and UAB officials.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Kathryn Fallon
Sent: Monday, February 18, 2013 3:26 PM
To: Wally Carlo, M.D.
Subject: Response Letter

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "bpoindex@iu.edu"
Subject: Re: DHSS letter re. research protections violations (IUSM subcontract)
Date: Monday, February 18, 2013 4:49:12 PM

Can we discuss in the am?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

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

From: Poindexter, Brenda B [mailto:bpoindex@iu.edu]
Sent: Monday, February 18, 2013 04:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: DHSS letter re. research protections violations (IUSM subcontract)

Ok - our dean of research wants me to respond by tomorrow...

Sent from my iPhone

On Feb 18, 2013, at 4:32 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> This will be on the SC agenda for 2/26 call.
>
> As you know, OHRP had requested all of the consent forms from NICHD for the SUPPORT study which you previously provided.

>
> Rose

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

>
> ----- Original Message -----
> From: Poindexter, Brenda B [mailto:bpoindex@iu.edu]
> Sent: Monday, February 18, 2013 04:08 PM
> To: Higgins, Rosemary (NIH/NICHD) [E]
> Subject: FW: DHSS letter re. research protections violations (IUSM subcontract)

>
> Rose,
> I just received this from our Office of Research Administration. I know that this was previously discussed when the inquiry was limited to just Wally's site. It appears that they have expanded this to include all NRN sites that participated in SUPPORT. Our University is requesting additional information. Is there already a statement that was drafted by NICHD? Perhaps we need a steering committee discussion if everyone received this?

> Thanks, Brenda

>
> -----Original Message-----
> From: Axe, Shawn L
> Sent: Monday, February 18, 2013 4:00 PM
> To: Poindexter, Brenda B; Wilson, Leslie Dawn
> Subject: FW: DHSS letter re. research protections violations (IUSM subcontract)
> Importance: High

>
> Hi,
> Dr. Jose received the attached correspondence from OHRP today about the SUPPORT trial.
> Could one of you give me a call when you have a few minutes?

- > Thank you,
- > Shawn
- >
- > Shawn Axe, CIP
- > Associate Director - Team 1
- > IU Human Subjects Office
- > Office of Research Administration
- > Indiana University
- > 980 Indiana Avenue | Lockefield Room 3322 Indianapolis, IN 46202
- > (317) 278-9211
- > <mailto:saxe@iu.edu>
- >
- >

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) (E); Wally Carlo, M.D.
Subject: FW: DHHS doc ----CONFIDENTIAL
Date: Thursday, February 14, 2013 10:15:54 AM

FYI

From: Das, Abhik
Sent: Tuesday, February 12, 2013 10:13 PM
To: Wallace, Dennis; Zaterka-Baxter, Kristin
Subject: RE: DHHS doc ----CONFIDENTIAL

I fully agree, this is just second guessing with the benefit of hindsight. And it is incredulous to me that 23 IRBs across the country from premier institutions all got it wrong!

Thanks
Abhik

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

From: Wallace, Dennis
Sent: Tuesday, February 12, 2013 08:38 PM Eastern Standard Time
To: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: DHHS doc ----CONFIDENTIAL

Abhik and Kris,

I did take half an hour and read through the materials last night. I actually found the whole thing quite interesting in that the entire trial was conducted within the oxygen saturation that reflects standard of care, yet the finding was that the participants should have been informed that the risks in the two arms were different (or at least potentially different). Based on my reading, I'm not sure that I agree with that finding. In fact if that finding were true, then adequate clinical information should have been available to make a decision to narrow the acceptable range for standard of care without the trial and the document also found that the trial was needed. Those two positions seem to me to be inconsistent.

Dennis

From: Das, Abhik
Sent: Tuesday, February 12, 2013 10:32 AM
To: Zaterka-Baxter, Kristin; Wallace, Dennis
Subject: RE: DHHS doc ----CONFIDENTIAL

They already have all the site consents; they got them from NICHD.

From: Zaterka-Baxter, Kristin
Sent: Monday, February 11, 2013 8:40 PM
To: Wallace, Dennis; Das, Abhik
Subject: RE: DHHS doc ----CONFIDENTIAL

Of course this needs to go to Rose given Juesta's ok but we are not the IRB of record for the NRN but

perhaps because we enter data in clinicaltrials.gov, it may appear we are. It seems like they are looking at the consent language (risks/benefits) in retrospect to analysis of the main trial and meta analysis more so than previous data published. In any respect, per the RFA and our NGA, RTI's sole function is to track IRB approvals. However, the NICHD P&P has this to say (NRN requirements, not necessarily OHRP – could just be splitting hairs):

Coordinators and/or Research Project Assistants

DCC coordinators and research project assistants work closely with the DCC PI to implement Steering

Committee decisions. They assist with obtaining and maintaining required IRB approvals, reviewing

the clinical sites' IRB consent forms for compliance with Network requirements, gathering documentation for IND applications and applying for Certificates of Confidentiality.

We do have all copies of sites IRB approval for SUPPORT and I need to check about all consents since this time was prior to *NICHD* requesting we somewhat officially obtain those as well as approvals but can certainly request them if needed.

Thanks,

Kris

From: Wallace, Dennis

Sent: Monday, February 11, 2013 5:14 PM

To: Caddell, Juesta M.; Zaterka-Baxter, Kristin; Das, Abhik

Subject: RE: DHHS doc ----CONFIDENTIAL

Juesta,

Thanks. I've printed the documents and will review them this evening.

Dennis

From: Caddell, Juesta M.

Sent: Monday, February 11, 2013 5:12 PM

To: Wallace, Dennis; Zaterka-Baxter, Kristin; Das, Abhik

Cc: Sax, E. Ward

Subject: FW: DHHS doc ----CONFIDENTIAL

CONFIDENTIAL—DO NOT FORWARD WITHOUT PERMISISON FROM CADDELL

Dennis, Kris and Abhik:

Please see the attached letter from OHRP that was received in the IRB office today. This is a follow up to an inquiry that was received earlier about the SUPPORT trial. I would like to discuss with you all. When the original inquiry came about this, we communicated with OHRP by e-mail and the RTI IRB was told that we did not need to respond. We subsequently sent a follow up message offering to help facilitate collection of the site consents if directed by the Steering Committee to do so. To my knowledge we never got a response to that offer—Dave Borasky left shortly thereafter so unless

the message was sent only to him and not to me there has been no response.

So I would like to discuss:

- Did other participating sites provide copies of their consents, was the DCC involved in collating those etc.
- To your knowledge have other sites gotten communication from OHRP regarding this and are they expected to respond as well or is UAB the only one.

I will then follow up with OHRP, but I would like to know what is going on behind the scenes before I do so.

Ward this is just an FYI for you.

Juesta M. Caddell, Ph.D.

Director, Office of Research Protection
RTI International/3040 Cornwallis Rd/RTP, NC 27709
Phone: 919.541.6523 Fax: 919.316.3897
E-mail: jmc@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"; "adas@rti.org"; "kzaterka@rti.org"; "dwallace@rti.org"
Subject: Re: Call
Date: Wednesday, February 13, 2013 2:16:16 PM

We will do this at 10 am, Feb 14.

Call in

(b)(6) with pass code (b)(6)

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

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

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, February 13, 2013 02:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'adas@rti.org' <adas@rti.org>
Subject: RE: Call

Both are ok with me.

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 13, 2013 1:04 PM
To: 'adas@rti.org'; Wally Carlo, M.D.
Subject: Call

I would like to have a call tomorrow if possible to discuss the communication from ohrp.

Let me know if 930 or 10 am would work?

Thanks

Rose

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

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:higginsr@rti.org)
To: ["adas@rti.org"](mailto:adas@rti.org)
Subject: Re: Call
Date: Wednesday, February 13, 2013 2:06:39 PM

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

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

From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Wednesday, February 13, 2013 02:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>
Subject: RE: Call

10 am works for me. Both Kris and Dennis at RTI have also seen this. Do you want me to ask them to join if they can?

Thanks

Abhik

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

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Wednesday, February 13, 2013 2:04 PM
To: Das, Abhik; 'wcarlo@peds.uab.edu'
Subject: Call

I would like to have a call tomorrow if possible to discuss the communication from ohrp.

Let me know if 930 or 10 am would work?

Thanks

Rose

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

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Re: SUPPORT
Date: Wednesday, February 13, 2013 9:50:08 AM

Had you received this document?

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, February 13, 2013 09:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT

Hi Rose.

Anytime tomorrow would be ok.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Wed, Feb 13, 2013 14:18:10 GMT+00:00
Subject: SUPPORT

Wally-

I would like to discuss with you and Abhik - do you have time tomorrow or Friday?
I am in San Francisco at a meeting and busy today until 330 PM PT.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: wcarlo@peds.uab.edu
Subject: SUPPORT
Date: Wednesday, February 13, 2013 9:16:19 AM
Attachments: [DHHS_FWA_5960_SUPPORT11.pdf](#)

Wally-

I would like to discuss with you and Abhik - do you have time tomorrow or Friday?
I am in San Francisco at a meeting and busy today until 330 PM PT.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)
Subject: Fw: as discussed
Date: Wednesday, February 13, 2013 9:06:08 AM
Attachments: [DHHS FWA 5960 SUPPORT11.pdf](#)

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, February 13, 2013 09:04 AM
To: blaisdellC@mail.nih.gov <blaisdellC@mail.nih.gov>
Subject: as discussed

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: blaisdelc@mail.nih.gov
Subject: as discussed
Date: Wednesday, February 13, 2013 9:04:30 AM
Attachments: [DHHS FWA 5960 SUPPORT11.pdf](#)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Maddox, Yvonne \(NIH/NICHD\) \[E\]](#)
Cc: [Ott, Sandra \(NIH/NICHD\) \[E\]](#)
Subject: Re: DHHS doc ----CONFIDENTIAL
Date: Wednesday, February 13, 2013 7:33:00 AM

I have given east coast times
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, February 13, 2013 07:17 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: Re: DHHS doc ----CONFIDENTIAL

Is that west coast time?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, February 13, 2013 07:14 AM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: Re: DHHS doc ----CONFIDENTIAL

I am only Available until 930 am this morning. I am open tomorrow except 11-1 pm
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 12, 2013 03:24 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: Re: DHHS doc ----CONFIDENTIAL

I am at an nichd workshop from 1030 am -7pm ET so before 1030 works.

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

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Tuesday, February 12, 2013 03:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: Re: DHHS doc ----CONFIDENTIAL

Tomorrow can work. We will send you some suggested times.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 12, 2013 01:36 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]

Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: Fw: DHHS doc ----CONFIDENTIAL

Yvonne

I would like to discuss with you at some point this week. I am in San Francisco at SMFM this week (perhaps early am Wednesday; or Thursday or Friday).

Dr. Das from RTI had contacted me late yesterday. I have not yet heard from Dr. Carlo.

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, February 12, 2013 01:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: DHHS doc ----CONFIDENTIAL

Rose:

Here is the scanned OHRP letter. Get a cup of coffee (or something stronger) before you sit down with it! Do you know if other NRN sites faced the same enquiry as UAB? I seem to remember Yale did, but don't know if there were others, or how they responded to OHRP.

Thanks

Abhik

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DHHS doc ----CONFIDENTIAL
Date: Tuesday, February 12, 2013 2:10:37 PM

I'm glad they are giving them an opportunity to respond.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 12, 2013 2:10 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re: DHHS doc ----CONFIDENTIAL

They are requesting a response from UAB by March 22.
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Tuesday, February 12, 2013 02:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DHHS doc ----CONFIDENTIAL

Uh-oh.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 12, 2013 1:37 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: Fw: DHHS doc ----CONFIDENTIAL

Yvonne

I would like to discuss with you at some point this week. I am in San Francisco at SMFM this week (perhaps early am Wednesday; or Thursday or Friday).

Dr. Das from RTI had contacted me late yesterday. I have not yet heard from Dr. Carlo.

Rose

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

From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Tuesday, February 12, 2013 01:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: DHHS doc ----CONFIDENTIAL

Rose:

Here is the scanned OHRP letter. Get a cup of coffee (or something stronger) before you sit down with it! Do you know if other NRN sites faced the same enquiry as UAB? I seem to remember Yale did, but don't know if there were others, or how they responded to OHRP.

Thanks

Abhik

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Subject: Document
Date: Tuesday, February 12, 2013 1:40:25 PM

I have the OHRP document we discussed this am - no need to scan or send

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

From: [Das, Abhik](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: FW: DHHS doc ----CONFIDENTIAL
Date: Tuesday, February 12, 2013 1:17:41 PM
Attachments: [DHHS_FWA_5960_SUPPORT.pdf](#)

Rose:

Here is the scanned OHRP letter. Get a cup of coffee (or something stronger) before you sit down with it! Do you know if other NRN sites faced the same enquiry as UAB? I seem to remember Yale did, but don't know if there were others, or how they responded to OHRP.

Thanks

Abhik



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: 240-453-8298
FAX: 240-453-6909
E-mail: Lisa.Buchanan@HHS.gov

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

E. Ward Sax, M.B.A.
V.P., Treasurer and Chief Risk Officer
Research Triangle Institute
3040 Cornwallis Road, P.O. Box 12194
Research Triangle Park, NC 27709-2194

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 Mr Sax:

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)

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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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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>.

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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.").

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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 (SpO_2), which is the percentage of hemoglobin in the infant's bloodstream that has oxygen bound to it. The amount of oxygen provided to the infant would then be adjusted to try to keep the SpO_2 within one of two discrete ranges of oxygen levels, *i.e.*, a "low" range of 85% to 89%, or a "high" range of 91% to 95%. Infants were randomly assigned to the low or the high range.

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

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

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

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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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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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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

Page 14 of 14

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

E. Ward Sax, M.B.A. -- Research Triangle Institute

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: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: ["adas@rti.org"](mailto:adas@rti.org)
Subject: Re: SUPPORT OHRP communication
Date: Monday, February 11, 2013 6:44:31 PM

I have not received anything from them but am out of the office
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

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

From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Monday, February 11, 2013 06:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT OHRP communication

Rose

I am sure you have seen this rather disturbing document?

Thanks

Abhik

Abhik Das
Senior Research Statistician
RTI International

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Cc: "doctorlevan@gmail.com"
Subject: RE: Question re poster
Date: Sunday, February 10, 2013 8:29:55 AM

Rose

Thanks a lot for your response,

Luc

Luc P. Brion, MD

Professor of Pediatrics

Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern
Medical Center at Dallas

5323 Harry Hines Boulevard, STOP 9063

Dallas, TX 75390-9063

Office: (214) 648-2835

Fax: (214) 648-2481

luc.brion@utsouthwestern.edu

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

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Sunday, February 10, 2013 7:16 AM
To: Luc Brion; Archer, Stephanie (NIH/NICHD) [E]
Cc: 'doctorlevan@gmail.com'
Subject: Re: Question re poster

Yes

Stephanie will send early in the week

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

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

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Sunday, February 10, 2013 07:19 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: doctorlevan@gmail.com <doctorlevan@gmail.com>
Subject: Question re poster

Rose

Is there a template to include in the poster for the PAS presentation for the NRN?

Luc

Sent from my iPhone

UT Southwestern Medical Center
The future of medicine, today.

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); mcunningham@rti.org
Subject: FW: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, February 08, 2013 9:05:00 AM
Attachments: [PAS2013EnrollmentDispositionLetter.pdf](#)

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]
Sent: Thursday, February 07, 2013 5:53 PM
To: Susan Hintz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT Enrollment accepted for Poster Presentation. See attached.

Yvonne



PAS PROGRAM OFFICE
3400 Research Forest Dr., Ste. B7
The Woodlands, TX 77381
Phone: (281) 419-0052 * Email: info@pas-meeting.org * www.pas-meeting.org

February 7, 2013

Yvonne Vaucher
yvaucher@ucsd.edu

RE: Antenatal Enrollment in Clinical Trials: Is Neurodevelopmental Outcome Representative? (Abstract #: 750115)

Dear Dr. Yvonne Vaucher:

The abstract listed below has been selected for a POSTER PRESENTATION 2013 Pediatric Academic Societies' Annual Meeting in Washington, DC, May 4-7. On behalf of the PAS Program Committee, we would like to thank you for your submission and extend our congratulations!

ABSTRACT TITLE: Antenatal Enrollment in Clinical Trials: Is Neurodevelopmental Outcome Representative?
PRESENTING AUTHOR: Yvonne Vaucher
PUBLICATION NUMBER: 3832.545
SESSION:** 3832 - Neonatology - General
SESSION DATE & TIME: Monday, May 6, 2013, 4:15 pm- 7:30 pm
ROOM: Hall D/E (Walter E. Washington Convention Center)
BOARD NUMBER: 545 (This number will be provided for you)

**In some cases, abstracts were moved from the author-designated theme or subspecialty to another to enhance scientific interchange. If you have questions about your abstract, please email info@pas-meeting.org or call the phone number listed above.

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For onsite assistance inquire at the PAS Information Desk at the Walter E. Washington Convention Center. Please be sure to read and adhere to the "Presenter Policies" available here: <http://www.pas-meeting.org/2013DC/CME/Index.asp>. Feel free to review and update your disclosures here: http://www.call4abstracts.com/pas_disclosure.

Once again, congratulations! We look forward to welcoming you to Washington, DC.

Sincerely,
The Pediatric Academic Societies



From: Cunningham, Meg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, February 08, 2013 8:53:40 AM

She sent an attachment in an original email, can you send this to me?

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 08, 2013 8:27 AM
To: 'Vaucher, Yvonne'; Susan Hintz
Cc: 'Finer, Neil'; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Congratulations!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, February 07, 2013 5:53 PM
To: Susan Hintz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT Enrollment accepted for Poster Presentation. See attached.

Yvonne

From: Luc Brion
To: doctortevan@gmail.com
Cc: Rashmin Savani; Higgins, Rosemary (NIH/NICHD) [E]; "wrage@rti.org"
Subject: Fwd: 2013 PAS and/or ESPR Abstract Notification
Date: Friday, February 08, 2013 6:03:48 AM

Congratulations !
Thanks for your hard work!
Luc

Sent from my iPhone

Begin forwarded message:

From: Sandra Varley <svarley@coetruman.com>
Date: February 7, 2013, 4:15:38 PM CST
To: "luc.brion@utsouthwestern.edu" <luc.brion@utsouthwestern.edu>
Subject: 2013 PAS and/or ESPR Abstract Notification

RE: 2013 PAS and/or ESPR Abstract Notification (#750229)

Dear Dr. Brion:

Thank you for submitting your abstract entitled "Changes in Therapy and Outcomes Associated with the Support Trial", abstract #750229, to the 2013 Pediatric Academic Societies' Annual Meeting, May 4-7, in Washington, DC and/or the 2013 Eastern SPR Annual Meeting, March 22-24, in Philadelphia, PA. We are pleased to inform you that your abstract has been selected for presentation.

For your official acceptance letter, which contains the PAS and/or ESPR presentation information and presentation instructions, please go to the following website. You will not receive this information via mail.

Website: <http://www.call4abstracts.com/pas>
Username: lucbrion

If you have forgotten your password, please select the "Forgot Password" button on the left side of the submission site to retrieve this information.

If you have any questions, please feel free to contact Coe-Truman Technologies Technical Support at 507-403-2305 or c4asupport@coetruman.com. If you have any questions regarding the presentation itself after viewing your acceptance letter, please contact the PAS Central Office at info@pas-meeting.org.

Sincerely,

Coe-Truman Technologies, Inc.
for the Pediatric Academic Societies and Eastern SPR

UT Southwestern Medical Center
The future of medicine, today.

From: Luc Brion
To: doctorlevan@gmail.com; Wraga, Lisa Ann
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Jameelah Shaheed
Subject: PAS Presentation notification letter
Date: Friday, February 08, 2013 5:11:39 AM
Attachments: Jackie LeVan PAS 2013 NRN disp letter.pdf

Jackie and Lisa;
Congratulations!
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal
Medicine
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063

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luc.brion@utsouthwestern.edu

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PAS 20 3 **PEDIATRIC ACADEMIC SOCIETIES**
DC **ANNUAL MEETING**
MAY 4 - MAY 7

PAS PROGRAM OFFICE
3400 Research Forest Dr., Ste. B7
The Woodlands, TX 77381
Phone: (281) 419-0052 * Email: info@pas-meeting.org * www.pas-meeting.org

February 7, 2013

Luc Brion
luc.brion@utsouthwestern.edu

RE: Changes in Therapy and Outcomes Associated with the Support Trial (Abstract #: 750229)

Dear Dr. Luc Brion:

The abstract listed below has been selected for a POSTER PRESENTATION 2013 Pediatric Academic Societies' Annual Meeting in Washington, DC, May 4-7. On behalf of the PAS Program Committee, we would like to thank you for your submission and extend our congratulations!

ABSTRACT TITLE: Changes in Therapy and Outcomes Associated with the Support Trial
PRESENTING AUTHOR: Jaclyn LeVan
PUBLICATION NUMBER: 2924.474
SESSION**: 2924 - Neonatology - General
SESSION DATE & TIME: Sunday, May 5, 2013, 4:15 pm - 7:30 pm
ROOM: Hall D/E (Walter E. Washington Convention Center)
BOARD NUMBER: 474 (This number will be provided for you)

**In some cases, abstracts were moved from the author-designated theme or subspecialty to another to enhance scientific interchange. If you have questions about your abstract, please email info@pas-meeting.org or call the phone number listed above.

No audiovisual, projections, or computer equipment requiring electrical power, are permitted in the poster session area

For onsite assistance inquire at the PAS Information Desk at the Walter E. Washington Convention Center. Please be sure to read and adhere to the "Presenter Policies" available here: <http://www.pas-meeting.org/2013DC/CME/Index.asp>. Feel free to review and update your disclosures here: http://www.call4abstracts.com/pas_disclosure.

Once again, congratulations! We look forward to welcoming you to Washington, DC.

Sincerely,
The Pediatric Academic Societies



From: [Cunningham, Meg](#)
To: [Kirpalani, Haresh](#); [Johnson, Karen \(Pediatrics\)](#); [Bell, Edward \(Pediatrics\)](#)
Cc: [Chaudhary, Aasma](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: Congratulation!
Date: Thursday, February 07, 2013 4:47:21 PM

OK, I will get this out tomorrow. I was working out the wording for the TOP06 with the programmers today and we just now finalized it.

Thanks,
Meg

From: [Kirpalani, Haresh \[mailto:KIRPALANIH@email.chop.edu\]](mailto:KIRPALANIH@email.chop.edu)
Sent: Thursday, February 07, 2013 4:42 PM
To: [Cunningham, Meg](#); [Johnson, Karen \(Pediatrics\)](#); [Bell, Edward \(Pediatrics\)](#)
Cc: [Chaudhary, Aasma](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kinnaird, Jill](#)
Subject: RE: Congratulation!

Hi Meg:

I think we should just get the places we have agreement on – out. I am anxious that those sites who have deferred to IRB should get going.

Including i.e. the defs on the points 5 and 6) are clarified – and Ed had responded to my straw-man – should get out.

I think this respiratory thing can go later, and should be OK. I am having that call with Ed tomorrow – so that we are both on the same page for this resp support.

Hi KAREN:

What you outline is what I will advocate.

Cheers H

From: [Cunningham, Meg \[mailto:mcunningham@rti.org\]](mailto:mcunningham@rti.org)
Sent: Thursday, February 07, 2013 3:45 PM
To: [Johnson, Karen \(Pediatrics\)](#); [Bell, Edward \(Pediatrics\)](#); [Kirpalani, Haresh](#)
Cc: [Chaudhary, Aasma](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kinnaird, Jill](#)
Subject: RE: Congratulation!

Will this be changing the memo I am preparing. I was hoping to send this tomorrow!

From: [Johnson, Karen \(Pediatrics\) \[mailto:karen-johnson@uiowa.edu\]](mailto:karen-johnson@uiowa.edu)
Sent: Thursday, February 07, 2013 2:05 PM
To: [Bell, Edward \(Pediatrics\)](#); [Kirpalani, Haresh](#)
Cc: [Chaudhary, Aasma](#); [Cunningham, Meg](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kinnaird, Jill](#)
Subject: RE: Congratulation!

I would like to outline all possible scenarios and be sure I have it right:
On any ventilator, regardless of FiO2 = "On Respiratory Support"
On CPAP, regardless of FiO2 = "On Respiratory Support"
On Nasal SIMV, regardless of FiO2 = "On Respiratory Support" ???
On Nasal Cannula of >1LPM, regardless of FiO2 = "On Respiratory Support"

On Nasal Cannula of ≤ 1 LPM, regardless of FiO₂ = "NO Respiratory Support"
Obviously, on nothing = "NO Respiratory Support"

So, when does an FiO₂ of < 0.35 come into play?

Karen

Karen Johnson, RN
Neonatal Research Network Coordinator
Pediatrics, Neonatology
8900 JPP
University of Iowa Children's Hospital
Iowa City, Iowa 52242
(319) 356-2924
pager (b)(6)

"Everyone who's ever taken a shower has an idea. It's the person who gets out of the shower, dries off and does something about it who makes a difference."

--Nolan Bushnell,
American engineer and entrepreneur

From: Bell, Edward (Pediatrics)
Sent: Thursday, February 07, 2013 12:56 PM
To: Kirpalani, Haresh; Johnson, Karen (Pediatrics)
Cc: Chaudhary, Aasma; Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]; Kinnaird, Jill
Subject: RE: Congratulation!

I'm fine with however you want to do it. You've thought a lot about this. If you still want to call, anytime in the afternoon is OK. I'll tell Jill to page me if I'm not in my office.

From: Kirpalani, Haresh [mailto:KIRPALANIH@email.chop.edu]
Sent: Thursday, February 07, 2013 12:53 PM
To: Bell, Edward (Pediatrics); Johnson, Karen (Pediatrics)
Cc: Chaudhary, Aasma; Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Congratulation!

Hi Ed:

I don't really agree – can we talk this out? When can I call you tomorrow? The reason is that weaning of these kids is so often simply not done at those levels. I do not think it is necessarily because they "need" it.

The effective 'CPAP' they may be getting it really extremely variable.
Brad Yoder's data sets seem to corroborate this.

Anyway, room for discussion here I think. Is the am after your rounds OK?
Cheers H

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Thursday, February 07, 2013 1:43 PM
To: Johnson, Karen (Pediatrics); Kirpalani, Haresh
Cc: Chaudhary, Aasma; Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Congratulations!

I think that is respiratory support. The cannula is presumably being used because someone thinks it is providing some unmeasured CPAP.

From: Johnson, Karen (Pediatrics)
Sent: Thursday, February 07, 2013 12:39 PM
To: Kirpalani, Haresh; Bell, Edward (Pediatrics)
Cc: Chaudhary, Aasma; Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Congratulations!

Thank you!

I do have another question that I was asked.

It seems our definitions of "On Respiratory Support" and "No Respiratory Support" are still a little confusing. And, I think the part that is confusing folks is the FIO₂ >0.35. I had asked about the kid who is on <0.35, but on a vent or CPAP and Haresh clarified that he/she would be in the "On" group. Now, I have been asked about kids at the other end: what about a baby on 1 or more LPM NC who is receiving 0.21 O₂. Which group do they land in?

Thanks,

Karen

Karen Johnson, RN
Neonatal Research Network Coordinator
Pediatrics, Neonatology
8900 JPP
University of Iowa Children's Hospital
Iowa City, Iowa 52242
(319) 356-2924
pager (b)(6)

"Everyone who's ever taken a shower has an idea. It's the person who gets out of the shower, dries off and does something about it who makes a difference."

--Nolan Bushnell,
American engineer and entrepreneur

From: Kirpalani, Haresh [mailto:KIRPALANI@email.chop.edu]
Sent: Thursday, February 07, 2013 9:29 AM
To: Bell, Edward (Pediatrics); Johnson, Karen (Pediatrics)
Cc: Chaudhary, Aasma; Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Congratulations!

I heard that the first Iowa kid is into TOP – well done!

H

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From: [Kathy Arnell](#)
To: ["Rich, Wade"; Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: Support
Date: Wednesday, January 30, 2013 4:42:40 PM
Attachments: [IRB approv & consents.pdf](#)

Hi Rose,

This would have been our last approved English consent in Aug. 2008. The study was closed to enrollment at our site on Feb. of 2009.

(You will see the Spanish version attached also, however the Spanish version was amended in Dec. 2008).

Best regards,

Kathy Arnell, RNC-NIC

NICU Research

Sharp Mary Birch Hospital for Women and Newborns

3003 Health Center Drive

San Diego, CA 92123

858 939.4966

From: Rich, Wade [<mailto:wrich@ucsd.edu>]
Sent: Wednesday, January 30, 2013 7:56 AM
To: Kathy Arnell
Cc: higginsr@mail.nih.gov
Subject: Support

Can you send Rose Higgins your last approved SUPPORT consent ?

Tx.

wade



041093
09/17/2008
Rasmussen
4-15

September 19, 2008

Maynard Rasmussen, MD
Sharp Mary Birch Hospital for Women
3003 Health Center Drive
San Diego, CA 92123

**RE: IRB #041093; NICHD Protocol
The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants**

Dear Dr. Rasmussen:

The Sharp HealthCare (SHC) Institutional Review Board (IRB) reviewed and approved the above-referenced research activity for continuance at the September 17, 2008 meeting. Included in this review were the following items:

- Research Status Report (signed 06 AUG 2008)
-
- Informed Consent and PHI Authorization (8/1/2008)

This study is scheduled to undergo annual review at the September 16, 2009 IRB meeting. Approval for this study will expire if annual review is not conducted on or before September 20, 2008. Please provide a completed research status report to the SHC IRB Office no later than Friday, August 31, 2009 to assure timely review and continuation of this study.

Changes or amendments to the study protocol, informed consent documents, and to other study-related documents, as well as new documents, tools or advertisements to be utilized as part of this study, must be reviewed and approved by the IRB before changes are implemented.

Thank you and please feel free to contact Caryn Burgess, IRB Administrator, at (858) 499-4836 if you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "David Bodkin", followed by a flourish.

David Bodkin, M.D.
Chair, IRB
Sharp HealthCare

/clb

SHARP ORGANIZATIONS

San Diego Hospital Association Sharp Memorial Hospital Grossmont Hospital Corporation Sharp Chula Vista Medical Center
Sharp Coronado Hospital and HealthCare Center Sharp Mesa Vista Hospital Sharp Mary Birch Hospital For Women
Sharp Vista Pacifica Sharp Mission Park Medical Centers Sharp Rees-Stealy Medical Centers Sharp Health Plan
SCMG Corporation Sharp HealthCare Foundation Grossmont Hospital Foundation Coronado Hospital Foundation

8695 Spectrum Center Boulevard San Diego, California 92123-1489

SHARP Mary Birch
Hospital for Women

INFORMED CONSENT

**The Surfactant Positive Airway Pressure and
Pulse Oximetry Trial in Extremely Low Birth
Weight Infants**

**The SUPPORT Trial of the NICHD
Neonatal Research Network**

IRB # 041093

Revised August 1, 2008

PRINCIPAL INVESTIGATOR:

Maynard Rasmussen, MD

APPROVED

SEP 10 2008

Neonatal Research Network
Principal Investigator

SPONSOR:

National Institute of Child Health and Human Development (NICHD)
Neonatal Research Network

APPROVED

SEP 11 2008

Revised August 1, 2008

IRB #041093

Page 2 of 9

The Support Trial of the NICHD

Participation in a Research Study

The Neonatologists at Sharp Mary Birch Hospital for Women (SMBHW) and the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study in extremely premature infants to find out more about:

- 1) Treatment with Continuous Positive Airway Pressure (CPAP) - pressure applied with a face mask or nasal prongs to help babies breathe easier and keep their lungs from collapsing
- 2) The ideal range of Oxygen Saturation - the amount of oxygen in the blood

You are being asked to allow your baby to be in this study because there is a possibility he/she will be born 12 to 16 weeks early (24-28 weeks gestation). We need to tell you about the study so you can decide if you want your baby to participate. You need to know why we are doing the study, if there might be any risks for your baby, and what we will expect from you and your baby.

Why is this Study Being Done?

- 1) To compare the treatment of extremely premature infants in the delivery room who receive CPAP with infants who are treated with a breathing tube in the windpipe (trachea) and surfactant (a medication which keeps the lungs from collapsing) to see if either treatment results in healthier lungs.
- 2) To compare treatment with lower oxygen saturation range (85-89%) with higher range (91-95%) to determine if either range results in healthier eyes.

Both of these approaches may be beneficial. This study will help determine which of these treatments work the best and are the safest for premature infants.

A number of studies have suggested that the early use of CPAP and the avoidance of mechanical ventilation (assisting the baby's breathing with a breathing machine) are associated with:

- 1) A decreased need for treatment with surfactant (a natural substance extremely premature infants lack and which helps keep the lungs from collapsing)
- 2) A decreased risk of death or need for oxygen at 36 weeks post-conceptual age (for a baby born at 24 weeks gestation and who is 12 weeks old, his/her post-conceptual age is 36 weeks)

Currently the most extremely premature infants are treated with mechanical ventilation and surfactant. Many studies have shown that surfactant therapy is associated with:

- 1) A decreased risk of the lungs collapsing
- 2) A decreased risk of developing leaks in the lungs
- 3) A decreased risk of death or needing oxygen at 36 weeks post-conceptual age

Retinopathy of Prematurity (ROP) is a common eye problem in extremely premature infants, because the blood vessels that nourish their eyes have not fully developed. ROP may result in

APPROVED

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Children's Hospital of Pittsburgh

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impairment of vision or even blindness, which may be caused by excessive levels of oxygen. Blood oxygen saturation levels in premature infants are commonly maintained between 80-95%. The ideal oxygen saturation in these extremely low birth weight infants (ELBW) is unknown. This study will compare the outcomes of infants whose oxygen saturation target is 85-89% vs. those whose target is 91-95% to see if either target decreases the risk of ROP.

How Many Infants will be Enrolled?

We plan to enroll approximately 1300 babies at NICHD Neonatal Research Network hospitals over a two-year period. Approximately 50 infants will be enrolled here at SMBHW.

What Does Participation in This Study Involve?

If you agree for your baby to be in this study, the following will happen to him/her: Prior to delivery, your baby will be randomly assigned (chosen by chance like a flip of a coin) to one of two treatment strategies. The treatments are as follows:

- 1) CPAP in the delivery room immediately after birth and continuing in the NICU
- Or
- 2) Placement of a breathing tube in his/her trachea (windpipe) in the delivery room followed by surfactant administration and mechanical ventilation (breathing for the baby using a machine).

Your baby will also be randomly assigned to a study oximeter (an oxygen saturation monitor that displays how much oxygen is in the blood). These oximeters will assist us in maintaining your baby's oxygen saturation target. It will also record your baby's oxygen saturations until he/she reaches 36 weeks post-conceptual age or no longer needs extra oxygen.

Routine neonatal intensive care will be provided during your baby's participation in the study. Your baby will be followed in our Infant Follow-up clinic at 6 and 12 months as standard of care for small babies. At 18-22 months corrected age your baby will receive a complete exam of his/her muscles, nerves, and mental and coordinated movement skills.

How Long Will Your Baby be in the Study?

Your baby will be in the study until 18-22 months post-conceptual age.

What are the Risks of the Study?

Each of the study treatments is already being used by many doctors across the country, 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.

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Some unknown risks may be learned during the study. If these occur, study personnel will inform you.

The only other risk of the study is confidentiality. Every effort will be made to keep your baby's medical record information confidential. Your baby will not be identified in any report or publication about this study. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

Are There Benefits to Taking Part in the Study?

Your baby may or may not receive any direct benefit from taking part in this study. However, your participation in this study may help us learn about better ways to treat babies requiring assistance with breathing.

What about Confidentiality?

Study personnel at SMBHW will collect clinical information from your baby's chart. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute at Research Triangle Park, North Carolina. The study log linking the code number information with your baby's identity will be kept under lock and key at SMBHW. Research records will be kept confidential to the extent provided by law.

Organizations that may inspect and/or copy your baby's research records for quality assurance and data analysis include the following groups: the United States Food and Drug Administration (FDA), the Sharp HealthCare Institutional Review Board (IRB), the study sponsor NICHD Neonatal Research Network, and the Office for Human Research Protections (OHRP).

Protected Health Information (PHI)

As a part of this research study you will be asked to sign a separate document giving your permission to use and disclose your baby's medical records. This document will tell you who will view your baby's records, how they will be used and how long they will be needed. It will also tell you what you can do if you no longer agree to have your baby's medical records used. Your signature will give us permission to use your baby's records. You will receive a copy of the signed document.

What are the Costs?

It is anticipated that taking part in this study will not lead to added costs to you and your insurance company. The costs of diagnostic tests and the treatment of your baby will be your responsibility and/or that of your insurance carrier. Sharp HealthCare and the investigators will be partially reimbursed by the sponsor for time, effort and oversight by the professional staff to perform procedures, tasks, and accurately collect and submit data.

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Research Related Injury?

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds are available to compensate you in the event of injury. Sharp HealthCare will not provide any compensation to you in the event your baby sustains a research related injury while participating in this study.

What are My Rights as a Participant?

Taking part in this study is voluntary. You may choose for your baby not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you or your baby are entitled. A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your baby's health, welfare, or your willingness to keep your baby in this study.

What Alternatives to the Study do I Have?

As an alternative to participation in this study you may have the baby's doctor decide which treatment your baby will receive. If you decide not to include your baby in this study, none of his/her medical information will be included in the study. Participation in research is entirely voluntary. You may refuse for your baby to participate or withdraw at any time without jeopardy to the medical care your baby will receive at Sharp Mary Birch Hospital for Women or loss of benefits to which your baby is entitled. If you withdraw your baby from the study, the attending physician will decide whether to maintain the current treatment or to change it, based on your baby's needs at the time of the decision. Data collection for research purposes will stop at that time.

Your baby's participation in this study may be stopped if the doctor feels that it is in your baby's best interest medically, or if the FDA or the IRB stops the study.

Who do I Call If I Have Questions or Problems?

For questions about the study or a research related injury, contact the principal investigator, Maynard Rasmussen, MD, at (858) 939-4176.

For questions about your rights as a research participant or to address complaints about the research, contact David J. Bodkin, M.D., Chair of the Sharp HealthCare Institutional Review Board (a group of people who review the research to protect your rights) via the:

Sharp's Office for the Protection of Research Participants (IRB)
8695 Spectrum Center Boulevard
San Diego, California 92123
Phone: (858) 499-4836

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Signature

Your signature below indicates that you have read the above about the SUPPORT Trial and have had a chance to ask questions to help you understand what your baby's participation will involve. You agree for your baby to participate in the study until you decide otherwise. You are not waiving your legal rights by signing this consent form.

Signature of Parent (or Legally Authorized Representative)	Printed Name	Date
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Signature of Witness	Printed Name	Date
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I _____ attest that the requirements for informed consent for the medical research project described in this form have been satisfied – that the participant's parent has been provided with a copy of the California Experimental Subject's Bill of Rights, that I have discussed the research project with the participant's parent and explained to him or her in non-technical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant's parent to ask questions and that all questions asked were answered.

Signature of Investigator	Printed Name	Date
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APPENDIX

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CALIFORNIA EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked for your infant to participate as a subject in an experimental procedure. Before you decide whether you want to participate in the experimental procedure, you have a right to:

1. Be informed of the nature and purpose of the experiment;
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
3. Be given a description of any discomforts and risks reasonably to be expected from your participation in the experiment;
4. Be given an explanation of any benefits reasonably to be expected from your participation in the experiment;
5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to you, and their relative risks and benefits;
6. Be informed of the avenues of medical treatment, if any, available to you after the experimental procedure if complications arise;
7. Be given an opportunity to ask any questions concerning the medical experiment or the procedures involved;
8. Be instructed that consent to participate in the experimental procedure may be withdrawn at any time and that you may discontinue participation in the medical experiment without prejudice;
9. Be given a copy of this form and the signed and dated written consent form; and
10. Be given the opportunity to decide to consent or not to consent to the medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on your decision.

I have carefully read the information contained above and I understand fully my rights as a potential subject in a medical experiment involving people as subjects.

Signature of Parent or Legal Guardian

Signature of Witness

Date

Date

Authorization to Use your Protected Health Information (PHI)

Protected Health Information: PHI is any personal health information through which your baby can be identified. We are asking for your permission to use your baby's PHI in this research study. If you do not sign this form, your baby cannot participate in the study. Your baby's protected health information may include information about blood samples, physical examinations, medical history, diagnostic test such as x-rays, head ultrasound, eye examinations and other data collected or reviewed during the course of the study or prior to the study, as described in the consent form up to 18-22 months post-conceptual age.

Who will disclose your PHI?

- Maynard Rasmussen, MD, Sharp Mary Birch Hospital for Women, and Sharp HealthCare

Who will see your PHI?

- The sponsor of the research study *National Institute of Child Health and Human Development (NICHD) Neonatal Research Network*
- Government agency, *National Institute of Health*, or the Food and Drug Administration (FDA)
- Sharp HealthCare committees that review research to help protect people who join research studies.

How long will Sharp HealthCare use and share my baby's information, and what will it be used for?

- What information will be used? Study records including information about what occurred during delivery, procedures, tests, treatment that your baby had done before or during his/her hospital stay, and other medical information about your baby's participation in this study.
- How long will your baby's information be used and shared? This authorization will expire in 20 years. However, you have the right to cancel this authorization at any time. Once your baby's PHI is disclosed to the groups listed above, it will no longer be protected by federal privacy laws and may be redisclosed..

If you decide not to share your information anymore:

- You must write to the study doctor and tell him that you no longer want to share your information. Write to the study doctor at: Maynard Rasmussen, MD, Sharp Mary Birch Hospital for Women, Neonatology Department, 3003 Health Center Dr., San Diego, CA 92123.

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- Your baby will no longer be a part of the research study.
- Your baby will still get the same medical care that you have always had at Sharp HealthCare.
- The research team can continue to use and disclose any of the protected information that they already have.

Do you have the right to see and copy your baby's research information?

- You can only see your baby's research information if it is also being used in your baby's medical records, or at the end of the study.
- If you agree to share your baby's information you must sign this form below. You will be given a copy of this form.

Print your baby's name

Date

Signature of Parent or Legal Guardian

Research Representative



Consentimiento Informado

Estudio de Presión Positiva con Surfactant a las Vías Respiratorias y Oximetría de Pulso en Infantes Extremadamente Bajos de Peso al Nacer

Prueba de RESPALDO para la Neonatal Research Network (Red de Investigación Neonatal) del NICHD

IRB # 041093

Revisado el 1 de Agosto del 2008

Investigador Principal:

Dr. Maynard Rasmussen

APPROVED
DATE: 8/1/08
BY: [Signature]

Patrocinado por:

Red de Investigación Neonatal del Instituto Nacional de Salud Infantil y Desarrollo Humano (NICHD por sus siglas en inglés)

(858) 939-3400 ■ 3003 Health Center Drive ■ San Diego, CA 92123

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01/17/2008

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Development/Staff/MS

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Prueba de Respaldo del NICHD

Participación en un Estudio de Investigación

Los Neonatólogos del hospital Sharp Mary Birch Hospital for Women (SMBHW) y la Neonatal Research Network (Red de Investigación Neonatal) del National Institute of Child Health and Human Development (Instituto Nacional de Salud Infantil y Desarrollo Humano - NICHD por sus siglas en inglés) están conduciendo un estudio de investigación en infantes extremadamente prematuros para conocer más acerca de:

- 1) El tratamiento con Presión Positiva Continua a las Vías Respiratorias (CPAP por sus siglas en inglés) – presión aplicada con mascarilla o cánulas en la nariz para ayudar al bebé a respirar más fácilmente y evitar que sus pulmones se colapsen.
- 2) El nivel ideal de Saturación de Oxígeno – la cantidad de oxígeno en la sangre.

Se le está solicitando a usted que permita a su bebé participar en este estudio porque existe la posibilidad de que él o ella nazcan de 12 a 16 semanas antes de término (con 24 a 28 semanas de gestación). Necesitamos informarle acerca del estudio para que usted pueda decidir si desea que su bebé participe. Necesita saber la razón por la cual estamos llevando a cabo el estudio, si pudiera haber riesgos para su bebé, y lo que esperamos de usted y de su bebé.

¿Por qué se está Llevando a Cabo este Estudio?

- 1) Para comparar el tratamiento de infantes extremadamente prematuros que reciben CPAP en la sala de parto con infantes a quienes se les aplica un tubo respiratorio en la tráquea y surfactant (un medicamento que evita que los pulmones se colapsen), y ver si uno de los dos tratamientos obtiene mejores resultados para la salud de los pulmones.
- 2) Para comparar el tratamiento con nivel bajo de saturación de oxígeno (85-89%) con un nivel más alto (91-95%), y así determinar si uno de éstos da como resultado mejor salud de los ojos.

Ambas maneras de tratarlo podrían ser de beneficio, pero hasta ahora no ha habido un estudio que compare el uso de CPAP con entubación y tratamiento con surfactant, empezando inmediatamente al nacer y continuando en la unidad de cuidados intensivos neonatales (NICU).

Varios estudios han sugerido que el uso temprano de CPAP, evitando el uso de ventilación mecánica (ayuda al bebé a respirar con una máquina respiradora), está relacionado con:

- 1) La reducción de la necesidad de tratamiento con surfactant (sustancia natural que les falta a los bebés extremadamente prematuros y que les ayuda a que no se colapsen sus pulmones).
- 2) La reducción del riesgo de muerte o de necesitar oxígeno a la edad de 36 semanas post conceptionales (para un bebé que nace a las 24 semanas de gestación y que tiene 12 semanas de nacido, su edad post concepcional es de 36 semanas).

Actualmente los infantes extremadamente prematuros son tratados con ventilación mecánica y surfactant. Varios estudios han demostrado que la terapia con surfactant está relacionada con:

- 1) Menor riesgo de que los pulmones se colapsen
- 2) Menor riesgo de desarrollar fugas en los pulmones
- 3) Menor riesgo de morir o de necesitar oxígeno a la edad post concepcional de 36 semanas.

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La Retinopatía de Premadurez (ROP por sus siglas en inglés) es un problema de los ojos común en infantes extremadamente prematuros, porque los vasos sanguíneos que nutren a los ojos no están completamente desarrollados. La ROP puede resultar en deterioro de la vista o hasta ceguera, la cual puede ser causada por niveles excesivos de oxígeno. Los niveles de saturación de oxígeno en la sangre de infantes prematuros se mantienen generalmente entre 80-95%. La saturación ideal de oxígeno en estos bebés extremadamente bajos de peso al nacer (ELBW por sus siglas en inglés) se desconoce.

¿Cuántos Infantes Participarán en este Estudio?

Esperamos inscribir a aproximadamente 1300 bebés en hospitales de la Red de Investigación Neonatal de NICHD durante un período de dos años. Aproximadamente 50 infantes serán inscritos aquí en SMBHW.

¿Qué es lo que Involucra la Participación en este Estudio?

Si usted acepta que su bebé entre en este estudio, le pasará lo siguiente. Antes del parto, y después de obtener su permiso, se asignará a su bebé al azar (como si se lanzara una moneda al aire) a una de las dos estrategias de tratamiento. Los tratamientos son los siguientes:

- 1) El CPAP en la sala de parto, inmediatamente después de nacer, y continuando en la unidad de cuidados intensivos (NICU).
- O
- 2) La colocación de un tubo respiratorio en la tráquea del bebé en la sala de parto, seguido por administración de surfactant y ventilación mecánica (bebé respira con uso de máquina).

Además de ser asignado a uno de los dos grupos descritos arriba, su bebé también será asignado al azar a uno de dos tipos de oxímetros (monitores de saturación de oxígeno que muestran cuanto oxígeno hay en la sangre). Los oxímetros (monitores de oxígeno) utilizados en esta prueba son dispositivos aprobados por la FDA. Para este estudio, los oxímetros fueron modificados para mostrar un valor que es ligeramente más alto o ligeramente más bajo que el nivel real de oxígeno cuando los valores están entre 85 y 95%. Fuera de estos niveles, el oxímetro trabaja igual que un dispositivo no modificado.

La saturación de oxígeno en su bebé será mantenida ya sea en el nivel alto (91-95%) o en el nivel bajo (85-89%). El tipo de oxímetro ("Lectura Alta" o "Lectura Baja") al cual su bebé será asignado no lo conocerán las enfermeras o los doctores que atienden a su bebé. Esta información solo la conocerá NICHD, pero se le dará al doctor de su bebé si se necesita. Su bebé permanecerá con ese tipo de oxímetro mientras esté bajo terapia de oxígeno, hasta que él o ella alcance la edad de 36 semanas de edad post concepcional.

Se le proporcionará cuidado intensivo neonatal de rutina a su bebé durante su participación en el estudio. Seguirá bajo observación médica en nuestra clínica de Seguimiento Médico para Infantes a los 6 y 12 meses de edad, recibiendo el estándar de atención para bebés pequeños. A los 18-22 meses de edad corregida, su bebé recibirá sin costo alguno para usted, un examen completo de sus músculos, sus nervios y su habilidad mental y coordinación de movimientos.

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¿Por Cuanto Tiempo Van a Estudiar a su Bebé?

Su bebé estará en el estudio hasta los 18-22 meses de edad post concepcional.

¿Existen Riesgos Asociados con este Estudio?

Todos los tratamientos que se proponen en este estudio son los mismos que se están usando actualmente en nuestra NICU, no se espera ningún riesgo mayor para su bebé. Los infantes que les toque estar en el grupo CPAP podrían, en algún momento, requerir entubación y ventilación asistida (métodos que les ayudan a respirar). Si el doctor que atiende a su bebé lo considera necesario, el hecho de que participa en el estudio no afectará esta decisión. Podría ser que se descubrieran riesgos durante el estudio que aún no se conocen. Si estos ocurrieran, el personal investigador le informará a usted.

El único otro riesgo del estudio es la confidencialidad. Se hará todo esfuerzo por mantener confidencial la información del expediente médico de su bebé. No se identificará a su bebé en ningún reporte o publicación acerca de este estudio. Las medidas que se tomarán para proteger la identidad de usted y de su bebé se describen en la sección sobre confidencialidad de este documento.

¿Existen Beneficios Asociados a la Participación en este Estudio?

Su bebé podría o no recibir beneficio directo por participar en ese estudio. Sin embargo, la participación de su bebé nos ayudará a encontrar mejores maneras de tratar a bebés que requieren ayuda para poder respirar.

¿Qué sucede con la Confidencialidad?

El personal encargado del estudio en SMBHW recopilará la información clínica del expediente de su bebé, a la cual se le pondrá una etiqueta con un número codificado. La información codificada se enviará al Centro de Colección de Datos de la Red Neonatal del NICHD al Research Triangle Institute en Research Triangle Park, North Carolina. La bitácora del estudio que enlaza la información codificada con la identidad de su bebé se mantendrá bajo llave en SMBHW. Los archivos de la investigación se mantendrán en forma confidencial hasta donde permite la ley.

Las organizaciones que pueden examinar o copiar los datos de investigación de su bebé para asegurar la calidad del estudio, así como para analizar datos, incluyen los siguientes grupos: la United States Food and Drug Administration (FDA), Sharp HealthCare Institutional Review Board (IRB), el patrocinador del estudio, NICHD Neonatal Research Network, y la Oficina de Protección de la Investigación Humana (Office for Human Research Protection - OHRP).

Información de Salud Protegida (PHI por sus siglas en inglés)

Como parte de este estudio de investigación, se le pedirá que firme un documento por separado en el cual usted otorga su autorización para que se tenga acceso a la información médica de su bebé. Este documento le indicará quien tendrá acceso a dicha información, por cuanto tiempo y como será usada la misma. De igual forma, le dirá lo que usted puede hacer en caso de que ya no

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deseara que se siga usando la información médica de su bebé. Su firma nos dará autorización para usar la información médica de su bebé. Usted recibirá una copia firmada de dicho documento.

¿Cuáles son los Costos?

Estamos anticipando que el participar en este estudio no representará ningún costo adicional para usted, ni para su compañía de seguro médico. Los costos de pruebas de diagnóstico y tratamiento de su bebé serán responsabilidad de usted y(o) de su compañía de seguro médico. Sharp HealthCare y los investigadores serán reembolsados parcialmente por el patrocinador, por su tiempo, esfuerzo y supervisión del equipo profesional para llevar a cabo los procedimientos, tareas, y coleccionar y presentar correctamente los datos obtenidos.

¿Qué Sucede en Caso de Lesiones Durante el Estudio?

En el caso de presentarse alguna lesión o enfermedad como resultado de dicho estudio, se dispone de tratamiento médico de emergencia pero se le proporcionará al precio acostumbrado. No existen fondos de compensación para usted en caso de lesiones. Sharp HealthCare no le proporcionará ninguna compensación a usted en el caso de que su bebé sufra algún daño relacionado con la investigación mientras esté participando en este estudio.

¿Cuáles son mis Derechos como Participante?

El tomar parte en este estudio es voluntario. Usted puede elegir que su bebé no participe o puede retirarlo del estudio en cualquier momento. El dejar el estudio no resultará en ninguna multa o pérdida de beneficios para los cuales usted o su bebé tienen derecho. Un grupo independiente de expertos, el Data Safety and Monitoring Board (Consejo de Seguridad y Monitoreo de Datos), estará revisando los datos de esta investigación a lo largo del estudio. Le diremos si alguna nueva información con respecto a este u otros estudios pudiera afectar la salud o el bienestar de su bebé, o su disponibilidad de permanecer en el estudio.

¿Qué Otras Alternativas Tengo Además de este Estudio?

Como alternativa a la participación en este estudio, usted puede pedirle al doctor de su bebé que decida cual tratamiento es el indicado para su bebé. Si usted decide no incluir a su bebé en este estudio, nada de su información médica será incluida en el mismo. La participación en esta investigación es enteramente voluntaria. Usted puede rehusarse a que su bebé participe en este estudio o retirarlo de su participación en cualquier momento, sin que esto afecte el cuidado médico que su bebé reciba en Sharp Mary Birch Hospital for Women, o que pierda su bebé los beneficios a que tenga derecho. Si usted retira a su bebé de dicho estudio, el doctor que lo está atendiendo decidirá si mantenerlo bajo el tratamiento que estaba recibiendo o si cambiarlo, basándose en las necesidades de su bebé en el momento en que se tome esa decisión. La colección de datos para fines del estudio de investigación se suspenderá en ese momento. La participación de su bebé en este estudio puede ser suspendida si su doctor siente que esto sería en beneficio médico de la salud de su bebé, o si la FDA o el IRB suspenden el estudio.

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¿A Quién debo Llamar si Tengo Dudas o Problemas?

Para cualquier pregunta acerca del estudio o con respecto a alguna lesión relacionada con la investigación, comuníquese con el investigador principal, Dr. Maynard Rasmussen, al teléfono: (858)939-4176.

Para cualquier pregunta acerca de sus derechos como participante en el estudio, o para presentar una queja acerca de la investigación, comuníquese con el Dr. David J. Bodkin, Presidente del Sharp HealthCare Institutional Review Board (un grupo de personas que revisan la investigación para proteger los derechos de usted) por la siguiente vía:

Sharp's Office for the Protection of Research Participants (IRB)
8695 Spectrum Court
San Diego, California 92123
Teléfono: (858) 499-4836

Firma

Su firma al calce indica que usted ha leído lo anterior acerca de la Prueba de Respaldo y ha tenido oportunidad de hacer preguntas que le ayuden a entender lo que involucra la participación de su bebé. Usted está de acuerdo en que su bebé participe en el estudio hasta que decida lo contrario. Usted no está renunciando a los derechos legales de su bebé al firmar este consentimiento.

Firma del Padre/Madre
(o su representante legal
autorizado)

Nombre en Letra de Molde

Fecha

Firma del Testigo

Nombre en Letra de Molde

Fecha

Yo _____ certifico que los requisitos para firmar el consentimiento informado del proyecto de investigación médica descrito en este documento han sido cumplidos, que se le ha proporcionado al padre y(o) a la madre del participante una copia de los "Derechos de los Sujetos que Participan en Experimentos en California," que he platicado del proyecto de investigación con el padre y(o) la madre del participante y les he explicado, en términos que entienden, toda la información contenida en este consentimiento informado, así como los riesgos y las reacciones adversas que se podría esperar razonablemente que ocurrieran. Además certifico que aconsejé al padre y(o) a la madre del participante que hicieran preguntas, y que todas sus preguntas fueron aclaradas.

Firma del Investigador

En Letra de Molde

Fecha

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DERECHOS DE LOS SUJETOS QUE PARTICIPAN EN EXPERIMENTOS EN CALIFORNIA

Se le ha solicitado que permita a su bebé participar como sujeto de un procedimiento experimental. Antes de que decida si va a participar en el procedimiento experimental, usted tiene derecho a:

1. Estar informado de la naturaleza y propósito del experimento.
2. Recibir una explicación sobre los procedimientos que se van a seguir en el experimento médico y de cualquier fármaco o dispositivo que se vaya a utilizar.
3. Recibir una descripción de cualquier incomodidad o riesgo que se pueda esperar razonablemente por participar en el experimento.
4. Recibir una explicación de cualquier beneficio que usted pueda esperar razonablemente por participar en el experimento.
5. Recibir información de cualquier procedimiento, droga o dispositivo alternativo apropiado, que pudiera ser provechoso para usted, y sus riesgos y beneficios correspondientes.
6. Estar informado de las vías de tratamiento médico, si las hubiera, que usted tiene a su disposición después del procedimiento experimental, en caso de que surgieran complicaciones.
7. Tener la oportunidad de hacer cualquier pregunta relacionada con el experimento médico o los procedimientos involucrados.
8. Recibir información de que puede retirar en cualquier momento su consentimiento para participar en el procedimiento experimental, y de que puede abandonar la participación en el experimento sin perjuicio alguno.
9. Recibir una copia de este formulario y el formulario de consentimiento firmado y fechado, y
10. Recibir la oportunidad de decidir si consiente o no consiente al experimento médico sin que intervenga ningún elemento de fuerza, fraude, dolo, coacción, coerción o una influencia indebida sobre su decisión.

He leído la información anterior con mucho cuidado y entiendo totalmente mis derechos como sujeto potencial de un experimento médico que involucra a personas como sujetos.

Firma del Padre/Madre o Tutor Legal

Firma del testigo

Fecha

Fecha

Revised August 1, 2008

IRB #041093

Page 8 of 9

Autorización para Usar su Información de Salud Protegida (PHI por sus siglas inglés)

Información de Salud Protegida: PHI es toda la información personal de salud mediante la cual se le puede identificar a su bebé. Estamos solicitando su permiso para usar el PHI de su bebé en este estudio de investigación. Si usted no firma esta forma, su bebé no podrá participar en este estudio. La información protegida de salud de su bebé puede incluir información acerca de muestras de sangre, exámenes físicos, historia médica, diagnósticos de rayos X, ultrasonidos de la cabeza, exámenes de ojos y otros datos recopilados o revisados durante el curso de este estudio o antes de este estudio, como se indica en la forma de consentimiento, hasta 18 a 22 meses de edad post concepcional.

¿Quién podrá disponer de su PHI?

- El Dr. Maynard Rasmussen, el hospital Sharp Mary Birch Hospital for Women, y Sharp HealthCare.

¿Quién va a ver su PHI?

- El patrocinador de dicho estudio *National Institute of Child Health and Human Development (NICHD) Neonatal Research Network* (Red de Investigación Neonatal del Instituto Nacional de la Salud Infantil y Desarrollo Humano)
- Las agencias gubernamentales *National Institute of Health* (Instituto Nacional de Salud) o la *Food and Drug Administration (FDA)* (Administración de Alimentos y Fármacos)
- Los comités de Sharp HealthCare que revisan la investigación para proteger a las personas que participan en estudios de investigación.

¿Cuánto tiempo usará y distribuirá Sharp HealthCare la información de su bebé y para qué será utilizada?

- ¿Qué información será usada? Datos médicos incluyendo información acerca de lo que ocurrió durante el parto, procedimientos, pruebas, tratamientos que su bebé haya tenido antes o durante su estancia en el hospital, y otra información médica acerca de la participación de su bebé en este estudio.
- ¿Por cuánto tiempo se usará y se compartirá la información de su bebé? Esta autorización expirará en 20 años. Sin embargo, usted tiene el derecho de cancelar esta autorización en cualquier momento. Una vez que la información protegida de salud de su bebé sea compartida con los grupos arriba mencionados, ya no estará protegida por las leyes federales de confidencialidad y podrá ser divulgada.

Revised August 1, 2008

IRB #041093

Page 9 of 9

Si decide que ya no quiere compartir su información:

- Usted tiene que escribir al doctor que conduce el estudio y decirle que ya no desea compartir la información de su bebé. Escriba a:

Maynard Rasmussen, MD
Sharp Mary Birch Hospital for Women
3003 Health Center Drive
San Diego, California 92123

- Su bebé ya no participará en el estudio de investigación.
- Su bebé continuará recibiendo la misma atención médica que siempre se le ha brindado en Sharp HealthCare.
- El equipo de investigación podrá continuar usando y divulgando la información protegida que ya hayan obtenido.

¿Tiene usted derecho a ver y recibir una copia de la información de su bebé obtenida por la investigación?

- Usted podrá ver la información de la investigación concerniente a su bebé únicamente si está siendo usada en su historial médico, o al final del estudio.
- Si usted está de acuerdo en compartir la información de su bebé, usted debe firmar a continuación. Se le dará una copia de este documento.

Nombre del bebé en letra de molde

Fecha

Firma del Padre/Madre o Tutor Legal

Representante de la Investigación

From: [Spong, Catherine \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Willinger, Marian \(NIH/NICHD\) \[E\]](#)
Subject: RE: NRN Program Official
Date: Monday, January 14, 2013 12:21:07 PM

nope

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, January 14, 2013 12:04 PM
To: Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN Program Official

Marian is on the DMSC, is that ok?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Monday, January 14, 2013 12:03 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN Program Official

I think that (b)(5)

Marian
John
Tonse
All ok

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, January 14, 2013 11:30 AM
To: Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: NRN Program Official

Hi

Cathy has been the PO for the NRN grants -- I am assuming this will change -- can it be (b)(5)

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Kennedy, Kathleen A](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality
Date: Thursday, January 10, 2013 8:57:34 AM

Yes

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Wednesday, January 09, 2013 10:29 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpointex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Hareesh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Tyson, Jon E; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; mgantz@rti.org
Subject: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality

Hi

Julie DiFiore, Richard Martin and Michele Walsh would like to submit the following specific aims as part of an R03 application. The SUPPORT Subcommittee has approved this request. Please send me a yes/no vote by Jan 14 to allow access to the data described in the specific aims.

Thanks
Rose

From: [Barbara Stoll](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality
Date: Thursday, January 10, 2013 12:00:31 AM

YES

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair
Department of Pediatrics, Emory University School of Medicine
President and CEO, Emory-Children's Center
SVP and Chief Academic Officer, Children's Healthcare of Atlanta
2015 Uppergate Dr
Atlanta GA 30322
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

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From: Bell, Edward (Pediatrics)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality
Date: Wednesday, January 09, 2013 12:01:53 PM

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, January 09, 2013 10:28 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Bell, Edward (Pediatrics); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarfo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; mgantz@rti.org
Subject: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality

Hi

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Thanks
Rose

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From: Ronald Goldberg, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality
Date: Wednesday, January 09, 2013 11:55:59 AM

Yes from Duke.

From: <Higgins>, NIH <higginsr@mail.nih.gov>
Date: Wednesday, January 9, 2013 11:28 AM
To: "(suhas.kallapur@cchmc.org)" <suhas.kallapur@cchmc.org>, Abbot Laptok <alaptok@wihri.org>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)" <AnnaMaria.hibbs@cwru.edu>, Barbara Stoll <barbara_stoll@oz.ped.emory.edu>, Brenda Poindexter <bpoindex@iupui.edu>, "D'Angio, Carl" <Carl_Dangio@URMC.Rochester.edu>, "Carlton, David P" <dpcarl@emory.edu>, Charles Cotten <michael.cotten@dm.duke.edu>, David Stevenson <d Stevenson@stanford.edu>, "dwallace@rti.org" <dwallace@rti.org>, Edward Bell <edwardbell@uiowa.edu>, Ronald Goldberg <ronald.goldberg@dm.duke.edu>, "Greg Sokol (gsokol@iupui.edu)" <gsokol@iupui.edu>, "Kirpalani, Hares" <KIRPALANI.H@email.chop.edu>, John Barks <jbarks@med.umich.edu>, Jon Tyson <Jon.F.Tyson@uth.tmc.edu>, Kathleen Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>, Krisa Meurs <vanmeurs@stanford.edu>, Kristi Watterberg <KWatterberg@salud.unm.edu>, Kurt Schibler <kurt.schibler@cchmc.org>, Luc Brion <Luc.Brion@utsouthwestern.edu>, "Martin Keszler (mkeszler@wihri.org)" <mkeszler@wihri.org>, Michelle Walsh <mcw3@po.cwru.edu>, "Meena Garg (mgarg@mednet.ucla.edu)" <mgarg@mednet.ucla.edu>, "Nelin, Leif" <Leif.Nelin@nationwidechildrens.org>, Pablo Sanchez <Pablo.Sanchez@utsouthwestern.edu>, richard polin <rap32@mail.cumc.columbia.edu>, "Robin Ohls (rohls@salud.unm.edu)" <rohls@salud.unm.edu>, Ronnie Guillet <Ronnie_Guillet@URMC.Rochester.edu>, Satyan Lakshminrusimha <slakshmi@buffalo.edu>, Barbara Schmidt <barbara.schmidt@uphs.upenn.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, Beena Sood <bsood@med.wayne.edu>, William Truog <wtruog@cmh.edu>, "Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU)" <UDEVASKAR@mednet.ucla.edu>, "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>
Cc: NIH/NICHD <archerst@mail.nih.gov>, "mgantz@rti.org" <mgantz@rti.org>
Subject: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality

Hi

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Thanks
Rose

From: Devaskar, Uday
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality
Date: Wednesday, January 09, 2013 11:53:19 PM

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 09, 2013 08:28 AM
To: (suhas.kallapur@cchmc.org) <suhas.kallapur@cchmc.org>; Abbot Laptook (alaptook@wihri.org) <alaptook@wihri.org>; Abhik Das (adas@rti.org) <adas@rti.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu) <AnnaMaria.hibbs@cwru.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@urmc.rochester.edu>; Carlton, David P <dpcarl@emory.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; dstevenson@stanford.edu <dstevenson@stanford.edu>; dwallace@rti.org <dwallace@rti.org>; Ed Bell (edward-bell@uiowa.edu) <edward-bell@uiowa.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Greg Sokol (gsokol@iupui.edu) <gsokol@iupui.edu>; Haresh Kirpalani (KIRPALANI@email.chop.edu) <KIRPALANI@email.chop.edu>; John Barks <jbarks@med.umich.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Kristi Watterberg (kwatterberg@salud.unm.edu) <kwatterberg@salud.unm.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Luc Brion (luc.brion@utsouthwestern.edu) <luc.brion@utsouthwestern.edu>; Martin Keszler (mkeszler@wihri.org) <mkeszler@wihri.org>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>; Garg, Meena; Nelin, Leif <Leif.Nelin@nationwidechildrens.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; Polin, Richard <rap32@mail.cumc.columbia.edu>; Robin Ohls (rohls@salud.unm.edu) <rohls@salud.unm.edu>; ronnie_guillet@urmc.rochester.edu <ronnie_guillet@urmc.rochester.edu>; Satyan Lakshminrusimha <slakshmi@buffalo.edu>; Schmidt, Barbara (Neonatology) <barbara.schmidt@uphs.upenn.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Sood, Beena [bsood@med.wayne.edu] <bsood@med.wayne.edu>; Truog, William (MD) <wtruog@cmh.edu>; Devaskar, Uday; Wally Carlo (wacarolo@uab.edu) <wacarolo@uab.edu>
Cc: Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>; mgantz@rti.org <mgantz@rti.org>
Subject: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality

Hi

Julie DiFiore, Richard Martin and Michele Walsh would like to submit the following specific aims as part of an R03 application. The SUPPORT Subcommittee has approved this request. Please send me a yes/no vote by Jan 14 to allow access to the data described in the specific aims.

Thanks

Rose

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality
Date: Wednesday, January 09, 2013 11:30:22 AM

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 09, 2013 11:29 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Das, Abhik; Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); [SCRN] Stoll, Barbara; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; Wallace, Dennis; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Hareesh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; Gantz, Marie
Subject: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality

Hi

Julie DiFiore, Richard Martin and Michele Walsh would like to submit the following specific aims as part of an R03 application. The SUPPORT Subcommittee has approved this request. Please send me a yes/no vote by Jan 14 to allow access to the data described in the specific aims.

Thanks
Rose

From: [Stevens, Timothy](#)
To: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: Clearance | Stevens, Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial
Date: Tuesday, January 08, 2013 9:08:24 AM

Hi Stephanie,

I have not heard from the publications committee. Should I be expecting something from them?

Thanks

Tim

From: Archer, Stephanie (NIH/NICHD) [E] [<mailto:archerst@mail.nih.gov>]
Sent: Thursday, December 27, 2012 9:03 AM
To: Stevens, Timothy
Subject: Clearance | Stevens, Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

Hi Tim,

Your manuscript, "Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial" has been cleared by NICHD for publication. I am still waiting on some PIs to get back to me with the final boilerplate information. I'll send out a reminder to them shortly.

Happy New Year,

Stephanie

Stephanie Wilson Archer
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Jon.E.Tyson@uth.tmc.edu](#); [Green, Charles \(Charles.Green@uth.tmc.edu\)](#)
Cc: [\(mcunningham@rti.org\)](#)
Subject: protocol
Date: Monday, January 07, 2013 10:12:00 AM

Hi Jon and Chuck –

Did you want to submit a draft of your protocol for posting on the private website in advance of your presentation this week at the SC meeting for the term follow up protocol?

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Navarrete, Cristina](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: SUPPORT Secondary paper
Date: Friday, January 04, 2013 5:19:54 PM

Hi Dr. Higgins,
I gave a draft to Dr. Duara and she has been in the process of reviewing it before sending it in for subcommittee review.
Thanks,
Cristina

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, January 02, 2013 3:45 PM
To: Navarrete, Cristina; Duara, Shahnaz
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT Secondary paper

Hi
Can you send me an update on:

Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

We think you have all the analyses needed to write the paper, correct? Can you let me know when you will have a draft ready for the SUPPORT Subcommittee?

Thanks
Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
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301-435-7909
301-496-5575
301-496-3790 (FAX)
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Thanks to everyone for an outstanding joint effort. Wonderful to see our work finally published. A report was distributed on Reuters Health News service yesterday.

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Subject: CONGRATULATIONS!!!!

Here is today's SUPPORT FU Publication.

Congratulations!!!
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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med* 2012;367:2495-504. DOI: 10.1056/NEJMoa1208506

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Methodology for limited ventilator strategy

CPAP Arm:

NICU management: CPAP infants could be intubated if they met any of the following criteria: an $\text{FiO}_2 > .50$ required to maintain an indicated $\text{SpO}_2 > 88\%$ for one hour, an arterial $\text{PaCO}_2 > 65$ torr documented on a single blood gas within 1 hour prior to intubation, or 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 within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $\text{PaCO}_2 < 65$ torr with a $\text{pH} > 7.20$, an $\text{SpO}_2 > 88\%$ with an $\text{FiO}_2 < 50\%$, a mean airway pressure (MAP) < 10 cm H_2O , ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be extubated within 24 hours of meeting all of the following criteria: $\text{PaCO}_2 < 50$ torr and $\text{pH} > 7.30$, $\text{FiO}_2 \leq .35$ with a $\text{SpO}_2 > 88\%$, a MAP < 8 cm H_2O , ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could 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. ¹

Methodology for oximeter blinding strategy

4.1.1 Randomization and Masking, Storing and Assigning Oximeters

Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the 26 - 27 6/7 week gestational age group.... Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO_2 arm of the study. They will be specified as one of the following:

- **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue** or **Orange** OR
- **Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue** or **Orange**.

The **Blue/Orange** codes will designate an assignment to either the **Low (85% - 89%)** or **High (91% -95%)** SpO_2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the

sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form**).

Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know"**. Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO₂) are available to accommodate the delivery. Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.²

Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u>	<u>Higher</u>
			<u>Saturation</u>	<u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) ^δ	849±186	852±193	858±186	844±192
Gestational age (weeks) ^δ	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10 th %) ^ε	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male ^ε	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White ^ε	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black ^ε	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic ^ε	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown ^ε	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation ^ε	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any ^ε	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section ^ε	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only ^ε	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married ^ε	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents ^ε	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education< high school degree ^ε	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

Income < \$30,000/year [€]	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language [€]	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP [€]	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD [¶] [€]	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL [€]	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC [€]	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis [€]	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids [€]	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) ^δ	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

^δ Mean ± SD

[€] no./total no.(%)

[¶] At 36 weeks postmenstrual age

*p<0.05, ** p<0.01, ***p<0.001 (Comparison for groups within each intervention arm)

Comparisons adjusted for stratification by center and gestational age and for familial clustering

Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT

<u>24 0/7-25 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07
<u>26 0/7-27 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31

Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS

<u>24 0/7-25 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22
<u>26 0/7-27 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95

Gross motor function level ≥ 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral pal	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78
Hearing impairment	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets

	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

*ARR (Adjusted relative risk)

** (adjusted mean ± standard error)

***(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups

Reason for Eye surgery	Lower N=31	Higher N=67	Total N=98
Retinopathy of Prematurity	26 (84%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)

References

1. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
2. SUPPORT Manual of Operations, January 4, 2005, Revised March 10, 2005

ORIGINAL ARTICLE

Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial

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ABSTRACT

BACKGROUND

Previous results from our trial of early treatment with continuous positive airway pressure (CPAP) versus early surfactant treatment in infants showed no significant difference in the outcome of death or bronchopulmonary dysplasia. A lower (vs. higher) target range of oxygen saturation was associated with a lower rate of severe retinopathy but higher mortality. We now report longer-term results from our pre-specified hypotheses.

METHODS

Using a 2-by-2 factorial design, we randomly assigned infants born between 24 weeks 0 days and 27 weeks 6 days of gestation to early CPAP with a limited ventilation strategy or early surfactant administration and to lower or higher target ranges of oxygen saturation (85 to 89% or 91 to 95%). The primary composite outcome for the longer-term analysis was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

RESULTS

The primary outcome was determined for 1234 of 1316 enrolled infants (93.8%); 990 of the 1058 surviving infants (93.6%) were evaluated at 18 to 22 months of corrected age. Death or neurodevelopmental impairment occurred in 27.9% of the infants in the CPAP group (173 of 621 infants), versus 29.9% of those in the surfactant group (183 of 613) (relative risk, 0.93; 95% confidence interval [CI], 0.78 to 1.10; $P=0.38$), and in 30.2% of the infants in the lower-oxygen-saturation group (185 of 612), versus 27.5% of those in the higher-oxygen-saturation group (171 of 622) (relative risk, 1.12; 95% CI, 0.94 to 1.32; $P=0.21$). Mortality was increased with the lower-oxygen-saturation target (22.1%, vs. 18.2% with the higher-oxygen-saturation target; relative risk, 1.25; 95% CI, 1.00 to 1.55; $P=0.046$).

CONCLUSIONS

We found no significant differences in the composite outcome of death or neurodevelopmental impairment among extremely premature infants randomly assigned to early CPAP or early surfactant administration and to a lower or higher target range of oxygen saturation. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute; SUPPORT ClinicalTrials.gov number, NCT00233324.)

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EXTREMELY PREMATURE INFANTS ARE AT high risk for death and neurosensory or developmental impairment in early childhood.¹⁻³ The risk of neurodevelopmental impairment increases with decreasing gestational age and greater severity of illness. Neurodevelopmental impairment is often a consequence of neonatal complications.⁴⁻¹² Although surfactant administration decreases the risk of death and bronchopulmonary dysplasia, randomized, controlled trials of various respiratory interventions have not shown significant reductions in mortality and morbidity or improvement in developmental outcomes.¹³⁻¹⁷ We previously reported results of the multicenter, randomized, controlled Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), which involved extremely premature infants (from 24 to 27 weeks of gestation); treatment with noninvasive continuous positive airway pressure (CPAP) shortly after birth, as compared with early intubation and surfactant administration, did not reduce rates of death or bronchopulmonary dysplasia or other major morbidity at 36 weeks of postmenstrual age.¹⁸

Although oxygen supplementation is necessary for survival in many preterm infants, several studies have shown that it increases the risk of retinopathy of prematurity,¹⁹ bronchopulmonary dysplasia,^{20,21} periventricular leukomalacia,²² and cerebral palsy.²³ Results from SUPPORT showed no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity among infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) versus a higher range (91 to 95%). However, in the lower-oxygen-saturation group, the risk of retinopathy of prematurity among infants who survived to discharge was decreased (8.6%, vs. 17.9% in the higher-oxygen-saturation group; relative risk, 0.52; 95% confidence interval [CI], 0.37 to 0.73; $P < 0.001$) and the risk of death was increased (19.9% vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; $P = 0.04$).²⁴

We now report the results of our longer-term follow-up of the infants in this study, assessing whether early, noninvasive CPAP with a limited ventilation strategy, as compared with early surfactant administration, and a lower, as compared with higher, target range of oxygen saturation would each decrease the incidence of death be-

fore assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

METHODS

STUDY DESIGN

SUPPORT was a randomized, controlled trial involving 1316 extremely preterm infants (gestational age, 24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009, who were enrolled at delivery at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days). Infants who were part of multiple births were randomly assigned, as a unit, to the same treatment group.

In the delivery room, the infants were randomly assigned to receive either CPAP immediately after delivery with a limited ventilation strategy, as described previously, if subsequent intubation was required, or intubation with surfactant administration within an hour after birth, followed by conventional ventilation.¹⁸ Using a 2-by-2 factorial design, we also randomly assigned participants to a target oxygen-saturation range of 85 to 89% (lower-oxygen-saturation group) or 91 to 95% (higher-oxygen-saturation group); we used pulse oximeters that were specially designed to maintain blinding (see the Supplementary Appendix, available with the full text of this article at NEJM.org).²⁴

The procedures for enrollment, intervention, and data collection have been reported previously.^{18,24} The trial 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. Written informed consent was obtained from the parent or guardian of each child before delivery. Two of the authors employed by RTI International vouch for the accuracy and completeness of the data and analyses reported, and the members of the SUPPORT subcommittee vouch for the fidelity of the trial to the study protocol (see the Supplementary Appendix).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

ASSESSMENTS

At 18 to 22 months of corrected age, surviving infants underwent a comprehensive neurodevelopmental assessment performed by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability. Cognitive function was assessed with the use of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III); scores are assessed relative to a standardized mean (\pm SD) of 100 ± 15 , with higher scores indicating better performance.²⁵ The modified Gross Motor Function Classification System (GMFCS) was used to classify gross-motor performance, with scores ranging from 0 (normal) to 5 (most impaired).²⁶ Moderate-to-severe cerebral palsy was defined as a nonprogressive disorder with abnormal muscle tone in at least one arm or leg that was associated with abnormal control of movement or posture and a GMFCS score of 2 or higher.^{27,28} Assessments of hearing impairment (defined as the inability to understand the oral directions of the examiner and to communicate, with or without hearing amplification) and visual impairment (defined as vision worse than 20/200) were based on examination and parental report.

Certified research staff collected demographic and neonatal-outcome data using standard definitions from the Neonatal Research Network. Demographic and outcome data included gestational age; birth weight; sex; status with respect to multiple gestation; race or ethnic group; and history of medical or surgical necrotizing enterocolitis (modified Bell's stage ≥ 2 , on a scale ranging from 1 to 3, with higher scores indicating greater severity of disease), intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia, late-onset sepsis, retinopathy of prematurity, bronchopulmonary dysplasia (physiological), and use of postnatal glucocorticoids. Socioeconomic variables included health insurance status, maternal marital status, maternal educational level, household income, language spoken at home, and status with respect to whether the child was living with biologic parents. Socioeconomic data were updated during the 18-to-22-month visit; these data were used if data from the neonatal period were not available.

OUTCOMES

The prespecified primary composite outcome for this trial was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age. This composite outcome was selected because infants who died before 18 months of corrected age could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the BSID-III of less than 70, a GMFCS score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment. Other prespecified outcomes at 18 to 22 months of corrected age were death and neurodevelopmental impairment. Exploratory secondary outcomes included the individual components of the neurodevelopmental-impairment assessment, levels of cognitive delay, and a comparison of outcomes within the higher and lower gestational-age strata.

STATISTICAL ANALYSIS

The sample-size calculations were based on Neonatal Research Network data for infants born in the year 2000; the details have been reported previously.^{18,24} Although the sample size for the study was estimated on the basis of hospital outcomes (i.e., death or bronchopulmonary dysplasia for the ventilation intervention, and death or retinopathy of prematurity for the oxygenation intervention), the final sample size was sufficient to detect an absolute reduction of 10 percentage points in the composite outcome of death or neurodevelopmental impairment, with the use of a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% in the surfactant and higher-oxygen-saturation groups and a 15% rate of loss to follow-up, as well as adjustment for familial clustering.

Data were entered on standard forms and were transmitted to RTI International, which stored, managed, and analyzed the data for the study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were performed with the use of chi-square tests for categorical variables and t-tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary

composite outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age could be assigned. 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. The denominator used to calculate the frequency of each outcome was the number of children for whom status with respect to that outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all 18-to-22-month outcomes were adjusted, as prespecified, for gestational-age strata, study center, and familial clustering (because infants who were part of multiple births were assigned to the same treatment group). Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the effect of characteristics that differed between the groups of children with and without follow-up, a sensitivity analysis using multiple imputation was conducted, in which missing values for the primary outcome were imputed on the basis of the treatment assignment, perinatal characteristics, and in-hospital outcomes.²⁹ Two-sided *P* values of less than 0.05 were considered to indicate statistical significance for all analyses; no adjustments were made for multiple comparisons.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The primary composite outcome of death or neurodevelopmental impairment was determined for 93.8% of the children (1234 of 1316) enrolled in the trial (Fig. 1). A total of 258 children were known to have died before 18 to 22 months of age. Of the 68 children for whom a neurodevelopmental assessment was missing, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment was determined for 98.6% of all children seen (976 of 990); 14 children had an incomplete evaluation that precluded the assignment of a neurodevelopmental-impairment status. The follow-up rate and the mean corrected age at neuro-

developmental assessment were similar for all treatment groups (Table 1).

As compared with the mothers of the 990 children who underwent a neurodevelopmental assessment at 18 to 22 months of corrected age, the mothers of the 68 children who did not undergo an assessment were less likely to be married (47% vs. 31%, *P*=0.01) and more likely to have only public health insurance (52% vs. 69%, *P*=0.008). No other demographic or neonatal characteristics differed significantly between the groups.

The demographic and clinical characteristics of the follow-up population are summarized in Table 1 and in Table S1 in the Supplementary Appendix. Almost all mothers received antenatal glucocorticoids. At follow-up, there were more children who were small for their gestational age and more children with severe retinopathy of prematurity in the higher-oxygen-saturation group than in the lower-oxygen-saturation group. As compared with the surfactant group, children in the CPAP group were more likely to have had necrotizing enterocolitis and less likely to have been exposed to postnatal glucocorticoids. A total of 32% of the infants in the CPAP group were intubated in the delivery room; 65% of the infants in the CPAP group received surfactant with limited ventilation.

PRIMARY OUTCOME

The frequency of the composite outcome of death or neurodevelopmental impairment did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups at 18 to 22 months of corrected age (Tables 2 and 3). Mortality before neonatal discharge accounted for 92% of the overall mortality observed by 18 to 22 months. Mortality did not differ significantly between the CPAP and surfactant groups but remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group. There were no significant differences in the primary outcome between treatment groups in subgroup analyses stratified according to gestational age at birth (Tables S2 and S3 in the Supplementary Appendix). The results of the sensitivity analysis using multiple imputations were virtually identical to the results of the analysis in which missing data were excluded (data not shown). There was no significant interaction be-

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

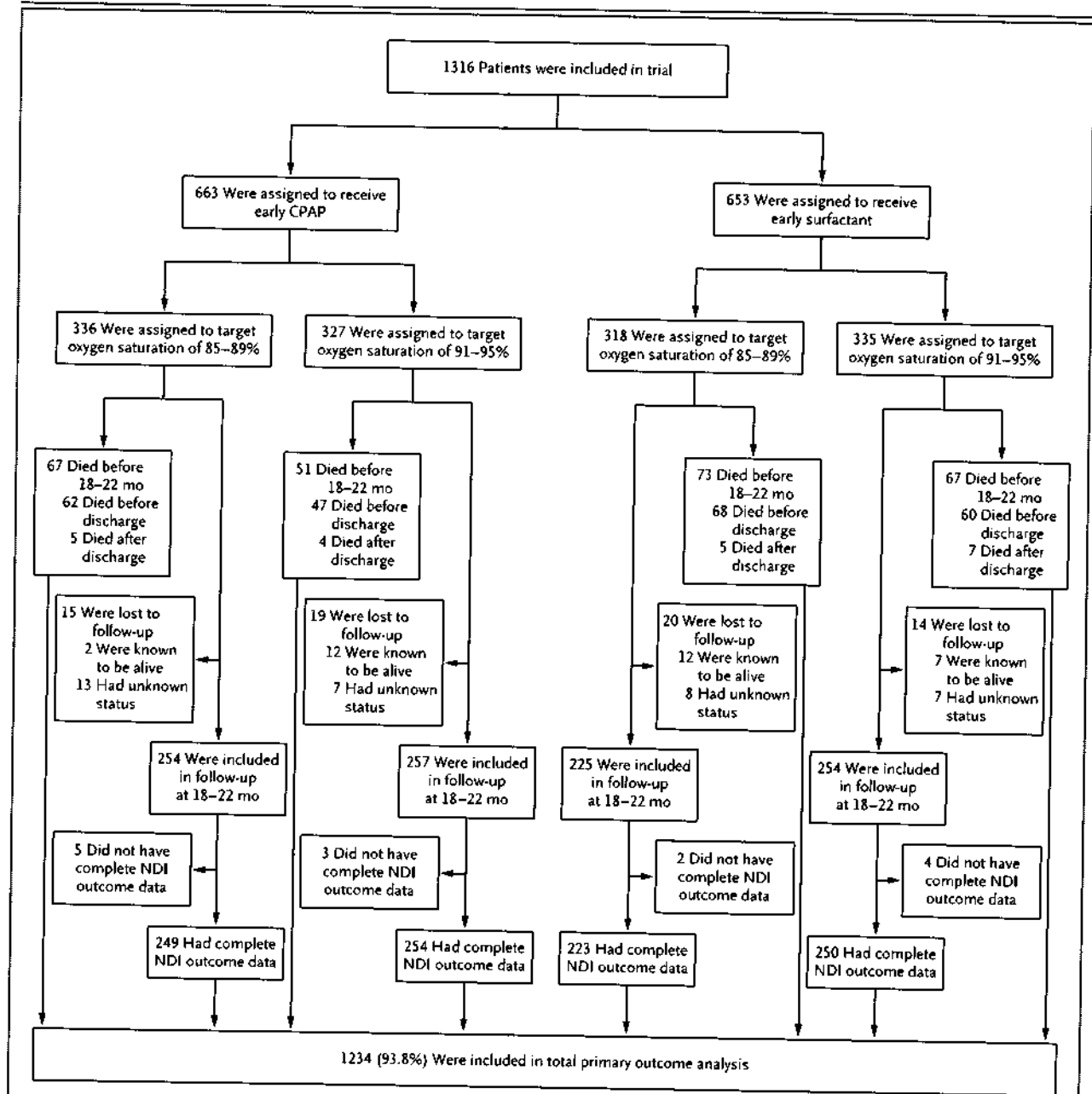


Figure 1. Enrollment, Randomization, and Outcomes.

The primary composite outcome was determined for 93.8% of the enrolled infants. A total of 258 children were known to have died before 18 to 22 months of corrected age. Of the 68 children with a missing neurodevelopmental assessment, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment (NDI) was determined for 98.6% of all children seen; 14 children had an incomplete evaluation that precluded the assignment of NDI status.

tween the two interventions with respect to the composite outcome of death or neurodevelopmental impairment or either of its components ($P > 0.70$ for all comparisons).

OTHER OUTCOMES

The incidences of the individual components of neurodevelopmental impairment (BSID-III cognitive composite score of < 70 , GMFCS score of ≥ 2 ,

Table 1. Demographic and Clinical Characteristics of the Follow-up Cohorts.*

Characteristic	CPAP (N=511)	Surfactant (N=479)	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=511)
Birth weight — g	849±186	852±193	858±186	844±192
Gestational age at birth — wk	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1.0
Small for gestational age — no. (%)†	23 (4.5)	32 (6.7)	17 (3.5)‡	38 (7.4)
Male sex — no. (%)	256 (50.1)	266 (55.5)	240 (50.1)	282 (55.2)
Multiple birth — no. (%)	138 (27.0)	114 (23.8)	124 (25.9)	128 (25.0)
Maternal use of antenatal glucocorticoids — no. (%)	493 (96.5)	456 (95.2)	462 (96.5)	487 (95.3)
Cesarean section — no. (%)	352 (68.9)	315 (65.8)	332 (69.3)	335 (65.6)
Neonatal outcome — no./total no. (%)§				
Severe retinopathy of prematurity	62/479 (12.9)	58/434 (13.4)	38/442 (8.6)¶	82/471 (17.4)
Bronchopulmonary dysplasia	193/511 (37.8)	187/479 (39.0)	177/479 (37.0)	203/511 (39.7)
Intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia	70/510 (13.7)	46/478 (9.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis	56/511 (11.0)**	30/479 (6.3)	42/479 (8.8)	44/511 (8.6)
Late-onset sepsis or meningitis	167/511 (32.7)	154/479 (32.2)	155/479 (32.4)	166/511 (32.5)
Use of postnatal glucocorticoids	34/508 (6.7)**	55/476 (11.6)	41/477 (8.6)	48/507 (9.5)
Corrected age at follow-up — mo	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

* Plus-minus values are means ±SD. There were no significant between-group differences, except as noted. Additional demographic characteristics of the cohorts are provided in Table S1 in the Supplementary Appendix. CPAP denotes continuous positive airway pressure.

† Infants who were small for gestational age were defined as those with a birth weight in less than the 10th percentile.

‡ P<0.01 for the comparison with the higher-oxygen-saturation group.

§ The comparisons of neonatal outcomes were adjusted for stratification factors (study center and gestational-age group) and familial clustering.

¶ P<0.001 for the comparison with the higher-oxygen-saturation group.

|| Assessment for bronchopulmonary dysplasia was performed at 36 weeks of postmenstrual age.

** P<0.05 for the comparison with the surfactant group.

moderate or severe cerebral palsy, hearing impairment, and blindness) among surviving infants did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups (Tables 2 and 3). Neither were there significant between-group differences in the individual components of neurodevelopmental impairment when the groups were stratified according to gestational age (Tables S2 and S3 in the Supplementary Appendix). However, in the lower-gestational-age stratum, mortality was higher in the surfactant group than in the CPAP group. Although the rates of severe retinopathy of prematurity and eye surgery were higher in the higher-oxygen-saturation group than in the lower-oxygen-saturation group, the rates of bilateral blindness, blindness of at least one eye, and other vision impairment

did not differ significantly between the groups at 18 to 22 months of corrected age (Table 4). There were no significant differences between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups in the rates of the composite outcome of death or individual neurodevelopmental-impairment components (data not shown), mean cognitive composite scores on the BSID-III, or the percentage of infants with cognitive composite scores of less than 80 points or less than 85 points (Table S4 in the Supplementary Appendix). Of the 976 children who were evaluated at 18 to 22 months of corrected age, 583 (60%) had normal status with respect to neuromotor, neurosensory, and cognitive development (with normal cognitive development defined as a BSID-III cognitive composite score of ≥85 points).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

Table 2. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the CPAP and Surfactant Groups.*

Variable	CPAP number/total number (percent)	Surfactant number/total number (percent)	Adjusted Relative Risk (95% CI)	P Value
Primary outcome determined	621/663 (93.7)	613/653 (93.9)	1.00 (0.97–1.03)	0.83
Death or NDI	173/621 (27.9)	183/613 (29.9)	0.93 (0.78–1.10)	0.38
Death before assessment at 18–22 mo of corrected age	118/643 (18.4)	140/638 (21.9)	0.83 (0.67–1.04)	0.10
NDI	55/503 (10.9)	43/473 (9.1)	1.16 (0.79–1.71)	0.44
BSID-III cognitive score <70†	36/502 (7.2)	36/472 (7.6)	0.95 (0.61–1.50)	0.84
GMFCS score ≥2‡	26/511 (5.1)	23/479 (4.8)	0.98 (0.57–1.69)	0.95
Moderate or severe cerebral palsy	21/511 (4.1)	19/479 (4.0)	0.93 (0.51–1.72)	0.82
Bilateral blindness	4/511 (0.8)	7/479 (1.5)	0.53 (0.16–1.78)	0.31
Hearing impairment	17/511 (3.3)	7/479 (1.5)	2.27 (0.96–5.37)	0.06

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic. NDI denotes neurodevelopmental impairment.

† Scores on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), are assessed relative to a standardized mean (\pm SD) of 100 \pm 15, with higher scores indicating better performance.

‡ Gross-motor function was assessed by means of the modified Gross Motor Function Classification System (GMFCS), with scores ranging from 0 to 5 and higher scores indicating greater impairment.

DISCUSSION

In this large, multicenter trial involving very-high-risk, extremely premature infants, we found no significant difference in the primary composite follow-up outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between infants randomly assigned to treatment with early CPAP and those assigned to early intubation and surfactant administration or between those randomly assigned to the lower-oxygen-saturation group and those assigned to the higher-oxygen-saturation group. Mortality did not differ significantly between the CPAP and surfactant groups, and mortality remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group — findings that are consistent with our earlier results.^{18,24} There were no significant differences between the CPAP and surfactant groups or between the higher-oxygen-saturation and lower-oxygen-saturation groups with respect to the frequencies among surviving infants of neurodevelopmental impairment and its components, including severe cognitive impairment (BSID-III

cognitive composite score, <70), moderate or severe cerebral palsy, moderate or severe motor impairment (GMFCS score, ≥2), hearing impairment, and bilateral blindness.

Recent trials have raised concern about using lower target ranges of oxygen saturation because of the possibility of increased mortality among extremely premature infants.^{21,30} In SUPPORT, the risk of death during the initial hospitalization was increased among neonates randomly assigned to the lower-oxygen-saturation group, as compared with those assigned to the higher-oxygen-saturation group, and among neonates in the lowest gestational-age stratum, mortality was increased in the surfactant group as compared with the CPAP group. As previously reported, the causes of death did not differ significantly between the lower-oxygen-saturation and higher-oxygen-saturation groups.²⁴ Although significant differences in mortality persisted at 18 to 22 months of corrected age, these differences largely reflected the differences in mortality before hospital discharge. There are other ongoing studies of this matter that, once completed, could inform decisions.³¹

Severe retinopathy of prematurity may be as-

Table 3. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation number/total number (percent)	Higher Oxygen Saturation number/total number (percent)	Adjusted Relative Risk (95% CI)	P Value
Primary outcome determined	612/654 (93.6)	622/662 (94.0)	1.00 (0.97–1.03)	0.79
Death or NDI	185/612 (30.2)	171/622 (27.5)	1.12 (0.94–1.32)	0.21
Death before assessment at 18–22 mo of corrected age	140/633 (22.1)	118/648 (18.2)	1.25 (1.00–1.55)	0.046
NDI	45/472 (9.5)	53/504 (10.5)	0.87 (0.60–1.28)	0.49
BSID-III cognitive score <70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58–1.43)	0.69
GMFCS score ≥ 2	26/479 (5.4)	23/511 (4.5)	1.17 (0.68–2.01)	0.56
Moderate or severe cerebral palsy	20/479 (4.2)	20/511 (3.9)	1.00 (0.54–1.83)	>0.99
Bilateral blindness	5/479 (1.0)	6/511 (1.2)	0.90 (0.28–2.90)	0.86
Hearing impairment	12/479 (2.5)	12/511 (2.3)	1.16 (0.54–2.49)	0.70

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic.

sociated with poor visual outcomes, even with treatment.^{32,33} In this study, infants in the lower-oxygen-saturation group who survived to discharge had a lower incidence of severe retinopathy of prematurity (8.6%, vs. 17.9% in the higher-oxygen-saturation group).²⁴ Although eye surgery was significantly less frequent in the lower-oxygen-saturation group than in the higher-oxygen-saturation group, there were no significant between-group differences with respect to rates of unilateral and bilateral blindness, nystagmus, strabismus, or the use of corrective lenses. We did not collect detailed data on visual function at the 18-to-22-month visit.

The strengths of this study include the large initial sample, which provided sufficient power to detect a clinically significant difference in the prespecified outcome of death or neurodevelopmental impairment, and the high percentage of surviving infants who underwent a comprehensive, standardized neurodevelopmental evaluation at 18 to 22 months of corrected age.

The study also has several limitations. The requirement for antenatal consent, which is associated with enrollment bias, may limit generalizability.^{34,35} In addition, the incidence of neurodevelopmental impairment in extremely premature infants in the present study was substantially lower than that previously reported by the Neonatal Research Network.³⁶ The present study used the BSID-III for cognitive assessment, where-

as previous Neonatal Research Network studies used an earlier edition, the BSID-II. Changes in the test design and standardization between the two editions may account for the lower incidence of neurodevelopmental impairment reported here.³⁶ Although the BSID-III scores in this study were higher than those previously reported for extremely premature infants, there were no significant differences between the treatment groups in this study.

Another limitation is the fact that the reported follow-up results are based on a single visit at 18 to 22 months of corrected age; other disabilities may not be evident until later in childhood. A subcohort of the SUPPORT study will be followed at school age to evaluate the longer-term neurodevelopmental outcome. Also, in comparing several secondary outcomes between pairs of treatments in this factorial-design trial (early CPAP vs. early surfactant treatment and lower vs. higher target ranges of oxygen saturation), we made no adjustments for multiple comparisons; appropriate caution should therefore be used in interpreting the reported results. Finally, differences in the neurodevelopmental outcome may have been blunted by the smaller difference in oxygen saturation between the higher-oxygen-saturation and lower-oxygen-saturation groups than was planned.²⁴

In conclusion, there were no significant differences in the composite outcome of death before

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

Table 4. Visual Outcome at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Strabismus	46/478 (9.6)	41/510 (8.0)	1.20 (0.80–1.80)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89–3.69)	0.10
Eyes track 180 degrees	462/476 (97.1)	493/507 (97.2)	1.00 (0.98–1.02)	0.93
Corrective lenses for both eyes†	21/468 (4.5)	20/493 (4.1)	1.15 (0.63–2.10)	0.65
Blind with some function in both eyes‡	3/450 (0.7)	2/475 (0.4)	1.57 (0.27–8.96)	0.61
Blind with no useful vision in both eyes‡	2/449 (0.4)	4/477 (0.8)	0.54 (0.10–2.96)	0.48
Other abnormal eye finding†‡	6/453 (1.3)	12/485 (2.5)	0.55 (0.21–1.46)	0.23
Blind in at least one eye	5/479 (1.0)	8/511 (1.6)	0.67 (0.22–2.02)	0.48
Eye surgery performed§	31/477 (6.5)	67/509 (13.2)	0.53 (0.35–0.78)	0.002

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness and other abnormal eye finding were not adjusted for study center, owing to the small numbers of patients with these characteristics.

† The reference group for relative risk was the group of children with vision that appeared to be normal in both eyes.

‡ Other abnormal eye finding was defined as an abnormality other than a condition requiring corrective lenses but not one severe enough for the child to be considered blind in that eye. Children whose eyes were classified in two different vision categories were included in the other-abnormal-eye-finding category.

§ Reasons for surgery are listed in Table S5 in the Supplementary Appendix.

assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between extremely preterm infants randomly assigned at delivery to early CPAP and those assigned to early intubation with surfactant administration or between infants assigned to lower oxygen saturation and those assigned to higher oxygen saturation. Early CPAP with a limited ventilation strategy can be considered as an alternative to early surfactant treatment, even in infants as immature as those at 24 weeks of gestational age. It is important to consider the

risk of death or neurodevelopmental impairment when deciding on oxygen-saturation targets in extremely preterm infants. Because mortality remained lower in the higher-oxygen-saturation group at the time of follow-up and there were no adverse visual or neurodevelopmental problems, lower oxygen-saturation targets cannot be recommended in these extremely preterm infants.

Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute.

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

APPENDIX

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OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

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From: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Also: Release
Date: Monday, December 24, 2012 11:26:32 AM

If you're contacted by the media today, go ahead and give the interview. Given that the govt. is closed, we'll go ahead and notify them on Wednesday, when it opens up again.

Have a good holiday, Rose.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Monday, December 24, 2012 11:17 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Release

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Eunice Kennedy Shriver
National Institute of Child Health
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Embargoed For Release
Wednesday December 26, 2012
5 p.m. Eastern Standard Time

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Benefits of higher oxygen, breathing device persist after infancy
Preterm infants still better off as toddlers, NIH network study confirms

By the time they reached toddlerhood, very preterm infants originally treated with higher oxygen levels continued to show benefits when compared to a group treated with lower oxygen levels, according to a follow-up study by a research network of the National Institutes of Health that confirms earlier network findings. Moreover, infants treated with a respiratory therapy commonly prescribed for adults with obstructive sleep apnea fared as well as those who received the traditional therapy for infant respiratory difficulties, the new study found.

In the original 2010 study, of infants born between 24 to 27 weeks of gestation, investigators in the Neonatal Research Network found:

- Infants were more likely to survive if they had received higher oxygen levels, although they were at higher risk of an eye condition that can impair vision or lead to blindness.
- Continuous positive airway pressure (CPAP), a treatment typically reserved for adults with obstructive sleep apnea, was as effective as standard therapy with a ventilator and surfactant (a sticky substance that coats the inside of the lungs).

For the current study, the researchers checked on the children's progress, comparing the groups' survival rates and cognitive and motor development 18 to 22 months after they were originally due to be born. The re-evaluation of the original study treatment groups examined:

- Children treated with oxygen saturation levels that were either low (85 percent to 89 percent) or high (91 percent to 95 percent).
 - Children treated with CPAP therapy and those treated with a ventilator and surfactant.

The researchers compiled the results of their analysis in terms of a combined primary outcome. This primary outcome took into account two possibilities: whether an infant either died in the first or second year of life or had a neurodevelopmental impairment—any of a number of conditions affecting the nervous system. These included cerebral palsy, blindness, hearing loss or low scores on tests of infant mental and motor development. The researchers selected this outcome because infants who died before 18 months of age could not be classified as having a neurodevelopmental impairment.

In terms of the primary outcome, the researchers found no differences between the groups.

When the researchers looked at outcome measures separately, however, they did observe differences. The researchers documented higher survival rates among children who received oxygen with higher saturation rates. The study's original findings showed that survivors in this group also had a greater risk of developing retinopathy of prematurity, an eye condition that can impair vision or cause blindness. Although those receiving higher oxygen levels were more likely to have had corrective eye surgery, by the time the children reached 18 to 22 months corrected age-- their age had they been born at the approximate time they were due. The researchers found that there was no difference in the rate of vision problems between the two groups.

"CPAP for infants has been available since the 1970s. This is the first study to compare surfactant treatment to CPAP in a large group of infants, and these results reassure us that CPAP is as good a choice in the first hour of life as traditional methods for very preterm babies who need help breathing," said senior author Rosemary D. Higgins, M.D., of the Pregnancy and Perinatology Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), one of two NIH institutes supporting the study. "We've also confirmed that higher oxygen targets improve survival and don't appear to threaten survivors' vision in the longer term."

The study also received funding from the National Heart, Lung and Blood Institute.

Their findings appear in the *New England Journal of Medicine*.

The research was conducted at hospitals affiliated with the NICHD-funded Neonatal Research Network.

More than 1,300 preterm infants born between 2005 and 2009 were included in the study. Between 18 and 22 months after the infants' original due date, researchers assessed whether the children had cerebral palsy and evaluated their vision, hearing, physical mobility and cognitive development.

The researchers found that 60 percent of the children showed typical physical and cognitive development for their age.

“Although these findings can give delivery room practitioners confidence in a suitable approach, they can’t help predict how these children will grow or how well they’ll do in school,” Dr. Higgins said. “Our group will continue to monitor the health of a subset of these children through childhood, to determine if there are any major differences between the groups.”

###

About the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): The NICHD sponsors research on development, before and after birth; maternal, child, and family health; reproductive biology and population issues; and medical rehabilitation. For more information, visit the Institute’s website at <http://www.nichd.nih.gov/>.

About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit <http://www.nih.gov>.

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Great news!

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Subject: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****
Importance: High

Hi

Congratulations to all!!!!

Here is the final SUPPORT Follow UP Paper and the supplementary appendix which will be published in the December 27, 2012 issue of NEJM.

PLESAE NOTE – This is under EMBARGO until 5 PM on December 26, 2012 and results are not to be disseminated or discussed prior to the embargo timeline.

Thanks again to all who made this happen!!

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Attachments: SUPPORT FU PUBLICATION 12.27.2012.pdf
SUPPORTWeb Appendix 1204Final2.pdf
NICHD Premies Oxygen followup.pdf
Importance: High

Here's everything for the SUPPORT FU paper – nice note from Susan Sherin!!

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Importance: High

Dear Rose,

Thanks for sharing this – it's wonderful to see this paying off! We were thrilled to be part of it.

Best wishes,

Susan

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FYI. Jim

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Subject: FW: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****
Importance: High

Hi

I want to sincerely thank NHLBI for all of their support with our Neonatal research Network SUPPORT trial. This is the final publication which will appear in the 12/27 issue of NEJM next week.

Again, thanks so much for all you have done!! HAPPY HOLIDAYS!!!

Rose

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Sent: Friday, December 21, 2012 10:49 AM
To: Yvonne Vaucher; mperalta@peds.uab.edu; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); mgantz@rti.org; Michele Walsh (mcw3@cwru.edu); Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com); goldso05@mc.duke.edu; Michael Acarregui (providence.org); Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; bpointindex@iupui.edu; Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org); (emcgowan@tuftsmedicalcenter.org); richard.ehrenkranz@yale.edu; Charlie Bauer (cbauer@med.miami.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary_myers@URMC.Rochester.edu); [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com)); [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); Jenna Gabrio (jgabrio@rti.org); (kzaterka@rti.org); newman@rti.org; Petrie, Carolyn; Pablo.Sanchez@UTSouthwestern.edu; Avory Fanaroff (aaf2@case.edu); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu);

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Subject: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****

Importance: High

Hi

Congratulations to all!!!!

Here is the final SUPPORT Follow UP Paper and the supplementary appendix which will be published in the December 27, 2012 issue of NEJM.

PLESAE NOTE – This is under EMBARGO until 5 PM on December 26, 2012 and results are not to be disseminated or discussed prior to the embargo timeline.

Thanks again to all who made this happen!!

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Subject: RE: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****
Date: Friday, December 21, 2012 4:25:00 PM
Attachments: NICHD Premies Oxygen followup.pdf

Here is the press release

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Jenna Gabrio \(jgabrio@rti.org\)](#)
Subject: SUPPORT Subcommittee Call 12 18 2012
Date: Friday, December 21, 2012 2:08:00 PM
Attachments: [SUPPORT Subcommittee Call 12 18 2012.doc](#)

Thanks
Rose

**SUPPORT Subcommittee Call
December 18, 2012**

Participants: Wade Rich, Julie DiFiore, Abbot Laptook, Yvonne Vaucher, Wally Carlo, Neil Finer, Abhik Das, Marie Gantz, Myriam Peralta, Nancy Newman, Michele Walsh, Kurt Schibler

NICHD: Rose Higgins, Stephanie Archer

Data Coordinating Center: Jenna Gabrio, Amanda Lewis-Evans

DiFiore Proposal

- Dr. DiFiore summarized the changes since the last submission.
 - Added 9 infants at Cleveland sites enrolled in trial. 6 in low and 3 in high groups. Infants who died look like they have a higher incidence toward intermittent hypoxic event of longer duration. These occur between 1 and 20 minutes of events. The pilot data suggests this is worth pursuing even though there will be some limitations.
- Question: When did intermittent events occur relative to time of infant's death?
 - It is a small number of infants, but it also depends when we define death. There are infants that died way past the monitoring period. There is not enough data available to monitor this. Pilot data shows curves diverging at about 3 weeks of age, but this is just crude analysis. We haven't been able to tease this out on a day-by-day basis.
- Question: How would you define peri-mortem window?
 - We don't have dates for withdrawal of care for early death, although on the clinical outcome form it does ask if respiratory support was withheld or withdrawn.
 - There was concern about whether there will be bias for infants that died.
 - Dr. Walsh clarified we would need to look at timing and cause of death and the proceed to classify them as with support withdrawn or support not withdrawn. If we find a huge cluster around time of death then we would not analyze this.
 - Investigators have not yet looked at baseline oximetry values before the intermittent events.
 - Question: If run children in two sat ranges, is the sat of 87 exposing the patient to intermittent desat, or is it independent?
 - Investigators noted that they avoided the baseline question because of skewing issues. They are looking at desats less than 80, which is what we they have defined as the event.
- Dr. Finer said that they should take a minute before each of the intermittent hypoxia event to see if they were being kept in target and to show if they were different or not. If they are different, we should determine if the low baseline sat we created for the infant is setting them up for more intermittent hypoxia.
 - Dr. Das said he did not see treatment groups in the analysis plan so was not sure how they were going to treat this.
 - The investigators clarified that it would be treated as a covariate in the analysis.
 - Dr. Finer suggested that they could reduce the skew by taking the median for the minute before on a point to point base. It would be better to do this analysis and be able to say that we tried to make this determination.
- It is not just the number of events that is important, but also if the infants that died have a longer duration than infants who survived with no difference in severity. The time interval between events is of primary interest.
- Richard Martin's animal model was discussed. Observing a similar pattern in infants would give us support for a biological study in infants.

- Investigators should clarify the primary outcome in the protocol. They would like to look at intermittent hypoxic events per day, mean duration, how many events in different time intervals, but this is not clear as it is currently written.
- Question: Why are you using a matched case-control analysis?
 - Want to determine the best way of getting control group for infants that died. Dr. Gantz said this would require some thought but we could consider truncating data for survivors. It may be easier to use all the data and control for the others as a covariate.
 - Dr. Walsh said that they may consider going for R03 funding because these are very demanding and time consuming analyses.
 - Dr. Das said that RTI can try to work out a required sample size for the effect the investigators are looking at, and we may not need the whole dataset. He noted that matching probably creates more problems than it prevents.
 - Investigators should state that the statistical analysis plan would be developed with help from RTI. The values should also be clarified in the text.
- Dr. Walsh would propose that they do a first pass at RTI and apply for outside funding for the additional data at the same time.
 - Subcommittee and Steering Committee would need to approve this protocol before Dr. Higgins can write a formal letter of support.
- **Action:** The subcommittee approved the protocol.

Other Business:

- Follow up paper will appear in December 27th issue of NEJM. There is an NICHD press release currently going through the approval process.
- We still need to get funding for Lisa Askie for the Neoprom work. She is planning to reapply for one of the Australian grants, but is also aware of the R03. It is possible for her to be the PI, but we would need to justify why the work is being done at a foreign location.
 - Dr. Higgins noted that it would be easier for a US applicant to setup a subcontract with her. There is a separate foreign process.
 - Question: Does RTI have similar expertise to look at this?
 - There are staff who have done metaanalysis in this area before, but Dr. Das does not think RTI is the right lead for this project.
 - Lisa Askie is planning to reapply for other funding but may need to look at other private sources if it is not coming from RTI.

Institute/Center: Eunice Kennedy Shriver National Institute of Child Health and Human Development

Other IC review: National Heart Lung and Blood Institute

Headline: Benefits of higher oxygen, breathing device persist after infancy

Preterm infants still better off as toddlers, NIH network study confirms

Planned Release Date: Pre-embargo distribution, Friday December 21st, for a December 26, 5 p.m. embargo lift.

Driving Event: Publication in New England Journal of Medicine

Rollout Plan: News release to call attention to publication. For distribution over NIH, NICHD press lists and Web sites.

Other Background / Hidden Factors: Followup study of a study with practice implications for treating conditions associated with preterm birth.

Spokespeople: Rosemary Higgins, M.D., Pregnancy and Perinatology Branch, NICHD

Relevant Web Links: <http://www.nichd.nih.gov>.

Funding: NICHD and NHLBI

Grant number: Not listed

Clinical trial number: Not listed

Embargoed For Release

Wednesday December 26, 2012

5 p.m. Eastern Standard Time

Contact:

Robert Bock or Marianne Glass Miller

301-496-5133

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Benefits of higher oxygen, breathing device persist after infancy

Preterm infants still better off as toddlers, NIH network study confirms

By the time they reached toddlerhood, very preterm infants originally treated with higher oxygen levels continued to show benefits when compared to a group treated with lower oxygen levels, according to a follow-up study by a research network of the National Institutes of Health that confirms earlier network findings. Moreover, infants treated with a respiratory therapy commonly prescribed for adults with obstructive sleep apnea fared as well as those who received the traditional therapy for infant respiratory difficulties, the new study found.

In the original 2010 [study](http://www.nichd.nih.gov/news/releases/pages/051610-preterm-survival.aspx) (<http://www.nichd.nih.gov/news/releases/pages/051610-preterm-survival.aspx>), of infants born between 24 to 27 weeks of gestation, investigators in the Neonatal Research Network found:

- Infants were more likely to survive if they had received higher oxygen levels, although they were at higher risk of an eye condition that can impair vision or lead to blindness.
- Continuous positive airway pressure (CPAP), a treatment typically reserved for adults with obstructive sleep apnea, was as effective as standard therapy with a ventilator and surfactant (a sticky substance that coats the inside of the lungs).

For the current study, the researchers checked on the children's progress, comparing the groups' survival rates and cognitive and motor development 18 to 22 months after they were originally due to be born. The re-evaluation of the original study treatment groups examined:

- Children treated with oxygen saturation levels that were either low (85 percent to 89 percent) or high (91 percent to 95 percent).
- Children treated with CPAP therapy and those treated with a ventilator and surfactant.

The researchers compiled the results of their analysis in terms of a combined primary outcome. This primary outcome took into account two possibilities: whether an infant either died in the first or second year of life or had a neurodevelopmental impairment—any of a number of conditions affecting the nervous system. These included cerebral palsy, blindness, hearing loss or low scores on tests of infant mental and motor development. The researchers selected this outcome because infants who died before 18 months of age could not be classified as having a neurodevelopmental impairment.

In terms of the primary outcome, the researchers found no differences between the groups.

When the researchers looked at outcome measures separately, however, they did observe differences. The researchers documented higher survival rates among children who received oxygen with higher saturation rates. The study's original findings showed that survivors in this group also had a greater risk of developing retinopathy of prematurity, an eye condition that can impair vision or cause blindness. Although those receiving higher oxygen levels were more likely to have had corrective eye surgery, by the time the children reached 18 to 22 months corrected age-- their age had they been born at the approximate time they were due. The researchers found that there was no difference in the rate of vision problems between the two groups.

“CPAP for infants has been available since the 1970s. This is the first study to compare surfactant treatment to CPAP in a large group of infants, and these results reassure us that CPAP is as good a choice in the first hour of life as traditional methods for very preterm babies who need help breathing,” said senior author Rosemary D. Higgins, M.D., of the Pregnancy and Perinatology Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), one of two NIH institutes supporting the study. “We’ve also confirmed that higher oxygen targets improve survival and don’t appear to threaten survivors’ vision in the longer term.”

The study also received funding from the National Heart, Lung and Blood Institute.

Their findings appear in the *New England Journal of Medicine*.

The research was conducted at hospitals affiliated with the NICHD-funded Neonatal Research Network (<http://www.nichd.nih.gov/research/supported/pages/nrn.aspx>).

More than 1,300 preterm infants born between 2005 and 2009 were included in the study. Between 18 and 22 months after the infants' original due date, researchers assessed whether the

children had cerebral palsy and evaluated their vision, hearing, physical mobility and cognitive development.

The researchers found that 60 percent of the children showed typical physical and cognitive development for their age.

“Although these findings can give delivery room practitioners confidence in a suitable approach, they can’t help predict how these children will grow or how well they’ll do in school,” Dr. Higgins said. “Our group will continue to monitor the health of a subset of these children through childhood, to determine if there are any major differences between the groups.”

###

About the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): The NICHD sponsors research on development, before and after birth; maternal, child, and family health; reproductive biology and population issues; and medical rehabilitation. For more information, visit the Institute’s website at <http://www.nichd.nih.gov/>.

About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit <http://www.nih.gov>.

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Stile, Christina \(NIH/NICHD\) \[E\]](#)
Subject: Final ASPA_0876_20121210_NIH_PR_Premies_Oxygen_Benefit_APPROVED
Date: Friday, December 21, 2012 1:13:00 PM
Attachments: [Final ASPA_0876_20121210_NIH_PR_Premies_Oxygen_Benefit_APPROVED.docx](#)

Christina

Thanks for your help

This is the last version I have from Bob – I need the final version with the NIH letterhead.

Thanks again

Rose

From: Cunningham, Meg
To: Blaisdell, Carol (NIH/NHLBI) [E]; cgleason@u.washington.edu; Willinger, Marian (NIH/NICHD) [E]; mcallen@ihmi.edu; merran.thomson@ic.ac.uk; RJB61@hscmail.mcc.virginia.edu; Weiner@Biostat.bsc.gwu.edu; Traci Clemons; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Confidential: Accepted SUPPORT Follow-up Manuscript
Date: Friday, December 21, 2012 11:42:38 AM
Attachments: SUPPORT EU PUBLICATION 12.27.2012.pdf
SUPPORTWeb Appendix 1204Final2.pdf

Dear SUPPORT DSMC Members,

Attached you will find the follow-up SUPPORT manuscript and the supplementary appendix which will be published in the December 27, 2012 issue of NEJM.

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We thank you for your participation in this trial.

Happy Holidays!

Meg

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Subject: RE: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****
Date: Friday, December 21, 2012 11:37:37 AM

Congratulations to the SUPPORT FU team, especially Yvonne, Myriam, Neil, Wally, and Marie. Well done.

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From: Higgins, Rosemary (NIH/NICHD) [E]
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Subject: RE: NEJM SUPPORT FU paper
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sure

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higginsr@mail.nih.gov

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Friday, December 21, 2012 11:11 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NEJM SUPPORT FU paper

I can copy you on this message, right?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 21, 2012 11:05 AM
To: Cunningham, Meg
Cc: Das, Abhik
Subject: NEJM SUPPORT FU paper

Meg –

Can you send the SUPPORT FU paper to the DSMC as a confidential communication (let them know about the embargo) and THANKS them for all their help

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Avroy Fanaroff"
Subject: RE: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****
Date: Friday, December 21, 2012 10:58:00 AM

How's (b)(6)

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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Avroy Fanaroff [mailto:aaf2@case.edu]
Sent: Friday, December 21, 2012 10:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****

Thanks
happy Holidays
another great year for the Network
Congratulations
Av

On Fri, Dec 21, 2012 at 10:49 AM, Higgins, Rosemary (NIH/NICHD) [E]
<higginsr@mail.nih.gov> wrote:

Hi

Congratulations to all!!!!

Here is the final SUPPORT Follow UP Paper and the supplementary appendix which will be published in the December 27, 2012 issue of NEJM.

**PLESAE NOTE – This is under EMBARGO until 5 PM on
December 26, 2012 and results are not to be disseminated or
discussed prior to the embargo timeline.**

Thanks again to all who made this happen!!

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research
Network
Pregnancy and Perinatology Branch

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--

Avroy A. Fanaroff, M.D.
Eliza Henry Barnes Professor of Neonatology
Rainbow Babies & Children's Hospital
Professor of Pediatrics
Case Western Reserve University School of Medicine
11100 Euclid Avenue
Cleveland, Ohio 44106
(216) 844-3387
aaf2@case.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Yvonne Vaucher; mperalta@peds.uab.edu; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); mgantz@rti.org; Michele Walsh (mcw3@cwru.edu); Abbot Laptook; Brad Yoder (Bradkey.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yoltan (kimberly.yoltan@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@gmail.com; golds005@mc.duke.edu; Michael.Acarregui@providence.org; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhntz@stanford.edu; bpindex@iunui.edu; Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org); richard.ehrenkranz@yale.edu; Charlie Bauer (cbauer@med.miami.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfuhrmc.edu; Gary Myers (gary_myers@URMC.Rochester.edu); (b)(6)@gmail.com; (b)(6)@ol.com
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); Jenna Gabrio (jgabrio@rti.org); (kzaterka@rti.org); newman@rti.org; Petrie, Carolyn; Pablo.Sanchez@UTSouthwestern.edu; Ivory Fanaroff (aaf2@case.edu); Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; Frantz, Ivan; "Duara, Shahnaz" (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale_ghelos@urmc.rochester.edu; carl_dangio@urmc.rochester.edu
Subject: *****CONFIDENTIAL SUPPORT FOLLOW UP NEJM PAPER*****
Date: Friday, December 21, 2012 10:49:00 AM
Attachments: SUPPORT FU PUBLICATION 12.27.2012.pdf
SUPPORTWeb Appendix 1204Final2.pdf
Importance: High

Hi

Congratulations to all!!!!

Here is the final SUPPORT Follow UP Paper and the supplementary appendix which will be published in the December 27, 2012 issue of NEJM.

PLESAE NOTE – This is under EMBARGO until 5 PM on December 26, 2012 and results are not to be disseminated or discussed prior to the embargo timeline.

Thanks again to all who made this happen!!

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301-435-7909
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Finer, Neil](mailto:Finer_Neil)
To: wcarlo@peds.uab.edu; [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD); mgantz@rti.org; adas@rti.org; mperalta@peds.uab.edu; [Rich, Wade](mailto:Rich.Wade)
Subject: Fwd: From the New England Journal of Medicine
Date: Friday, December 21, 2012 6:21:09 AM
Attachments: [12122708.pdf](#)
[ATT00001.htm](#)

FYI
Happy Holidays
Neil

Sent from my iPhone

Begin forwarded message:

From: "mediasupport@nejm.org" <<mailto:mediasupport@nejm.org>>"
<mediasupport@nejm.org<<mailto:mediasupport@nejm.org>>>
To: "Finer, Neil" <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>
Subject: From the New England Journal of Medicine

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Dear Dr. Finer,

Congratulations. This coming week the New England Journal of Medicine (NEJM) is publishing your Original Article, "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial." Attached is a PDF of the final version. This electronic file is intended for your personal, noncommercial use. We have also attached any associated articles.

EMBARGO

This material is under our press embargo until Wednesday at 5 p.m. Eastern time. You may answer questions from the press, but please get assurances that nothing will be made public until that release time.

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Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief

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From: Bell, Edward (Pediatrics)
To: "McBrien, James, D"
Cc: Truog, William (MD); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Manuscript Entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" *Sent on Behalf of William E. Truog, MD*
Date: Friday, December 21, 2012 12:39:33 AM
Attachments: Review of Kennedy et al Evaluating ROP screening.doc

Here's my review.

From: McBrien, James, D [mailto:jdmcbrien@cmh.edu]
Sent: Monday, December 17, 2012 10:39 AM
To: Bell, Edward (Pediatrics)
Cc: Truog, William (MD); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Manuscript Entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" *Sent on Behalf of William E. Truog, MD*

The enclosed manuscript entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants"; is being sent for internal Neonatal Network Research review. Would you be able to review the manuscript by December 31, 2012? There are no particular guidelines for the review except to look at study design, validity, clarity of results, and appropriateness of interpretation.

Thanks,

Jim

Electronic mail from Children's Mercy Hospitals and Clinics. This communication is intended only for the use of the addressee. It may contain information that is privileged or confidential under applicable law. If you are not the intended recipient or the agent of the recipient, you are hereby notified that any dissemination, copy or disclosure of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the message to Children's Mercy Hospital's Information Security Officer via return electronic mail at informationsecurityofficer@cmh.edu and expunge this communication without making any copies. Thank you for your cooperation.

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Review of Kennedy et al: Evaluating retinopathy of prematurity screening guidelines for 24-27 week gestational age infants

In this manuscript, the authors report their analysis of the ages at which severe ROP was diagnosed in the cohort of infants enrolled in SUPPORT, who had regular ophthalmologic examinations according to the standard recommendations at the time, 2005-2009. Analysis of the data showed that infants with severe ROP would have been correctly identified in time to allow treatment if indicated had the examinations been done according to the 2006 screening recommendations of the AAP, AAO, and AAPOS. Of note, these data showed that severe ROP is diagnosed at earlier postmenstrual age in more preterm infants, contrary to previous reports. Another notable finding is that 10% of infants with severe ROP reached this status only after discharge home, and these infants could not be predicted before discharge to home. The only way to identify and treat these infants is by continuing regular examinations after discharge. I don't know if this critically important point is well known from other studies, but its importance should be emphasized in this paper. I suggest you report these 14 infants as a percent of infants with severe ROP (10.1%), not just as the percent of all screened infants (1.4%). This makes clear that this is not a rare event and underscores the importance of assuring good follow-up after discharge of infants whose retinal vasculature has not yet fully matured.

The paper is well written, and the methods are solid. My specific comments and suggestions are mainly minor. The tables and figures are good, although there seems to be a problem with Figure 2:

1. Figure 2 is a nice way to present the data, but there may be some problems with the way the bars are generated. Maybe it's because the denominators used to compute the percents are not the expected ones. The bars that should add up to 100% do not seem to. For example, for 24 weeks, shouldn't the first and second bars add up to 100? Since the first (dark gray) is <40 and the second (blue) is <60, their total is <100. Similarly, shouldn't the sum of the black (died before exam) and medium blue (severe ROP) bars be equal to the gray (severe ROP or death) bar? It does not seem to be.
2. On title page and elsewhere (e.g. second paragraph of Discussion), you should use a space between the quantity and units (1000 g).
3. Results, 4th paragraph: "The distributions for age of onset for each ~~week~~ 2-week interval of completed gestation at birth are shown in Figure 3."
4. Results, 4th paragraph and Discussion, 1st paragraph: You refer to "prior studies" and "previous studies" without citing them. You need references here.
5. Table 2, Footnote 2: Shouldn't this be "data missing for 1 infant"?

This paper reports useful analyses of this important cohort and deserves to be published.

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Michele Walsh \(mcw3@cwru.edu\)](#); [Julie Di Fiore \(jmd3@case.edu\)](#) ([jmd3@case.edu](#))
Subject: SUPPORT secondary proposal
Date: Thursday, December 20, 2012 9:14:00 AM

Hi

Once you update the proposal we discussed earlier in the week, please send it to me so that I can get SC approval.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: [Finer, Neil](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Vaucher, Yvonne](#); [Wally Carlo \(wacarlo@uab.edu\)](#)
Cc: [Rich, Wade](#)
Subject: Re: PDF of Your Article for NEJM
Date: Tuesday, December 18, 2012 4:43:37 PM

Yes these look correct
Neil

From: <Higgins>, Rosemary Higgins <higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>>
Date: Tuesday, December 18, 2012 11:22 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>, Yvonne Vaucher <yvaucher@ucsd.edu<<mailto:yvaucher@ucsd.edu>>>, "Wally Carlo (wacarlo@uab.edu<<mailto:wacarlo@uab.edu>>)" <wacarlo@uab.edu<<mailto:wacarlo@uab.edu>>>
Subject: FW: PDF of Your Article for NEJM

Are these the final versions or do you have an updated version? I want to share with the authors/PI's in advance of the publication next week.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Friday, November 30, 2012 6:30 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo, M.D.; adas@rti.org<<mailto:adas@rti.org>>; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: FW: PDF of Your Article for NEJM

FYI
These look good to me
Neil

From: Nejm Article [<mailto:nejmarticle@mms.org>]
Sent: Friday, November 30, 2012 2:06 PM
To: Finer, Neil
Cc: Laurencot, Elizabeth
Subject: PDF of Your Article for NEJM

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: "Susan Hintz"
Subject: RE: would you mind?
Date: Tuesday, December 18, 2012 3:32:00 PM
Attachments: [11.16.2012 BRAZIL NEC TALK.pptx](#)
[11.17.2012 Brazil extreme prematurity.pptx](#)

Here are two of the talks - feel free to use any of the slides - the NEC one was focused and the extreme prematurity one was broad.

Good luck to you.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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-----Original Message-----

From: Susan Hintz [<mailto:rhintz@stanford.edu>]
Sent: Tuesday, December 18, 2012 3:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: would you mind?

Hi Rose,

Would you mind if I took a look at your neurodevelopmental outcomes of extremely preterm infants talk from Brazil? I have to whittle down my usual ND outcomes talk (which is way long) for an upcoming meeting, and I wanted to see what you had highlighted in terms of studies. I promise not to steal any slides!!

Thanks

Susan



NICHD
NEONATAL RESEARCH NETWORK

NECROTIZING ENTEROCOLITIS SHORT AND LONG TERM OUTCOMES



Topics to be covered

NEC Background

Short term outcomes

Long Term outcomes

Need for research

RESEARCH NETWORK



NEC Background

Incidence

Generally 5-15% of very low birth weight (VLBW) infants

Risk factors

Prematurity

Cyanotic congenital heart disease

Antepartum hemorrhage

5 minute Apgar < 7



Bell's Staging for NEC

IA - Suspected NEC – Temperature instability, apnea, bradycardia, lethargy, gastric residuals, mild abdominal distension, emesis, guaiac + stools

X-ray – normal or intestinal dilatation; mild ileus

IB – Suspected NEC - IA + bright red blood per rectum

IIA – definite NEC - above + ↓ plt, mild metabolic acidosis, ↓ bowel sounds, mild abdominal tenderness

X-ray intestinal dilatation, pneumatosis intestinalis

IIB – definite NEC – above + abdominal tenderness, cellulitis

X-ray +/- portal vein gas, +/- ascites

Bell's Staging for NEC

IIIA – Advanced NEC – same as IIB + hypotension, bradycardia, severe apnea, respiratory/metabolic acidosis, DIC neutropenia, anuria, generalized peritonitis, abdominal distension

X-ray - ascites

IIIB – Advanced NEC with perforation

X-ray - pneumoperitoneum

NEC Treatment

Medical management

Nasogastric suction

IV fluids

Broad spectrum antibiotics

Surgical management

Peritoneal drain

Laparotomy

Necrotizing Enterocolitis - incidence

ALLIANCE FOR ENTEROCOLITIS RESEARCH NETWORK



NEC – Medical and Surgical

RESEARCH NETWORK

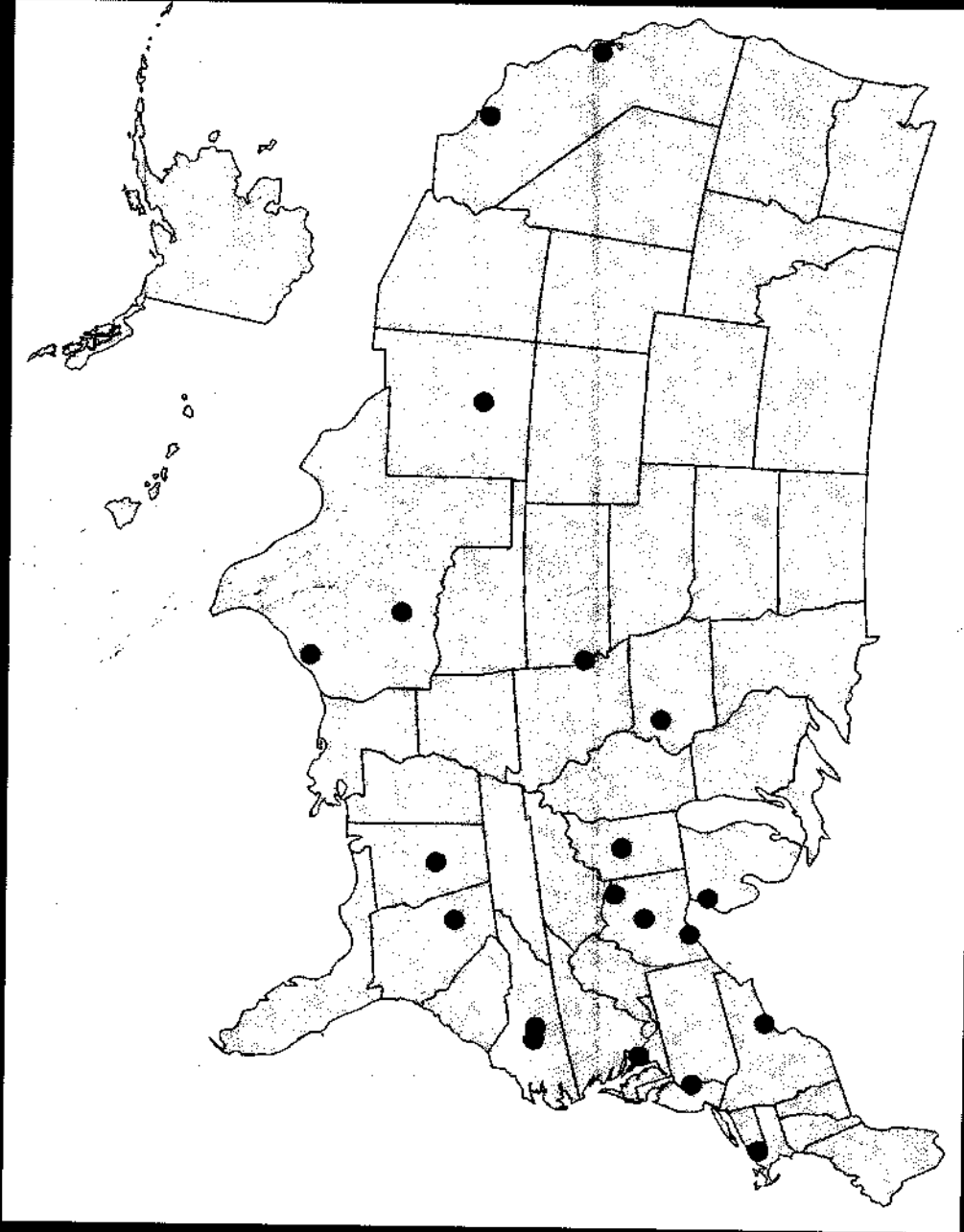


NEC – short term outcomes

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NICHD NRN 2011-2016



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Outcomes after NEC

NEC remains a potentially devastating complication of prematurity

NEC mortality 55% (Blakely M Ann Surg 2005)

High risk for death, short-term morbidities

Hartman G, et. al. 1988; Rowe M, et. al. 1994; Horwitz J, et. al. 1995; Dimmitt R, et. al. 2000; Chwals W, et. al. 2001; Blakely M, et. al. 2005

INTERNATIONAL RESEARCH NETWORK



Blakely, et. al. *Pediatrics* 2006; 117:e680

DRAIN = 80 LAP = 76

4 lost

5 lost

PAEDIATRIC SURGICAL RESEARCH NETWORK



Need for a new trial

Need for RCT of surgical interventions for NEC with

NEC Steps Trial (RL Moss, *NEJM* 2006)

Critically important, well-designed RCT of short-term outcomes after lap or drain in VLBW infants

In hospital/ outcomes similar; challenge now to determine whether neurodevelopmental outcomes differ by treatment



Summary for Trial

ELBW infants with severe NEC or IP at extremely high risk for adverse 18-22 month neurodevelopmental outcome

Surgical strategy associated with best outcome is not known - need for RCT

Surgical expertise & commitment, and follow-up programs:

Neonatal Research Network uniquely positioned to undertake this trial

PEDIATRIC SURGEONS ARE KEY

NICHD
NEONATAL RESEARCH



Role of Surgeons

Allow randomization

Assist with patient follow
up

Get trial DONE!!!

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Barriers to recruitment

Physician refusal

Parent refusal

Timing of presentation and staff availability

Acute presentation and overwhelming situation for parents

Transfer with the expectation of “one procedure”

Infant in extremis (coding, rapid escalation of therapy, etc)



Physician refusal

Education regarding existing literature

Education of referral centers as to need for the trial

Steering committee discussion

Surgeon meeting – APSA

Surgeon teleconference to discuss importance of study

Reinforcement of need for evidence based practice

Parent refusal

Equipose with presentation

Fellow consent

Neonatology driven consent

Pre-perforation consent (not allowed at all sites)

Education of staff at sites

Dearth of evidence based practice

Reinforce need for the study



Timing of presentation and staff availability

RFA mandates 24 hour coverage for trials

Pre-perforation consent

Creative alternatives for alternates to consent (fellows, neonatology, attending, etc)

overwhelming situation for parents

? Brochure for NEST study to be given to parents prior to illness

Description of NRN research network site and ongoing studies

Site dependent –relationship with individual care providers and research staff

Infant in extremis (coding, rapid escalation of therapy, etc

Unless pre-consented, very little can be done for these individual cases

2 cases in this category thus far

Opportunities for recruitment – what are successful sites currently doing??

Non-surgeon or non-neonatologist are getting acute consent (surgical fellow, neonatal fellow, coordinator, etc)

Pre-perforation consent

Neutral presentation and reinforcement of lack of evidence based practice for parents

Individual champions at individual sites – site specific

Education – at the site as well as referral sites

Opportunities for recruitment – what are successful sites currently doing??

Specific study surgeon

Not practical at all sites due to referral patterns

Requires time extra commitment on the part of individual surgeon(s)

Staff education (nursing, physician, research) – this question is unanswered and needs to be answered – get folks on board

Updates at regular staff and research meetings – how are we doing, getting the study on everyone's radar screen

Food for thought



“An ounce of patience is sometimes better
than a bushel full of brains”

RESEARCH NETWORK





NICHD
NEONATAL RESEARCH NETWORK

Outcomes Following Extreme Prematurity



Topics To Be Covered

Burden of Preterm birth

Pregnancy dating

NICHD NRN Short term mortality experience

NICHD NRN Short term (in hospital) morbidity experience

Outcomes beyond hospital discharge

RESEARCH NETWORK



Definition of Preterm Birth

< 37 weeks

Late preterm 34-36 weeks

Moderate preterm 32-33 weeks

Very preterm 28-< 32 weeks

Extremely preterm < 28 weeks

RESEARCH NETWORK



Global Burden of Preterm Birth

15 million infants per year (> 1 out of 10)

> 1 million deaths per Year

Survivors – disabilities including learning, vision, hearing

GLOBAL RESEARCH NETWORK



Preterm Births – International Data

India:	3 519 100
China:	1 172 300
Nigeria:	773 600
Pakistan:	748 100
Indonesia:	675 700
The United States of America:	517 400
Bangladesh:	424 100
The Philippines:	348 900
The Democratic Republic of the Congo:	341 400
Brazil:	279 300

INTERNATIONAL RESEARCH NETWORK



Topics To Be Covered

Burden of Preterm birth

Pregnancy dating

NICHD NRN Short term mortality experience

NICHD NRN Short term (in hospital) morbidity experience

Outcomes beyond hospital discharge

NATIONAL RESEARCH NETWORK



Accuracy of LMP in Assessing Pregnancy Length

Random error: >7d variation (± 2 SD) in
cycle length and presumably ovulation
Menstrual cycle 21-35 days

Systematic error: Accumulating evidence
that true GA often under-estimated
among infants having the lowest GA
estimates



Early Ultrasound



Better than an accurate LMP

Error (± 2 SD) claimed to be as low as
 ± 0.5 -1 week at 12-14 weeks

Yet, almost all studies involve unmasked sonographer(s) and a relatively healthy population likely to have AGA infants

At 20-30 weeks, ACOG notes ± 2 weeks, a large error for treatment decisions.

Am J Obstet Gynecol 1996;174:278; Ultrasound Obstet Gyn 1996;8:397 ; Ultrasound Obstet Gyn 2005 26:504.

ALL RESEARCH NETWORK



Commonly Recommended Thresholds for Intensive Care

- ≥ 24 to 25 weeks GA, initiate intensive care
- ≤ 22 weeks, give comfort care
- 23-24 weeks, decide with parents
- Thresholds vary
- Difference of only 1-2 weeks will often change decision



Topics To Be Covered

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Pregnancy dating

NICHD NRN Short term mortality experience

NICHD NRN Short term (in hospital) mortality experience

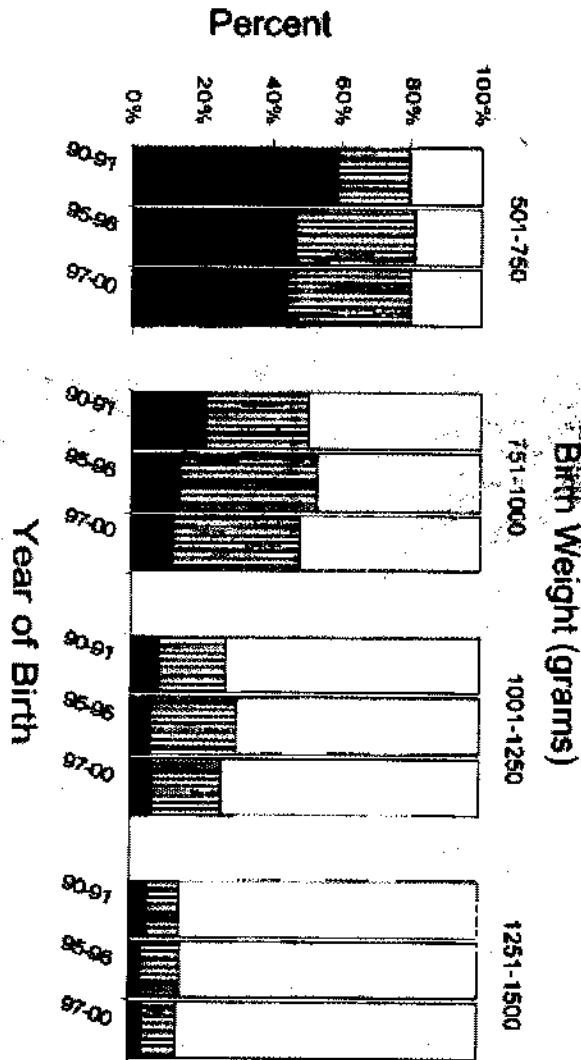
Outcomes beyond hospital discharge

NATIONAL RESEARCH NETWORK



Extreme Prematurity and Mortality Over Time

FIGURE 1
Changes in mortality, morbidity, and morbidity-free survival over time



Comparison of mortality, morbidity, and morbidity-free survival for very low birthweight infants cared for in NICHD Neonatal Research Network centers (n = 12) in 1990-91, 1995-96, and 1997-2000 by 250-g birthweight intervals, based on singleton infants born in the centers.



Extreme Prematurity and Survival

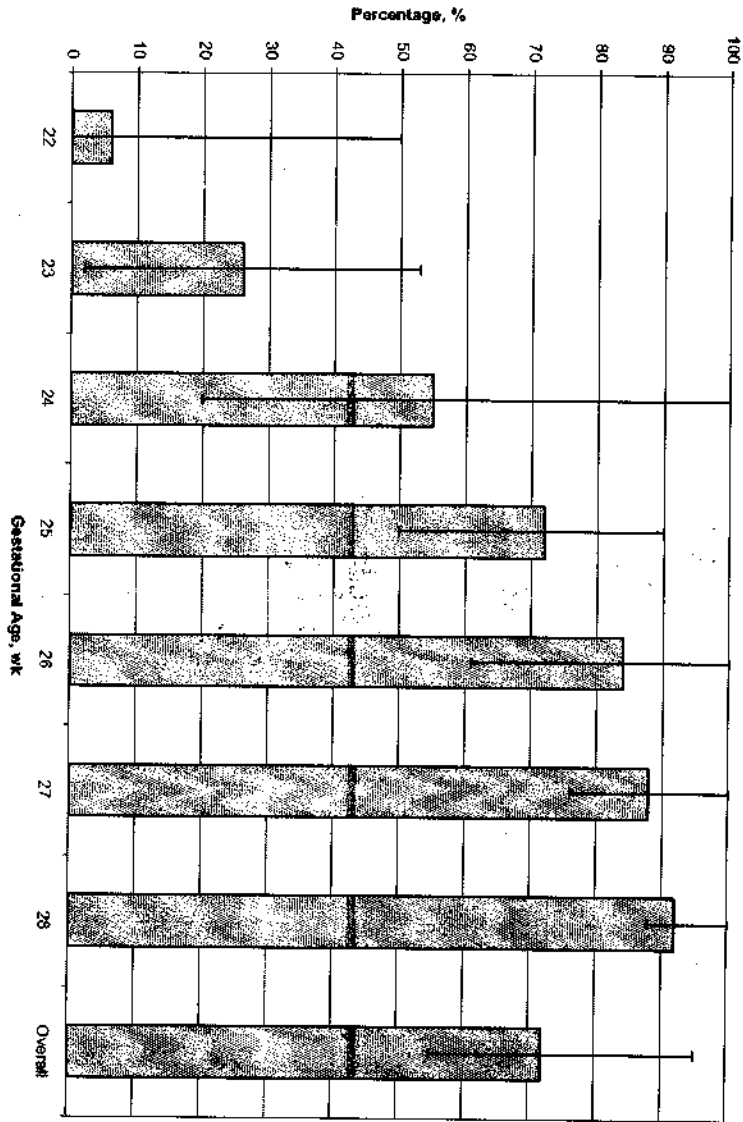


FIGURE 1
Survival to discharge according to GA among 95/75 VLBW infants born in NICHD NRN centers between January 1, 2003, and December 31, 2007. The thin lines indicate ranges across centers.

Topics To Be Covered

Burden of Preterm birth

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Outcomes beyond hospital discharge

NATIONAL RESEARCH NETWORK



Extreme Prematurity and Length of Stay

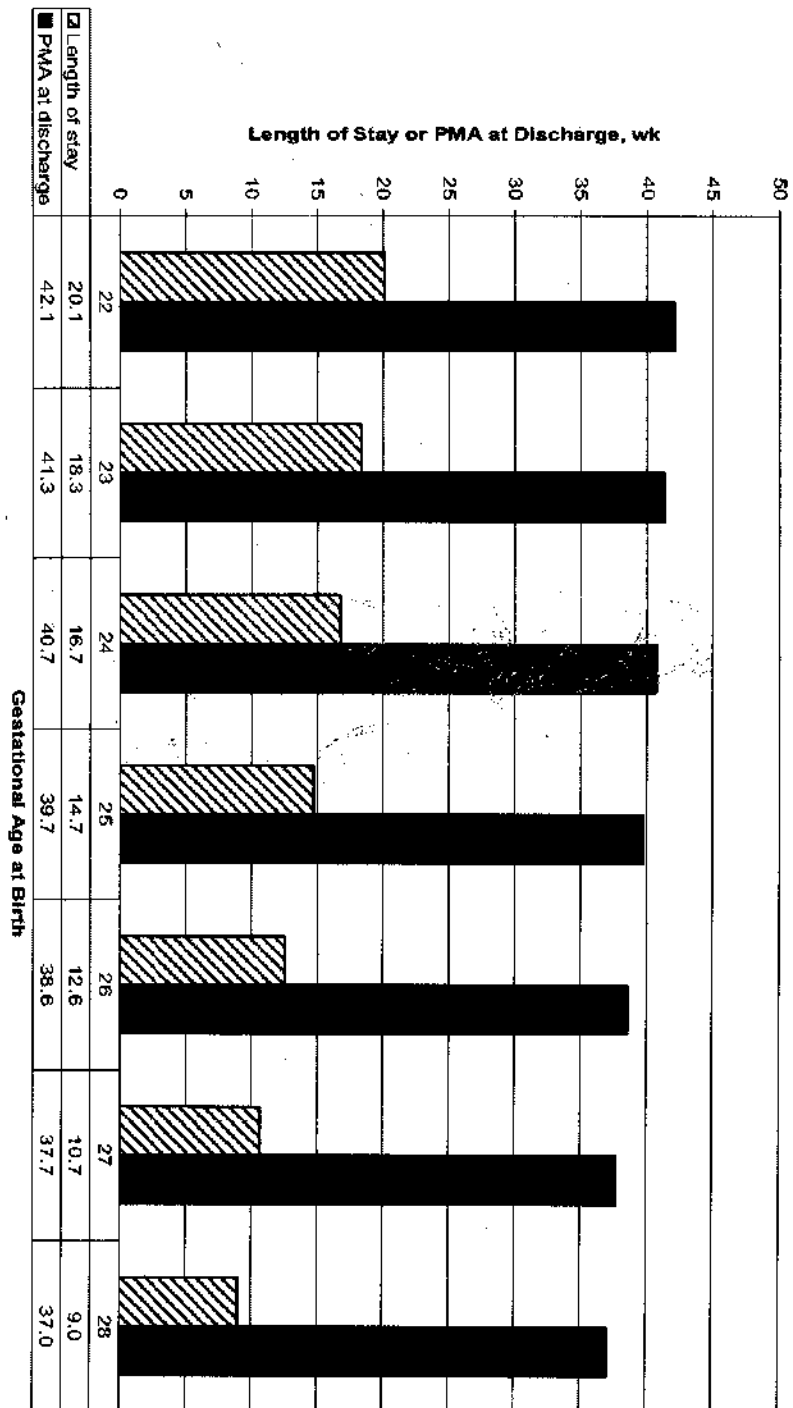


FIGURE 2
 Median length of hospitalization (in weeks) and median PMA at discharge (in weeks) according to GA at birth among 6369 VLBW infants who were born in NICHD NRN centers between January 1, 2003, and December 31, 2007, and survived to discharge.

Extreme Prematurity and Morbidity Bronchopulmonary Dysplasia

NATIONAL RESEARCH NETWORK



Extreme Prematurity and Morbidity Intraventricular Hemorrhage

NIH RESEARCH NETWORK



Extreme Prematurity and Morbidity Infection

ALL RESEARCH NETWORK

Extreme Prematurity and Morbidity Patent Ductus Arteriosus**

CONATIONAL RESEARCH NETWORK



Extreme Prematurity and Morbidity Retinopathy of Prematurity

RESEARCH NETWORK

Extreme Prematurity and Morbidity Necrotizing Enterocolitis

NATIONAL RESEARCH NETWORK



Association of Antenatal Corticosteroids With Mortality and Neurodevelopmental Outcomes Among Infants Born at 22 to 25 Weeks' Gestation

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Betty R. Vohr, MD
Barbara J. Stoll, MD
Richard A. Ehrenkranz, MD
William W. Andrews, PhD, MD
Dennis Wallace, PhD
Abhik Das, PhD
Edward F. Bell, MD
Michelle C. Walsh, MD, MS
Abbot R. Laptook, MD
Seetha Shankaran, MD
Brenda B. Ponderexter, MD, MS
Ellen C. Hale, RN, BS, CCRC
Nancy S. Newman, RN
Alexis S. Davis, MD, MS, EPI

Context Current guidelines, initially published in 1995, recommend antenatal corticosteroids for mothers with preterm labor from 24 to 34 weeks' gestational age, but not before 24 weeks due to lack of data. However, many infants born before 24 weeks' gestation are provided intensive care.

Objective To determine if use of antenatal corticosteroids is associated with improvement in major outcomes for infants born at 22 and 23 weeks' gestation.

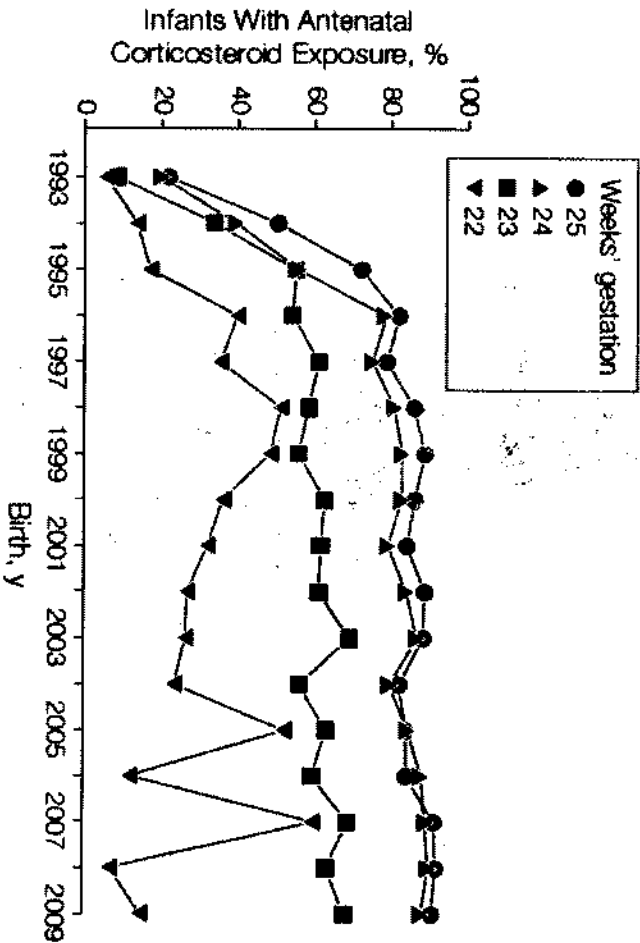
Design, Setting, and Participants Cohort study of data collected prospectively on inborn infants with a birth weight between 401 g and 1000 g (N=10 541) born at 22 to 25 weeks' gestation between January 1, 1993, and December 31, 2009, at 23 academic perinatal centers in the United States. Certified examiners unaware of exposure to antenatal corticosteroids performed follow-up examinations on 4924 (86.5%) of the infants born between 1993 and 2008 who survived to 18 to 22 months. Logistic regression models generated adjusted odds ratios (AORs), controlling for maternal and neonatal variables.

Main Outcome Measures Mortality and neurodevelopmental impairment at 18 to 22 months' corrected age.

Results Death or neurodevelopmental impairment at 18 to 22 months was significantly lower for infants who had been exposed to antenatal corticosteroids and were born at 23 weeks' gestation (83.4% with exposure to antenatal corticosteroids vs 90.5% without exposure; AOR, 0.58 [95% CI, 0.42-0.80]), at 24 weeks' gestation (68.4% with exposure to antenatal corticosteroids vs 80.3% without exposure; AOR, 0.62 [95% CI, 0.49-0.78]), and at 25 weeks' gestation (52.7% with exposure to antenatal corticosteroids vs 67.9% without exposure; AOR, 0.61 [95% CI, 0.50-0.74]) but not in those infants born at 22 weeks' gestation (90.7% with exposure to antenatal corticosteroids vs 93.1% with

Antenatal Corticosteroid use over time

Figure. Frequency of Exposure to Antenatal Corticosteroids by Gestational Age and Year of Birth



The administration of antenatal corticosteroids increased over the 10-year period but remained lower at the lower gestational ages. The ranges for sample size by year are 15 to 36 for 22 weeks' gestation, 85 to 140 for 23 weeks' gestation, 134 to 325 for 24 weeks' gestation, and 162 to 333 for 25 weeks' gestation.

Topics To Be Covered

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Outcomes beyond hospital discharge

RESEARCH NETWORK



Outcomes Beyond NICU Discharge

Web based outcomes tool

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Intensive Care for Extreme Prematurity — Moving Beyond Gestational Age

Jon E. Tyson, M.D., M.P.H., Nehal A. Parikh, D.O., John Langer, M.S.,
Charles Green, Ph.D., and Rosemary D. Higgins, M.D., for the National Institute
of Child Health and Human Development Neonatal Research Network*

RESEARCH NETWORK

Web Based Outcomes Tool Study

Population (n = 4446)

Mean GA estimate = 23.9 weeks

Mean BW = 648 g

45% Black; 35% White; 17% Hispanic

92% received prenatal care

71% received antenatal steroids

83% received intensive care (Mechanical Ventilation)

(range: 23% at 22 weeks to 99% at 25 weeks)

**Recruited 1997-2003



Definitions

NDI (Neurodevelopmental Impairment)

Bayley II MDI or PDI < 70

Moderate or severe cerebral palsy

Bilateral blindness

Bilateral hearing loss requiring hearing aids or cochlear implants

PNDI (Profound Neurodevelopmental Impairment)

Bayley II MDI < 50

Palisano GMFS 5



Web based outcomes tool

NATIONAL RESEARCH NETWORK



Substantial Center Differences

Among centers with ≥ 100 ventilated infants, ratio of observed/expected outcomes for their population:

Death	0.68-1.38
Death or PNDI	0.75-1.23
Death or NDI	0.85-1.17

Also within center variation in ratio of observed/expected for different outcomes.

Limitations

Center-based observational study. Effect of ANS due at least in part to obstetric commitment to optimize infant outcome

No attempt to measure long term burdens or costs

GA estimate likely to be more closely related to outcome in populations that virtually always have early sonogram.

Available evidence does indicate that we should

Move beyond GA thresholds and shift the focus from estimated GA estimate to estimated probability of favorable (unfavorable) outcome.

Develop & test practical methods to use multiple risk factors in assessing this probability

Death and NDI - ANS

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Moderate to Severe Cerebral Palsy at 18-22 months – Impact of ANS

RESEARCH NETWORK



Neurodevelopmental outcome and infection

Infants 401-1000 grams

Classified as

Uninfected

Clinical infection

Sepsis – positive blood culture

Sepsis plus NEC

Meningitis (with or without sepsis)

Neurodevelopmental outcome at 18-22 months

Neurodevelopmental outcome and infection

RESEARCH NETWORK



Bayley II and III

Bayley III underestimates delay (Anderson Arch Ped Adol Med, 2010)

Australian cohort

Bayley II language and cognitive scores are higher than

Bayley II MDI scores (Moore J Pediatr, 2012)

EPICURE 2 cohort

Bayley III may overestimate cognitive performance compared to Bayley II (Vohr, J Pediatr 2012)

NICHD Cohort

ALL RESEARCH NETWORK



Factors associated with increased long term morbidity

Chronic Lung Disease/Bronchopulmonary Dysplasia

Grade 3 or 4 IVH; periventricular leukomalacia

Steroids for BPD

Infection

NEC

Male gender

RESEARCH NETWORK



Factors associated with decreased long term morbidity

Increased birth weight

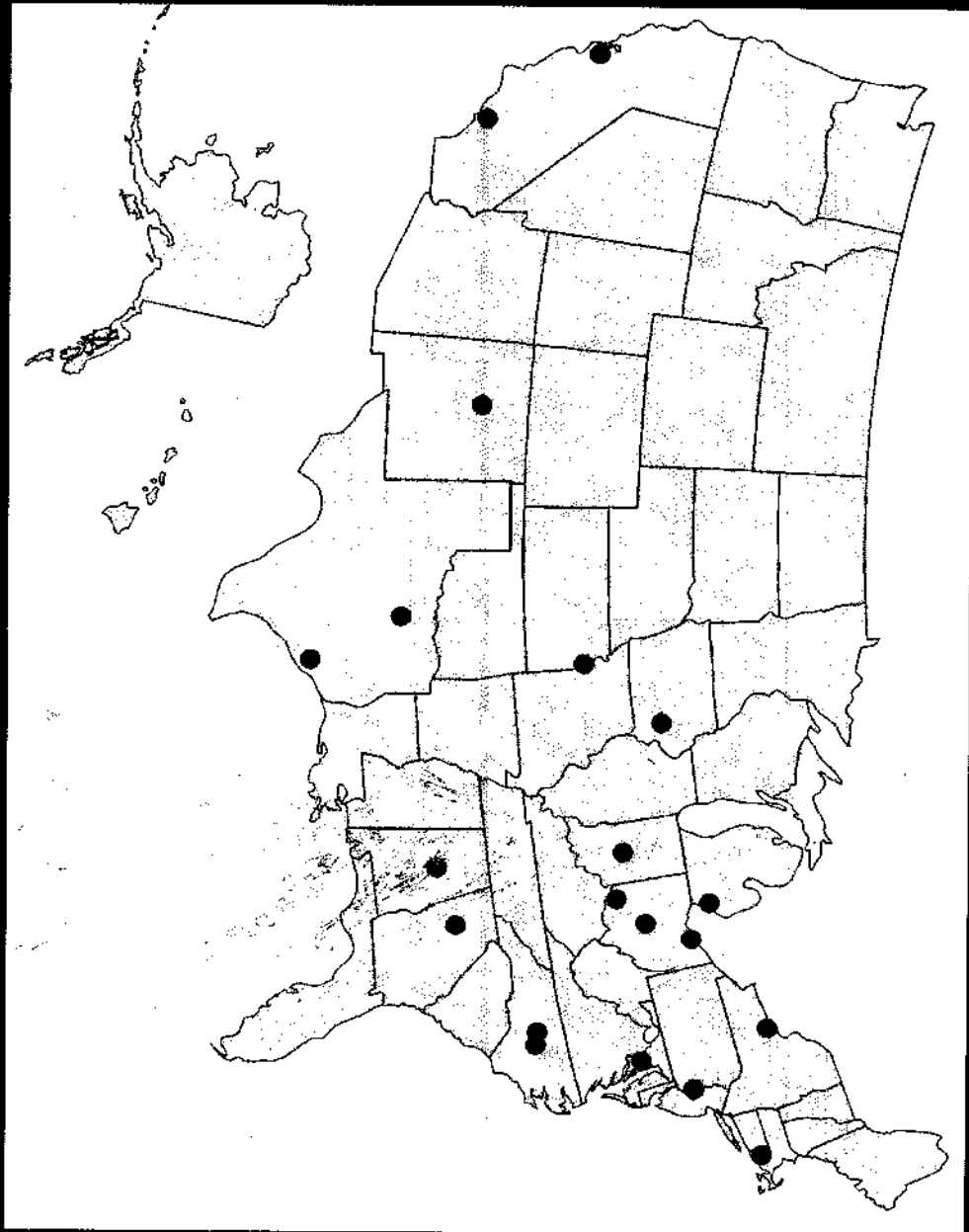
Increase gestational age

Female gender

Higher maternal education

RESEARCH NETWORK

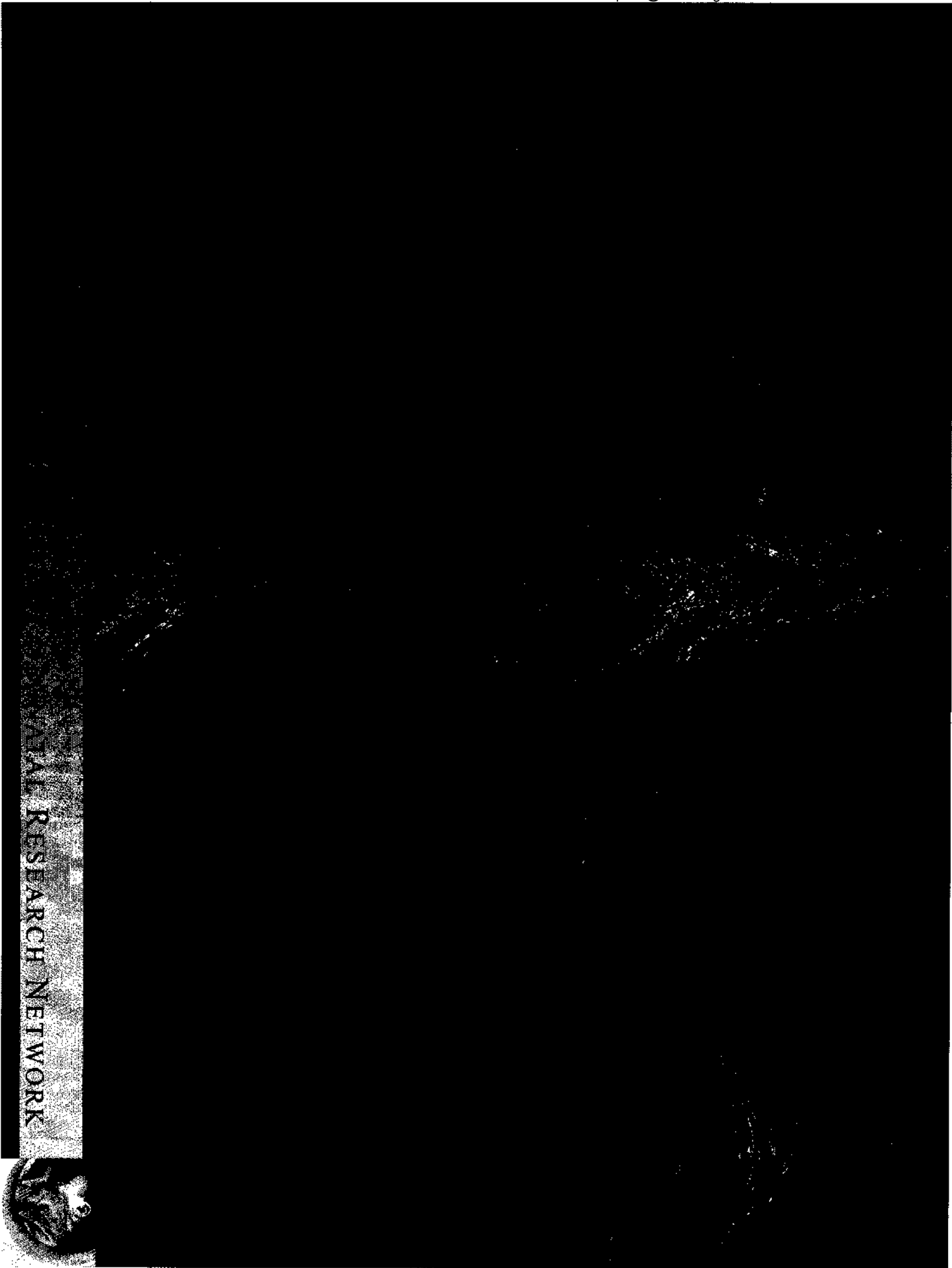
NICHD NRN 2011-2016



- Brown University
- Case Western Reserve University
- Children's Mercy Hospital, University of Missouri
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of California -- Los Angeles
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center
- Wayne State University

GENETIC RESEARCH NETWORK





RESEARCH NETWORK



From: Higgins, Rosemary (NIH/NICHD) [E]
To: nfiner@ucsd.edu
Subject: FW: SUPPORT Subcommittee Call - 12/18, Tu, 3:00 PM ET
Date: Tuesday, December 18, 2012 2:59:00 PM
Attachments: Cover letter IH SUPPORT study Dec 2012.doc.doc
IH in High vs Low sat groups SUPPORT DiFiore.pdf.pdf
SUPPORT trial proposal - Patterns of IH assoc with mortality REVISED.docx.docx

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From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Thursday, December 13, 2012 3:20 PM
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@ccchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu; Yvonne Vaucher
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Becky Brazeel; Brenda Vecchio; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Suzanne Sayers; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call - 12/18, Tu, 3:00 PM ET

Dear all,

The SUPPORT subcommittee call to discuss the revised proposal has been scheduled for:

Tuesday, 12/18
3:00 pm ET

Dial:
Within the USA

or

Outside the USA

Then, enter Participant Passcode:

Unfortunately we couldn't find a time that worked for everyone so Wade and Marie will be unable to join. Myriam may also be unable to join but will try to call in.

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

12/3/2012

To the SUPPORT committee,

Attached is revised proposal for the study entitled, *Patterns of intermittent hypoxia associated with mortality in the SUPPORT trial RCT*. We have clarified and expanded the study design to respond to the committee comments and concerns. We wish to highlight that the saturation analysis planned is significantly different than the analyses previously conducted by Dr. Carlo and Dr. Gantz – the prior analyses focused on average saturation in each randomized arm, this proposal looks at patterns of variation and intermittent hypoxia within the randomized arms. We have included promising pilot data from a comparable GA cohort of infants at CWRU who were **NOT** enrolled in the SUPPORT trial. These data suggest that differences in intermittent hypoxia patterns between infants who died and survivors may be identifiable despite the low resolution SpO2 data.

We ask for approval from the SUPPORT subcommittee for the study protocol so that we may apply for RO3 funding to support data analysis at the Cleveland site and statistical analysis at RTI.

We hope you find this proposal worthy of pursuing.

Sincerely,

Julie Di Fiore BSEE

Richard Martin MD

Michele Walsh, MD MSEpi

Low Oxygen Saturation Target Range is Associated with Increased Incidence of Intermittent Hypoxemia

Juliann M. Di Fiore, BSEE¹, Michele Walsh, MD¹, Lisa Wrage, MPH², Wade Rich, RRT³, Neil Finer, MD³, Waldemar A. Carlo, MD⁴, and Richard J. Martin, MD¹, on behalf of the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

Objective To test the hypothesis that preterm infants randomized to a low vs high O₂ saturation target range have a higher incidence of intermittent hypoxemia.

Study design A subcohort of 115 preterm infants with high resolution pulse oximetry enrolled in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial were randomized to low (85%-89%) or high (91%-95%) O₂ saturation target ranges. Oxygen saturation was monitored until 36 weeks postmenstrual age or until the infant was breathing room air without respiratory support for ≥ 72 hours.

Results The low target O₂ saturation group had a higher rate of intermittent hypoxemia ($\leq 80\%$ for ≥ 10 seconds and ≤ 3 minutes) prior to 12 days and beyond 57 days of life ($P < .05$). The duration shortened ($P < .0001$) and the severity increased ($P < .0001$) with increasing postnatal age with no differences between target saturation groups. The higher rate of intermittent hypoxemia events in the low target group was associated with a time interval between events of < 1 minute.

Conclusion A low O₂ saturation target was associated with an increased rate of intermittent hypoxemia events that was dependent on postnatal age. The duration and severity of events was comparable between target groups. Further investigation is needed to assess the role of intermittent hypoxemia and their timing on neonatal morbidity. (*J Pediatr* 2012;161:1047-52).

Intermittent hypoxemia may be associated with morbidity in preterm infants. In newborn animal models, administered intermittent hypoxemia paradigms have been shown to impair dopamine signaling,¹ contribute to neurological handicap,¹⁻³ and exacerbate retinal neovascularization.⁴ Although intermittent hypoxemia events are common in preterm infants, data relating to the prevalence of these events have been limited. Pulse oximetry technology has enabled noninvasive recording of spontaneous intermittent hypoxemic events in preterm infants over prolonged periods of time. This has allowed for accurate documentation of the temporal changes in the incidence of intermittent hypoxemia events over the first few months of life. Recent data in a previous cohort of preterm infants of 24-28 weeks gestation have shown relatively few intermittent hypoxemia events over the first week of life, a progressive increase in events until approximately 5 weeks postnatal age followed by a decline thereafter.⁵

The multi-center Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) examined the role of high vs low O₂ saturation target ranges on retinopathy of prematurity (ROP). Following randomization to lower (85%-89%) or higher (91%-95%) O₂ saturation target ranges, infants in the lower target group were found to have a lower incidence of severe ROP. This was associated with an unexpected higher mortality in infants targeted to low baseline O₂ saturation in 2 separate clinical trials.^{6,7} The effect of these oxygenation target ranges on the occurrence of intermittent hypoxemia is unknown. As a lower baseline O₂ saturation target may increase hypoxic vulnerability and the likelihood of intermittent hypoxemia, we prospectively designed this study to test the hypothesis that infants randomized to a low compared with high O₂ saturation target range would have an increase in the incidence of intermittent hypoxemia.

GA	Gestational age
GEE	Generalized estimating equation
PMA	Postmenstrual age
RR	Relative rate
ROP	Retinopathy of prematurity
ROS	Reactive O ₂ species
SaO ₂	Arterial O ₂ saturation
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial

From the ¹Division of Neonatology, Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH; ²Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; ³Division of Neonatology, Department of Pediatrics, University of California, San Diego, CA; ⁴Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

*List of members of the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network is available at www.jpeds.com (Appendix).

Supported by grants from the National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Child Health and Human Development Cooperative Multicenter Neonatal Research Network (HD021364-23). Data collected at participating sites of the NICHD Neonatal Research Network were transmitted to RTI International, the data coordinating center for the network, which stored, managed, and analyzed the data for this study. The authors declare no conflicts of interest.

0022-3476/\$ - see front matter. Copyright © 2012 Mosby Inc. All rights reserved. <http://dx.doi.org/10.1016/j.jpeds.2012.06.046>

Methods

The study population included a new subcohort of 115 pre-term infants enrolled in the multi-center SUPPORT study from 2 sites: Rainbow Babies and Children's Hospital, Cleveland, and University of California San Diego. Enrollment criteria for the main trial included infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation. Infants born in other hospitals and those known to have major anomalies were excluded. Using a permuted-block randomization design, with stratification according to study center and gestational age (GA) (24 weeks 0 days-25 weeks 6 days or 26 weeks 0 days-27 weeks 6 days), infants were randomized to a low (85%-89%) or high (91%-95%) O₂ saturation target group within 2 hours of birth. Infants who were part of multiple births were randomly assigned to the same group.

Electronically altered pulse oximeters (Radical SET; Masimo, Irvine, California) were used to blind the staff to the randomization group. The nursing response was dictated by the individual caregiver and center. The clinical staff was blinded as to the randomization group and instructed to maintain infants in an O₂ saturation range of 88%-92%, with altered monitors showing target levels of 88%-92% with a maximum offset of 3%. For example, a displayed value of 90% corresponded to an actual O₂ saturation value of 87% in the low target group and 93% in the high target group.⁶ Actual values were displayed when the O₂ saturation values were <85% or ≥95% in both treatment groups. Limits of 85% and 95% that would trigger a monitor alarm were suggested, but they could be changed for individual patients. Centers received quarterly feedback for compliance in time spent in target range.

Due to the massive file sizes, storage, and analysis costs, only 2 centers from the main trial collected data with the highest resolution of 2 seconds averaging and 2 seconds sample rate needed for this data analysis (main SUPPORT study settings: 16 seconds averaging and 10 seconds sample rate). These files included up to 3.6 million O₂ saturation values per subject. Targeting of O₂ saturation and high resolution data collection began within 2 hours after birth and continued until 36 weeks postmenstrual age (PMA) or until the infant was breathing air without respiratory support for ≥72 hours, whichever came first. Respiratory support was defined as high frequency ventilation, conventional mechanical ventilation, nasal synchronized intermittent mandatory ventilation, continuous positive airway pressure, nasal cannula, or hood. If the infant was off respiratory support for <72 hours and then support was re-administered, monitoring would have continued throughout that period. Infants weaned to room air for >72 hours but re-administered supplemental O₂ were returned to the original randomization group.

The study was approved by the Institutional Review Board at each site and by RTI International, which is the independent data coordinating center for the Neonatal Research

Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Additional Institutional Review Board approval and waiver of consent was obtained to perform secondary analysis of de-identified data.

Respiration and apnea were not recorded for this study. We defined an intermittent hypoxemia event as a fall in O₂ saturation to ≤80% for ≥10 seconds and ≤3 minutes. To eliminate periods of fluctuations around the threshold point but include rapid cycles of hypoxia as can occur with periodic breathing, the minimal time interval between events was set to 4 seconds. Events were identified by custom software. The software output was verified by hand scoring of events in 4 1-hour segments in 5 randomly chosen infants. Events were then characterized by their duration and the time interval between each event (Figure 1). The time interval between each event was calculated as the time between the end of the intermittent hypoxemia event (designated by the return of O₂ saturation above 80%) and the beginning of the next intermittent hypoxemia event (designated by a fall below 80%). The severity, or nadir, of each event was also documented. For each postnatal day for each subject, a calculation was made of the total number, mean duration, and time interval between intermittent hypoxemia events. These values were then used in the model.

Demographic and clinical variables were compared between high and low arterial oxygen saturation (SaO₂) target groups using *t* tests or generalized estimating equation (GEE) regression models, adjusting for SUPPORT study stratification variables site and GA group, where appropriate. Due to sparse data a Fisher exact test was used to evaluate death. To model counts of intermittent hypoxemia events, a GEE regression model assuming a negative binomial distribution was used. The GEE model was prespecified to include SaO₂ target group and time variables and provided robust SE estimates, which take into account the correlations within multiple-birth clusters, including correlations between repeated measurements. Variables included in the final model for intermittent hypoxemia events were SaO₂ target group, linear and quadratic terms for postnatal age, interactions between SaO₂ target group and postnatal age variables, GA group, and respiratory support (yes or no, per day). An additional quadratic term that allowed the quadratic relationship of postnatal age and intermittent hypoxemia events to vary

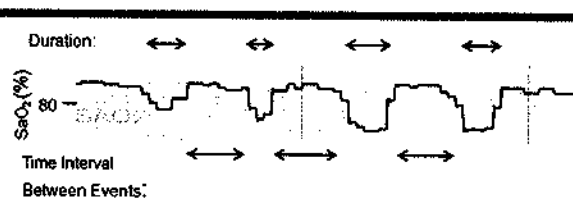


Figure 1. A raw SaO₂ waveform with the duration of the event, denoted by arrows above, and the time interval between events, denoted by arrows below.

before and after 28 days was also included; this spline regression approach provided a better fit than simpler models.⁸ Also considered were interactions between GA group and postnatal age, between GA group and SaO₂ target group, and between the additional quadratic term and SaO₂ target group, as well as variables for sex, race, center, continuous positive airway pressure vs surfactant treatment group (an additional randomization of the main SUPPORT trial protocol), and caffeine use. Each of these additional terms considered were not significant and because of this and the small sample size, were not included in the final model. Similar models for the subsets of intermittent hypoxemia events that occurred with a time interval of <1 minute and 1-20 minute between events were run using the same final set of variables as the overall model. Additional models were run to model duration and severity of intermittent hypoxemia events. These models included variables for treatment group, linear and quadratic terms for age, GA group, and center.

Results

The population of 115 infants had a mean birth weight of 830 ± 181 g and GA of 25.8 ± 1.0 weeks. There were 50 infants in the GA range 24-25 weeks 6 days, and 65 infants in the GA range 26-27 weeks 6 days. Fifty-one percent of the infants were male and 35% were non-Hispanic white. Characteristics of infants randomized to the high (n = 62) and low (n = 53) target group are presented in the Table. There were no differences between groups in birth weight, GA, incidence of bronchopulmonary dysplasia, severe ROP, or death before discharge. In this small cohort, there was a trend towards a higher mortality at 36 weeks in the low target group (P = .09), mirroring the finding in the main trial, but this did not reach statistical significance. Caffeine use occurred on approximately 80% of days during the monitoring period in both infant groups. There were no differences between low

and high target groups with respect to use of postnatal steroids (5.7% vs 4.8%), proportion discharged on diuretics (14.3% vs 14.0%), or inhaled bronchodilators (2% vs 3.5%). Infants in the low target group received respiratory support for 86% of the monitoring period compared with 92% in the high target group (relative rate [RR] low vs high target, 0.93, 95% CI 0.86-0.99, P = .029). The median baseline pulse oximetry oxygen saturation during days receiving O₂ supplementation was comparable with the main trial with a median pulse oximetry oxygen saturation of 92% (IQR: 91-94%) and 94% (IQR: 93-94%) in the low and high target groups, respectively.

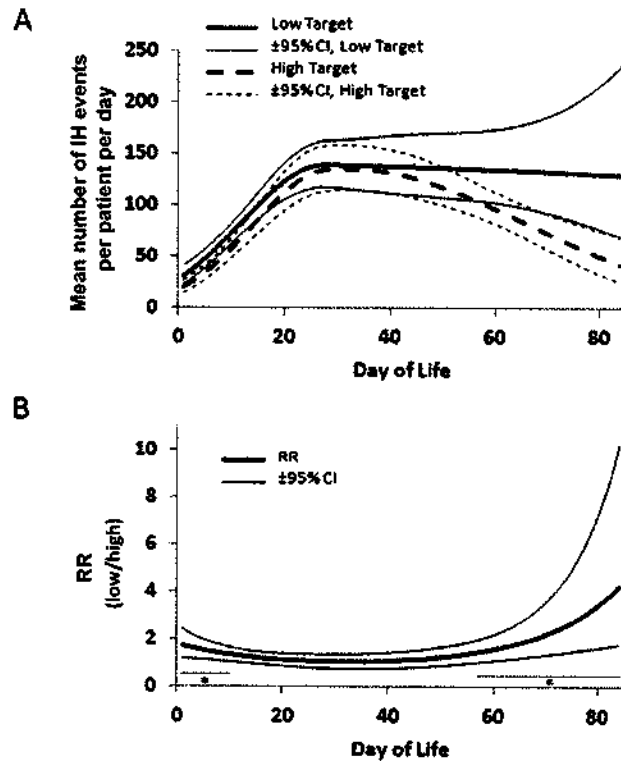
The model-based estimates showed an increase in intermittent hypoxemia events over the first 3 weeks of life in both infant groups followed by a decrease in intermittent hypoxemia events in the high target group compared with a plateau in the low target group (Figure 2, A). The

	Low target (53)	High target (62)	P value*
Birth weight (g), mean (SD)	855 (191)	808 (171)	.16
GA (wk), mean (SD)	25.8 (1.1)	25.8 (1.0)	.75
BPD (O ₂ at 36 wk), n/N (%)	14/50 (28%)	24/62 (39%)	.45
Death before 36 wk PMA, n (%)	3 (6%)	0 (0%)	.09
Death before discharge, n (%)	4 (7.5%)	3 (4.8%)	.70
Severe ROP, n/N (%)	8/49 (16%)	13/58 (22%)	.41
Death or severe ROP, n/N (%)	12/53 (22.6%)	15/60 (25%)	.64
Caffeine, n/N (%) of monitored d	2245/2838 (79%)	2757/3417 (81%)	.87
Respiratory support,† n/N (%) of monitored d	2451/2849 (86%)	3085/3369 (92%)	.03

BPD, bronchopulmonary dysplasia.

*P values from: t tests for birth weight and GA; GEE models, adjusting for stratification factors (study center and GA age group), and familial clustering for BPD, ROP, death or ROP, caffeine, respiratory support; Fisher exact tests for death.

†High frequency jet ventilation, continuous positive airway pressure, conventional ventilation, nasal cannula, nasal synchronized intermittent mandatory ventilation, or hood.



Low Target group: n = 45 49 53 49 44 38 27 12 3
High Target group: n = 51 57 56 52 47 43 31 17 2

Figure 2. A, The model based estimates showed an increase in intermittent hypoxemia events over the first 3 weeks of life in both infant groups followed by a decrease in intermittent hypoxemia events in the high target group compared with a plateau in the low target group. B, The RR of intermittent hypoxemia events (the ratio of the adjusted mean number of intermittent hypoxemia events in the low target group/the adjusted mean number of intermittent hypoxemia events in the high target group, per day) revealed a higher rate of intermittent hypoxemia events from <12 days, and >57 days of age in the low target group (*P < .05). IH, intermittent hypoxemia.

adjusted RR of intermittent hypoxemia events (the ratio of the adjusted mean number of intermittent hypoxemia events in the low target group/the adjusted mean number of intermittent hypoxemia events in the high target group, per day), revealed a significantly higher rate of intermittent hypoxemia events prior to 12 days, and beyond 57 days of age in the low target group ($P < .05$; Figure 2, B). Higher rates of intermittent hypoxemia events were associated with lower GA, (adjusted RR 1.24, 95% CI, 1.01-1.5, $P = .032$), and respiratory support, adjusted (RR 1.85, 95% CI 1.52-2.49, $P < .0001$).

The mean duration of intermittent hypoxemia events shortened ($P < .0001$) and the severity worsened ($P < .0001$) with increasing day of life (Figure 3). However, there were no differences in duration or severity between infant groups.

There was a wide range in the time interval between sequential intermittent hypoxemia events both within and between infants. To address the association between the timing of intermittent hypoxemia events and the O₂ saturation target group, the number of intermittent hypoxemia events was documented for 3 time interval ranges: (1) <1 minute; (2) 1-20 minutes; and (3) >20 minutes between intermittent

hypoxemia events. The highest incidence of events occurred with a time interval between events of <1 minute, followed by a time interval of 1-20 minutes between events. There were relatively few intermittent hypoxemia events that occurred with a time interval of >20 minutes between events. Intermittent hypoxemia events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of intermittent hypoxemia events in the low target group at <15 and >54 days of life ($P < .05$). After 65 days of life, there were a significantly higher number of intermittent hypoxemia events with a time interval of 1-20 minutes between events in the low target group ($P < .05$) with no differences between groups for intermittent hypoxemia events with a time interval of >20 minutes between events.

The above analysis examined the number and characteristics of intermittent hypoxemia events by increasing postnatal age. In addition, the effect of PMA on the occurrence of intermittent hypoxemia events was also assessed. The number of intermittent hypoxemia events was not significantly different by treatment group, at any PMA, indicating that postnatal rather than PMA is a major determinant of the relationship between intermittent hypoxemia and treatment group over time.

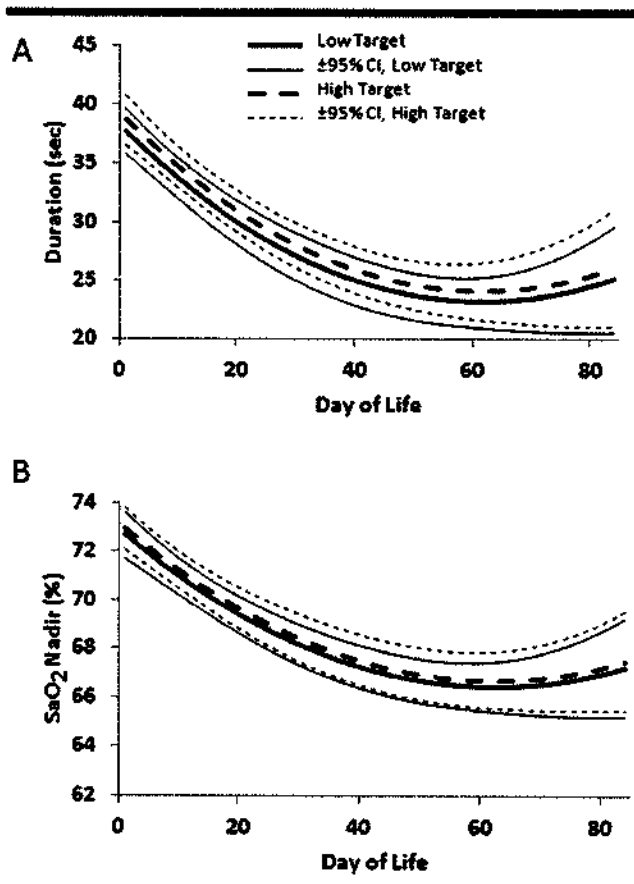


Figure 3. Intermittent hypoxemia event A, duration decreased and B, severity worsened with increasing postnatal age in both the low and high target groups with no differences between groups.

Discussion

This study showed an escalation in the incidence of intermittent hypoxemia events at <12 and >57 days of life in the low O₂ saturation target group. In both groups, events became shorter and more severe with increasing postnatal age with no differences between groups. Lastly, the higher incidence of intermittent hypoxemia in the low target group was predominantly associated with a time interval between events of <1 minute.

Intermittent hypoxemia events are ubiquitous in preterm infants.⁹⁻¹¹ Nonetheless, the precise incidence of these events is needed in order to address their potential pathophysiologic consequences. The higher incidence of intermittent hypoxemia in the low target group is consistent with McEvoy et al¹² showing a relationship between O₂ levels and intermittent hypoxemia in former preterm infants with chronic lung disease. Although these events are thought to be a consequence of immature respiratory control, this study and previous data in a similar infant cohort⁵ suggest that other developmentally-regulated pathologic mechanisms may be contributing. Relatively few events occurred during the first week of life with a significantly higher incidence of intermittent hypoxemia events in the low target group. This early time period may be a reflection of hypoxic depression compounded with peripheral chemoreceptor inhibition of breathing known to occur during the transition from fetal to neonatal life. The increased incidence in events in the low target group >57 days of age may be due to a low baseline alveolar PO₂ in the low target group which, in a model based analysis, has been shown to cause early onset of desaturation.¹³ It remains unclear why this low reserve did not

consistently result in a higher number of intermittent hypoxemia events throughout the monitoring period. It is also possible that the higher incidence of events >57 days is due to relatively well infants coming off of monitors earlier, thus comparing ill infants in the low target group with relatively well infants in the high target group. However, there were no group differences in severity of illness variables such as caffeine use, postnatal steroids, incidence of bronchopulmonary dysplasia, and proportion discharged on diuretics or inhaled bronchodilators.

Caffeine use and respiratory support are main clinical therapies for apnea and accompanying desaturation. Although caffeine has been shown to decrease apnea,¹⁴ interestingly, it has been shown to have little effect on desaturation episodes.¹⁵ Both infant groups spent a comparable percentage of the monitoring period on caffeine therapy; therefore, it is unlikely that caffeine use affected the results of this study. Respiratory support was associated with a higher incidence of events within each treatment group. However, with the high target group having a higher percentage of time receiving respiratory support, this cannot explain the increased incidence of intermittent hypoxemia in the low target infants.

Both groups showed a comparable duration and severity of intermittent hypoxemia events. Previous data have suggested that preterm infants with increased apnea have an augmented ventilatory response to acute hypoxia.¹⁶ Thus, although more susceptible to initiation of a hypoxic event, low target group infants may have been able to rally a compensatory ventilatory response and recover as well as high target group infants.

The lower incidence of severe ROP in the main trial is in contrast to our previous findings of an association between intermittent hypoxemia and severe ROP.⁵ This may be due to an initial enhanced hyperoxia-induced inhibition of angiogenesis in the high O₂ target group. Animal models have suggested that the timing of patterns of intermittent hypoxemia events may also affect morbidity. During the recovery phase following acute hypoxic exposure, reactive O₂ species (ROS) has been shown to increase after a delayed response of several minutes.¹⁷ Current preterm infant data from our group suggest that ROP is associated with a time interval between events of 1-20 minutes, consistent with the ability to initiate an increase in ROS. In contrast, the higher number of events in the low target group occurred with a time interval between events of <1 minute, which may have limited the ROS response. The effect of the duration of recovery time between intermittent hypoxemia events on the resultant oxidative stress response has yet to be determined and merits further investigation.

Data are limited on the long-term consequences of intermittent hypoxemia events in preterm infants.¹⁸ Apnea of prematurity during hospitalization¹⁹ and cardiorespiratory events in the home²⁰ have been associated with neurodevelopmental impairment, with only 1 study showing mean O₂ saturation during apnea as a predictor of motor scores.²¹ Further analysis is ongoing to assess the relationship between intermittent hypoxemia events and neurodevelopmental outcome in this cohort.

As an intention to treat study design with 2 dichotomous groups, this study was limited by the challenge of keeping infants in the O₂ saturation target range.^{22,23} Similar to this study, the main SUPPORT trial revealed overlap in the median level of O₂ saturation between groups with median O₂ saturation levels slightly higher than targeted levels in both groups.⁶ Lowering the median saturation and increasing the time in the actual low target level may have resulted in an even higher incidence of events. Data used in this analysis were collected until 3 days after respiratory support was discontinued or until 36 weeks PMA. The GEE model assumption that data are missing completely at random may be violated because infants who dropped out due to a poor outcome (ie, death), or a favorable outcome (ie, discharged or on room air without support), are likely to differ from those who remained on respiratory support through 36 weeks PMA. Thus, the model results should be interpreted as applying only to the subset of infants who were alive and on respiratory support at that time. Lastly, enrollment for this study was limited because of memory storage and analysis costs with only 2 sites acquiring data at a high enough resolution to adequately detect intermittent hypoxemia events.

In conclusion, a low O₂ saturation target range is associated with an increased incidence of intermittent hypoxemia that is dependent on postnatal age. These events tend to occur <1 minute apart but are of comparable duration and severity regardless of level of O₂ exposure. Preliminary results from 3 clinical trials have supported an association between low O₂ targets and increased mortality.^{6,7} Although the etiology of such a mortality increase is unknown at this time, we speculate that the higher incidence of intermittent hypoxemia in the low target group might provide insight to unraveling underlying pathophysiology. Describing the dynamic changes in incidence and timing of events with increasing age is important as it may add insight into the contribution of multiple factors that influence both central and peripheral respiratory control during the transitional phase of fetal to neonatal respiration. Further studies are needed to assess the contribution of timing of events on neonatal morbidity. We speculate that to minimize episodes of intermittent hypoxemia, the optimal O₂ saturation target may need to be adjusted by postnatal age. ■

The authors are indebted to their medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

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Appendix

The following investigators, in addition to those listed as authors, are members of the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network:

Dr Abhik Das (DCC Principal Investigator) and Dr Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

NRN Steering Committee Chairs: Alan H. Jobe, MD, PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

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Eunice Kennedy Shriver National Institute of Child Health and Human Development—Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

RTI International (U10 HD36790)—Abhik Das, PhD; W. Kenneth Poole, PhD; Marie G. Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN, BSN.

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University of California—San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461)—Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN.

Patterns of intermittent hypoxia associated with mortality in the SUPPORT trial RCT

J Di Fiore, M Walsh, R Martin, W Carlo, N Finer and the SUPPORT subcommittee

Dec 3, 2012

Background:

We have previously shown an association between patterns of intermittent hypoxia (IH) and morbidity. In preterm infants of 24-28wks gestation receiving normal clinical care, severe retinopathy of prematurity (ROP) was associated with an increase in the incidence of IH events during the first 8 weeks of life [Di Fiore 2010]. In a comparable cohort of infants enrolled in the SUPPORT trial, we have shown an increase in IH events in the low target group [Di Fiore 2012 J Peds in press]. However, there was also a lower incidence of severe ROP in the low target group. Closer examination of the patterns of these IH events revealed differences in timing and patterns. IH events associated with ROP were found to be less severe, longer in duration and occurring with a time interval of 1-20 minutes between events [Di Fiore 2012 Peds Research]. In contrast, IH patterns in the low compared to high target group revealed no differences in duration or severity and a shorter time interval of <1 minute between IH events [Di Fiore 2012 J Peds, in press]. **With our current custom software we have established our ability to identify variations in IH patterns associated with morbidity. We now seek to characterize the incidence, severity, duration and timing of IH events in preterm infants as they relate to infant mortality.**

The time interval between IH events may be crucial for the initiation of an oxidative stress response. Fabian et al have shown, in a rodent model, an increase in superoxide anion concentration, a marker of oxidative stress, during the reoxygenation phase following hypoxic exposure. This increase took a few minutes to occur followed by a return to baseline values after approximately 20 minutes. Therefore, this timing may explain the higher incidence of IH events but lower occurrence of severe ROP in the low target group, in that the IH events in the low target group may occur too close together to allow for an oxidative stress cascade leading to severe ROP. **It should also be noted that, as oxidative stress has been shown to occur during the reoxygenation phase following hypoxia exposure, intermittent hypoxia is a potentially much different oxidative stressor than sustained hypoxia.**

In addition to a lower incidence of severe ROP, the SUPPORT trial showed a higher mortality in the low target group. Similar quantification of IH patterns in infants who died compared to survivors may give insight into at risk patterns of intermittent hypoxia associated with mortality. We have currently looked at a pilot group of infants, of 24-28 wks gestation, at the Cleveland site with high resolution (2 sec averaging and 2 sec sample rate) SpO₂ data. Patterns of IH were compared between 17 infants who expired

and those who had survived by 22 months of age. 9/17 infants who expired were enrolled in the SUPPORT trial and 8/17 infants had SpO₂ data acquired during the same time period but not enrolled in the SUPPORT trial. Expired infants were compared with 60 surviving infants of comparable gestational age but not enrolled in the SUPPORT trial.

Our preliminary findings in this small infant cohort suggest a higher incidence of IH events in the infants who expired. These IH events were longer in duration and occurred with a time interval of 1-20 minutes between events. This pattern is similar to the pattern seen in infants with severe ROP. The SUPPORT trial cohort includes 237 infants who expired. Comparison of this large infant cohort with SUPPORT infant survivors may clarify an association between mortality and IH patterns and the possible interactive role of the baseline target range. **Therefore, the purpose of this study is to compare oxygen saturation patterns in infants enrolled in the SUPPORT trial who died compared to survivors.**

Hypothesis:

Mortality will be associated with exacerbations in IH patterns including increased incidence, duration, and severity and a time interval between IH events of 1-20 minutes.

Methods:

Oxygen saturation patterns will be reviewed for infants who died and compared to infants who survived in both target groups. The incidence of IH events, defined as a fall in SpO₂ <80% for >20 sec and < 3 minutes, will be recorded. An upper limit of 3 minutes was arbitrarily chosen to distinguish intermittent from sustained hypoxemia. **IH patterns will be quantified using custom written software to summarize the mean/median of the duration and severity of IH events, and the time interval between IH events, in addition to sophisticated measures of variability including standard deviation and histogram entropy.**

Our criteria for death include a window up to 22 months of age. Therefore, a potential confounder is the age at the time of death as death can occur within or outside of the SpO₂ monitoring period. If the sample size allows we will look separately at infants who died within and outside of the SpO₂ monitoring period. For infants expiring within the monitoring period, the current proposal includes the entire duration of SpO₂ monitoring. **If information is available in the SUPPORT database on the timing of the decision to withdraw care additional analysis can be performed to assess the effect of removing this time period from the analysis.**

The current SUPPORT trial dataset is limited by the long averaging time (16 sec) and low sample rate (1 sample per 10 sec or .1 Hz). Based on the Nyquist sampling theorem, the low sample rate will limit our detection of events to those >20 sec in duration. Our preliminary data reveal a mean duration of approximately 25 sec in the infants who survived and 35 seconds in the infants who expired. Previous data by Vagedes et al have shown an overestimation in the number of IH events >20 sec with an averaging time of 16 sec. Therefore, the current signal processing parameters will

bias towards an increased occurrence of IH events in both infant groups with a slightly higher bias in infants who died. As this averaging time is commonly used in the clinical setting, we will assess the ability of the SUPPORT trial SpO₂ monitoring settings to distinguish IH patterns between infants who died and those who survived. In addition, we will investigate the possibility of implementing a mathematical model to reverse the bias due to prolonged averaging time.

The SUPPORT trial algorithm used by Masimo to blind the oximeters to the low and high targets does not allow for one to one mapping back to the original SpO₂ values in the SpO₂ range of 85-95%. The analysis proposed above is restricted to SpO₂ values <80% which are not affected by the re-mapping limitations.

Sample Size:

Sample of convenience based on 237 infant deaths (130 in the low target and 107 in the high target groups) with age matched controls.

Statistics:

Statistical analysis of all measures will be performed on daily averages computed for each subject. Our previous modeling of at risk IH patterns and severe ROP was analyzed by both postnatal and post menstrual age. Although both age parameters revealed differences between infant groups the postnatal age model revealed group comparisons at an earlier day of life. Therefore, data will be analyzed by post natal age. A logarithmic or square root transformation will be applied if the original data are skewed. A t-test will be used for demographic comparisons between infant groups. Longitudinal profiles of deaths and survivors will be estimated and compared using linear mixed models. Models will include terms for gestational age, race, gender, multiple birth, and their interactions with terms involving day. Analyses will be conducted using SAS version 9.2 (SAS Institute, Cary, NC).

This analysis will have to be adjusted for age matched controls. Details pertaining to the number of matched controls needed per infant expired and the appropriate statistical model will need to be discussed with RTI.

Issues:

1. Is there a higher occurrence of SGA in low vs high target expired infants? If so, add as additional covariant in analysis?

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ORIGINAL ARTICLE

Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial

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ABSTRACT

BACKGROUND

Previous results from our trial of early treatment with continuous positive airway pressure (CPAP) versus early surfactant treatment in infants showed no significant difference in the outcome of death or bronchopulmonary dysplasia. A lower (vs. higher) target range of oxygen saturation was associated with a lower rate of severe retinopathy but higher mortality. Our prespecified hypothesis was that early CPAP and a lower target range of oxygen saturation would each decrease the risk of death or neurodevelopmental impairment. We now report longer-term results.

METHODS

Using a 2-by-2 factorial design, we randomly assigned infants born between 24 weeks 0 days and 27 weeks 6 days of gestation to early CPAP with a limited ventilation strategy or early surfactant administration and to lower or higher target ranges of oxygen saturation (85 to 89% or 91 to 95%). The primary composite outcome for the longer-term analysis was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

RESULTS

The primary outcome was determined for 1234 of 1316 enrolled infants (93.8%); 990 of the 1058 surviving infants (93.6%) were evaluated at 18 to 22 months of corrected age. Death or neurodevelopmental impairment occurred in 27.9% of the infants in the CPAP group (173 of 621 infants), versus 29.9% of those in the surfactant group (183 of 613) (relative risk, 0.93; 95% confidence interval [CI], 0.78 to 1.10; $P=0.38$), and in 30.2% of the infants in the lower-oxygen-saturation group (185 of 612), versus 27.5% of those in the higher-oxygen-saturation group (171 of 622) (relative risk, 1.12; 95% CI, 0.94 to 1.32; $P=0.21$). Mortality was increased with the lower-oxygen-saturation target (22.1%, vs. 18.2% with the higher-oxygen-saturation target; relative risk, 1.25; 95% CI, 1.00 to 1.55; $P=0.046$).

CONCLUSIONS

We found no significant differences in the composite outcome of death or neurodevelopmental impairment among extremely premature infants randomly assigned to early CPAP or early surfactant administration and to a lower or higher target range of oxygen saturation. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute; SUPPORT ClinicalTrials.gov number, NCT00233324.)

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EXTREMELY PREMATURE INFANTS ARE AT high risk for death and neurosensory or developmental impairment in early childhood.¹⁻³ The risk of neurodevelopmental impairment increases with decreasing gestational age and greater severity of illness. Neurodevelopmental impairment is often a consequence of neonatal complications.⁴⁻¹² Although surfactant administration decreases the risk of death and bronchopulmonary dysplasia, randomized, controlled trials of various respiratory interventions have not shown significant reductions in mortality and morbidity or improvement in developmental outcomes.¹³⁻¹⁷ We previously reported results of the multicenter, randomized, controlled Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), which involved extremely premature infants (from 24 to 27 weeks of gestation); treatment with noninvasive continuous positive airway pressure (CPAP) shortly after birth, as compared with early intubation and surfactant administration, did not reduce rates of death or bronchopulmonary dysplasia or other major morbidity at 36 weeks of postmenstrual age.¹⁸

Although oxygen supplementation is necessary for survival in many preterm infants, several studies have shown that it increases the risk of retinopathy of prematurity,¹⁹ bronchopulmonary dysplasia,^{20,21} periventricular leukomalacia,²² and cerebral palsy.²³ Results from SUPPORT showed no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity among infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) versus a higher range (91 to 95%). However, in the lower-oxygen-saturation group, the risk of retinopathy of prematurity among infants who survived to discharge was decreased (8.6%, vs. 17.9% in the higher-oxygen-saturation group; relative risk, 0.52; 95% confidence interval [CI], 0.37 to 0.73; $P < 0.001$) and the risk of death was increased (19.9% vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; $P = 0.04$).²⁴

We now report the results of our longer-term follow-up of the infants in this study, assessing whether early, noninvasive CPAP with a limited ventilation strategy, as compared with early surfactant administration, and a lower, as compared with higher, target range of oxygen saturation would each decrease the incidence of death be-

fore assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

METHODS

STUDY DESIGN

SUPPORT was a randomized, controlled trial involving 1316 extremely preterm infants (gestational age, 24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009, who were enrolled at delivery at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days). Infants who were part of multiple births were randomly assigned, as a unit, to the same treatment group.

In the delivery room, the infants were randomly assigned to receive either CPAP immediately after delivery with a limited ventilation strategy, as described previously, if subsequent intubation was required, or intubation with surfactant administration within an hour after birth, followed by conventional ventilation.¹⁸ Using a 2-by-2 factorial design, we also randomly assigned participants to a target oxygen-saturation range of 85 to 89% (lower-oxygen-saturation group) or 91 to 95% (higher-oxygen-saturation group); we used pulse oximeters that were specially designed to maintain blinding (see the Supplementary Appendix, available with the full text of this article at NEJM.org).²⁴

The procedures for enrollment, intervention, and data collection have been reported previously.^{18,24} The trial 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. Written informed consent was obtained from the parent or guardian of each child before delivery. Two of the authors employed by RTI International vouch for the accuracy and completeness of the data and analyses reported, and the members of the SUPPORT subcommittee vouch for the fidelity of the trial to the study protocol (see the Supplementary Appendix).

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ASSESSMENTS

At 18 to 22 months of corrected age, surviving infants underwent a comprehensive neurodevelopmental assessment performed by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability. Cognitive function was assessed with the use of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III); scores are assessed relative to a standardized mean (\pm SD) of 100 ± 15 , with higher scores indicating better performance.²⁵ The modified Gross Motor Function Classification System (GMFCS) was used to classify gross-motor performance, with scores ranging from 0 (normal) to 5 (most impaired).²⁶ Moderate-to-severe cerebral palsy was defined as a nonprogressive disorder with abnormal muscle tone in at least one arm or leg that was associated with abnormal control of movement or posture and a GMFCS score of 2 or higher.^{27,28} Assessments of hearing impairment (defined as the inability to understand the oral directions of the examiner and to communicate, with or without hearing amplification) and visual impairment (defined as vision worse than 20/200) were based on examination and parental report.

Certified research staff collected demographic and neonatal-outcome data using standard definitions from the Neonatal Research Network. Demographic and outcome data included gestational age; birth weight; sex; status with respect to multiple gestation; race or ethnic group; and history of medical or surgical necrotizing enterocolitis (modified Bell's stage ≥ 2 , on a scale ranging from 1 to 3, with higher scores indicating greater severity of disease), intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia, late-onset sepsis, retinopathy of prematurity, bronchopulmonary dysplasia (physiological), and use of postnatal glucocorticoids. Socioeconomic variables included health insurance status, maternal marital status, maternal educational level, household income, language spoken at home, and status with respect to whether the child was living with biologic parents. Socioeconomic data were updated during the 18-to-22-month visit; these data were used if data from the neonatal period were not available.

OUTCOMES

The prespecified primary composite outcome for this trial was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age. This composite outcome was selected because infants who died before 18 months of corrected age could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the BSID-III of less than 70, a GMFCS score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment. Other prespecified outcomes at 18 to 22 months of corrected age were death and neurodevelopmental impairment. Exploratory secondary outcomes included the individual components of the neurodevelopmental-impairment assessment, levels of cognitive delay, and a comparison of outcomes within the higher and lower gestational-age strata.

STATISTICAL ANALYSIS

The sample-size calculations were based on Neonatal Research Network data for infants born in the year 2000; the details have been reported previously.^{18,24} Although the sample size for the study was estimated on the basis of hospital outcomes (i.e., death or bronchopulmonary dysplasia for the ventilation intervention, and death or retinopathy of prematurity for the oxygenation intervention), the final sample size was sufficient to detect an absolute reduction of 10 percentage points in the composite outcome of death or neurodevelopmental impairment, with the use of a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% in the surfactant and higher-oxygen-saturation groups and a 15% rate of loss to follow-up, as well as adjustment for familial clustering.

Data were entered on standard forms and were transmitted to RTI International, which stored, managed, and analyzed the data for the study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were performed with the use of chi-square tests for categorical variables and t-tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary

composite outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age could be assigned. 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. The denominator used to calculate the frequency of each outcome was the number of children for whom status with respect to that outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all 18-to-22-month outcomes were adjusted, as prespecified, for gestational-age strata, study center, and familial clustering (because infants who were part of multiple births were assigned to the same treatment group). Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the effect of characteristics that differed between the groups of children with and without follow-up, a sensitivity analysis using multiple imputation was conducted, in which missing values for the primary outcome were imputed on the basis of the treatment assignment, perinatal characteristics, and in-hospital outcomes.²⁹ Two-sided P values of less than 0.05 were considered to indicate statistical significance for all analyses; no adjustments were made for multiple comparisons.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The primary composite outcome of death or neurodevelopmental impairment was determined for 93.8% of the children (1234 of 1316) enrolled in the trial (Fig. 1). A total of 258 children were known to have died before 18 to 22 months of age. Of the 68 children for whom a neurodevelopmental assessment was missing, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment was determined for 98.6% of all children seen (976 of 990); 14 children had an incomplete evaluation that precluded the assignment of a neurodevelopmental-impairment status. The follow-up rate and the mean corrected age at neuro-

developmental assessment were similar for all treatment groups (Table 1).

As compared with the mothers of the 990 children who underwent a neurodevelopmental assessment at 18 to 22 months of corrected age, the mothers of the 68 children who did not undergo an assessment were less likely to be married (47% vs. 31%, $P=0.01$) and more likely to have only public health insurance (52% vs. 69%, $P=0.008$). No other demographic or neonatal characteristics differed significantly between the groups.

The demographic and clinical characteristics of the follow-up population are summarized in Table 1 and in Table S1 in the Supplementary Appendix. Almost all mothers received antenatal glucocorticoids. At follow-up, there were more children who were small for their gestational age and more children with severe retinopathy of prematurity in the higher-oxygen-saturation group than in the lower-oxygen-saturation group. As compared with the surfactant group, children in the CPAP group were more likely to have had necrotizing enterocolitis and less likely to have been exposed to postnatal glucocorticoids. A total of 32% of the infants in the CPAP group were intubated in the delivery room; 65% of the infants in the CPAP group received surfactant with limited ventilation.

PRIMARY OUTCOME

The frequency of the composite outcome of death or neurodevelopmental impairment did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups at 18 to 22 months of corrected age (Tables 2 and 3). Mortality before neonatal discharge accounted for 92% of the overall mortality observed by 18 to 22 months. Mortality did not differ significantly between the CPAP and surfactant groups but remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group. There were no significant differences in the primary outcome between treatment groups in subgroup analyses stratified according to gestational age at birth (Tables S2 and S3 in the Supplementary Appendix). The results of the sensitivity analysis using multiple imputations were virtually identical to the results of the analysis in which missing data were excluded (data not shown). There was no significant interaction be-

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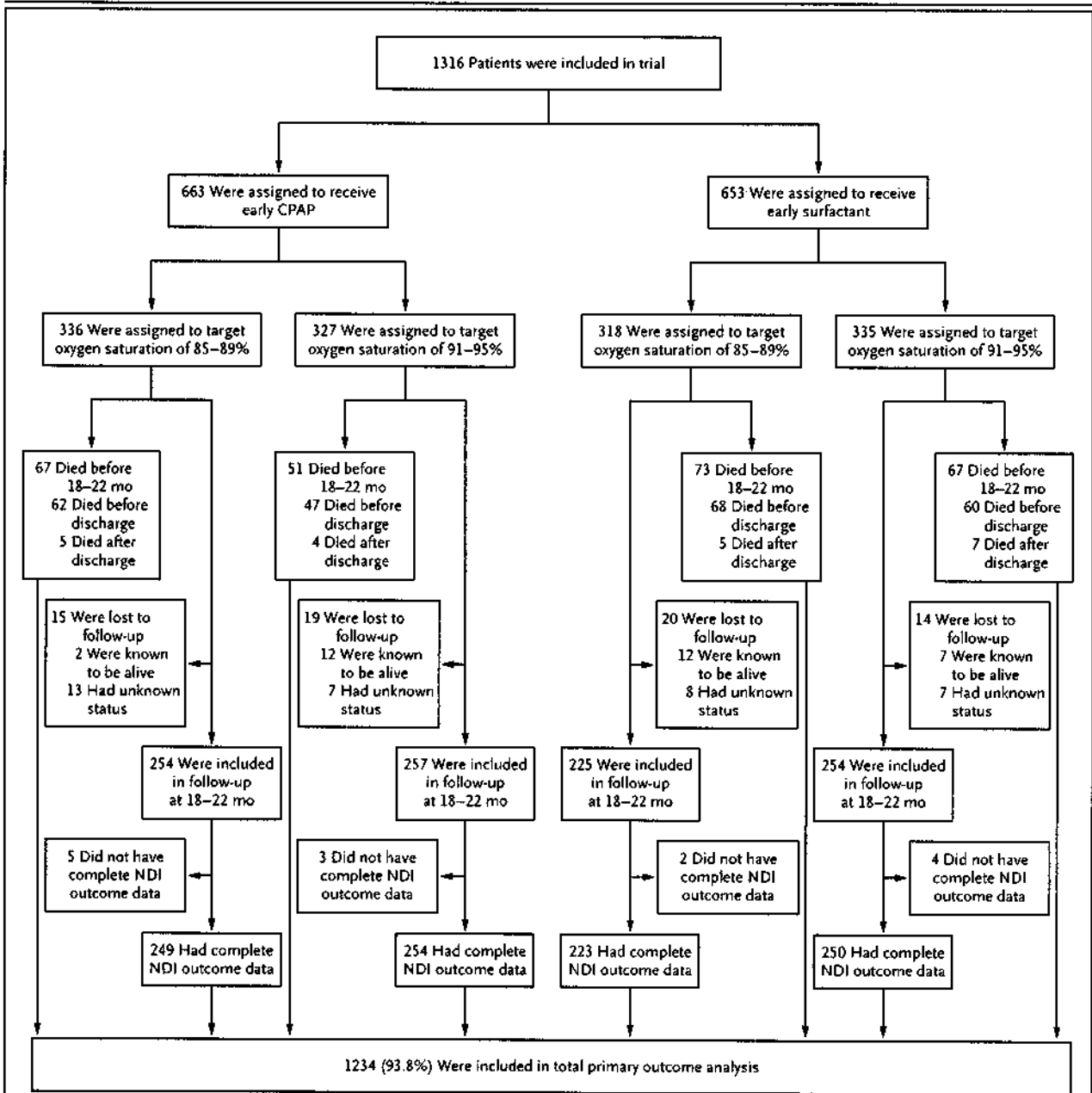


Figure 1. Enrollment, Randomization, and Outcomes.

The primary composite outcome was determined for 93.8% of the enrolled infants. A total of 258 children were known to have died before 18 to 22 months of corrected age. Of the 68 children with a missing neurodevelopmental assessment, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment (NDI) was determined for 98.6% of all children seen; 14 children had an incomplete evaluation that precluded the assignment of NDI status.

tween the two interventions with respect to the composite outcome of death or neurodevelopmental impairment or either of its components ($P > 0.70$ for all comparisons).

OTHER OUTCOMES

The incidences of the individual components of neurodevelopmental impairment (BSID-III cognitive composite score of < 70 , GMFCS score of ≥ 2 ,

Table 1. Demographic and Clinical Characteristics of the Follow-up Cohorts.*

Characteristic	CPAP (N=511)	Surfactant (N=479)	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=511)
Birth weight — g	849±186	852±193	858±186	844±192
Gestational age at birth — wk	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age — no. (%)†	23 (4.5)	32 (6.7)	17 (3.5)‡	38 (7.4)
Male sex — no. (%)	256 (50.1)	266 (55.5)	240 (50.1)	282 (55.2)
Multiple birth — no. (%)	138 (27.0)	114 (23.8)	124 (25.9)	128 (25.0)
Maternal use of antenatal glucocorticoids — no. (%)	493 (96.5)	456 (95.2)	462 (96.5)	487 (95.3)
Cesarean section — no. (%)	352 (68.9)	315 (65.8)	332 (69.3)	335 (65.6)
Neonatal outcome — no./total no. (%)§				
Severe retinopathy of prematurity	62/479 (12.9)	58/434 (13.4)	38/442 (8.6)¶	82/471 (17.4)
Bronchopulmonary dysplasia	193/511 (37.8)	187/479 (39.0)	177/479 (37.0)	203/511 (39.7)
Intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia	70/510 (13.7)	46/478 (9.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis	56/511 (11.0)**	30/479 (6.3)	42/479 (8.8)	44/511 (8.6)
Late-onset sepsis or meningitis	167/511 (32.7)	154/479 (32.2)	155/479 (32.4)	166/511 (32.5)
Use of postnatal glucocorticoids	34/508 (6.7)**	55/476 (11.6)	41/477 (8.6)	48/507 (9.5)
Corrected age at follow-up — mo	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

* Plus-minus values are means ±SD. There were no significant between-group differences, except as noted. Additional demographic characteristics of the cohorts are provided in Table S1 in the Supplementary Appendix. CPAP denotes continuous positive airway pressure.

† Infants who were small for gestational age were defined as those with a birth weight in less than the 10th percentile.

‡ P<0.01 for the comparison with the higher-oxygen-saturation group.

§ The comparisons of neonatal outcomes were adjusted for stratification factors (study center and gestational-age group) and familial clustering.

¶ P<0.001 for the comparison with the higher-oxygen-saturation group.

|| Assessment for bronchopulmonary dysplasia was performed at 36 weeks of postmenstrual age.

** P<0.05 for the comparison with the surfactant group.

moderate or severe cerebral palsy, hearing impairment, and blindness) among surviving infants did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups (Tables 2 and 3). Neither were there significant between-group differences in the individual components of neurodevelopmental impairment when the groups were stratified according to gestational age (Tables S2 and S3 in the Supplementary Appendix). However, in the lower-gestational-age stratum, mortality was higher in the surfactant group than in the CPAP group. Although the rates of severe retinopathy of prematurity and eye surgery were higher in the higher-oxygen-saturation group than in the lower-oxygen-saturation group, the rates of bilateral blindness, blindness of at least one eye, and other vision impairment

did not differ significantly between the groups at 18 to 22 months of corrected age (Table 4). There were no significant differences between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups in the rates of the composite outcome of death or individual neurodevelopmental-impairment components (data not shown), mean cognitive composite scores on the BSID-III, or the percentage of infants with cognitive composite scores of less than 80 points or less than 85 points (Table S4 in the Supplementary Appendix). Of the 976 children who were evaluated at 18 to 22 months of corrected age, 583 (60%) had normal status with respect to neuromotor, neurosensory, and cognitive development (with normal cognitive development defined as a BSID-III cognitive composite score of ≥85 points).

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Table 2. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the CPAP and Surfactant Groups.*

Variable	CPAP	Surfactant	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Primary outcome determined	621/663 (93.7)	613/653 (93.9)	1.00 (0.97–1.03)	0.83
Death or NDI	173/621 (27.9)	183/613 (29.9)	0.93 (0.78–1.10)	0.38
Death before assessment at 18–22 mo of corrected age	118/643 (18.4)	140/638 (21.9)	0.83 (0.67–1.04)	0.10
NDI	55/503 (10.9)	43/473 (9.1)	1.16 (0.79–1.71)	0.44
BSID-III cognitive score <70†	36/502 (7.2)	36/472 (7.6)	0.95 (0.61–1.50)	0.84
GMFCS score ≥2‡	26/511 (5.1)	23/479 (4.8)	0.98 (0.57–1.69)	0.95
Moderate or severe cerebral palsy	21/511 (4.1)	19/479 (4.0)	0.93 (0.51–1.72)	0.82
Bilateral blindness	4/511 (0.8)	7/479 (1.5)	0.53 (0.16–1.78)	0.31
Hearing impairment	17/511 (3.3)	7/479 (1.5)	2.27 (0.96–5.37)	0.06

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic. NDI denotes neurodevelopmental impairment.

† Scores on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), are assessed relative to a standardized mean (\pm SD) of 100 ± 15 , with higher scores indicating better performance.

‡ Gross-motor function was assessed by means of the modified Gross Motor Function Classification System (GMFCS), with scores ranging from 0 to 5 and higher scores indicating greater impairment.

DISCUSSION

In this large, multicenter trial involving very-high-risk, extremely premature infants, we found no significant difference in the primary composite follow-up outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between infants randomly assigned to treatment with early CPAP and those assigned to early intubation and surfactant administration or between those randomly assigned to the lower-oxygen-saturation group and those assigned to the higher-oxygen-saturation group. Mortality did not differ significantly between the CPAP and surfactant groups, and mortality remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group — findings that are consistent with our earlier results.^{18,24} There were no significant differences between the CPAP and surfactant groups or between the higher-oxygen-saturation and lower-oxygen-saturation groups with respect to the frequencies among surviving infants of neurodevelopmental impairment and its components, including severe cognitive impairment (BSID-III

cognitive composite score, <70), moderate or severe cerebral palsy, moderate or severe motor impairment (GMFCS score, ≥ 2), hearing impairment, and bilateral blindness.

Recent trials have raised concern about using lower target ranges of oxygen saturation because of the possibility of increased mortality among extremely premature infants.^{24,30} In SUPPORT, the risk of death during the initial hospitalization was increased among neonates randomly assigned to the lower-oxygen-saturation group, as compared with those assigned to the higher-oxygen-saturation group, and among neonates in the lowest gestational-age stratum, mortality was increased in the surfactant group as compared with the CPAP group. As previously reported, the causes of death did not differ significantly between the lower-oxygen-saturation and higher-oxygen-saturation groups.²⁴ Although significant differences in mortality persisted at 18 to 22 months of corrected age, these differences largely reflected the differences in mortality before hospital discharge. There are other ongoing studies of this matter that, once completed, could inform decisions.³¹

Severe retinopathy of prematurity may be as-

Table 3. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Primary outcome determined	612/654 (93.6)	622/662 (94.0)	1.00 (0.97–1.03)	0.79
Death or NDI	185/612 (30.2)	171/622 (27.5)	1.12 (0.94–1.32)	0.21
Death before assessment at 18–22 mo of corrected age	140/633 (22.1)	118/648 (18.2)	1.25 (1.00–1.55)	0.046
NDI	45/472 (9.5)	53/504 (10.5)	0.87 (0.60–1.28)	0.49
BSID-III cognitive score <70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58–1.43)	0.69
GMFCS score ≥2	26/479 (5.4)	23/511 (4.5)	1.17 (0.68–2.01)	0.56
Moderate or severe cerebral palsy	20/479 (4.2)	20/511 (3.9)	1.00 (0.54–1.83)	>0.99
Bilateral blindness	5/479 (1.0)	6/511 (1.2)	0.90 (0.28–2.90)	0.86
Hearing impairment	12/479 (2.5)	12/511 (2.3)	1.16 (0.54–2.49)	0.70

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic.

sociated with poor visual outcomes, even with treatment.^{32,33} In this study, infants in the lower-oxygen-saturation group who survived to discharge had a lower incidence of severe retinopathy of prematurity (8.6%, vs. 17.9% in the higher-oxygen-saturation group).²⁴ Although eye surgery was significantly less frequent in the lower-oxygen-saturation group than in the higher-oxygen-saturation group, there were no significant between-group differences with respect to rates of unilateral and bilateral blindness, nystagmus, strabismus, or the use of corrective lenses. We did not collect detailed data on visual function at the 18-to-22-month visit.

The strengths of this study include the large initial sample, which provided sufficient power to detect a clinically significant difference in the prespecified outcome of death or neurodevelopmental impairment, and the high percentage of surviving infants who underwent a comprehensive, standardized neurodevelopmental evaluation at 18 to 22 months of corrected age.

The study also has several limitations. The requirement for antenatal consent, which is associated with enrollment bias, may limit generalizability.^{34,35} In addition, the incidence of neurodevelopmental impairment in extremely premature infants in the present study was substantially lower than that previously reported by the Neonatal Research Network.³⁶ The present study used the BSID-III for cognitive assessment, where-

as previous Neonatal Research Network studies used an earlier edition, the BSID-II. Changes in the test design and standardization between the two editions may account for the lower incidence of neurodevelopmental impairment reported here.³⁶ Although the BSID-III scores in this study were higher than those previously reported for extremely premature infants, there were no significant differences between the treatment groups in this study.

Another limitation is the fact that the reported follow-up results are based on a single visit at 18 to 22 months of corrected age; other disabilities may not be evident until later in childhood. A subcohort of the SUPPORT study will be followed at school age to evaluate the longer-term neurodevelopmental outcome. Also, in comparing several secondary outcomes between pairs of treatments in this factorial-design trial (early CPAP vs. early surfactant treatment and lower vs. higher target ranges of oxygen saturation), we made no adjustments for multiple comparisons; appropriate caution should therefore be used in interpreting the reported results. Finally, differences in the neurodevelopmental outcome may have been blunted by the smaller difference in oxygen saturation between the higher-oxygen-saturation and lower-oxygen-saturation groups than was planned.²⁴

In conclusion, there were no significant differences in the composite outcome of death before

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Table 4. Visual Outcome at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	number/total number (percent)			
Strabismus	46/478 (9.6)	41/510 (8.0)	1.20 (0.80–1.80)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89–3.69)	0.10
Eyes track 180 degrees	462/476 (97.1)	493/507 (97.2)	1.00 (0.98–1.02)	0.93
Corrective lenses for both eyes†	21/468 (4.5)	20/493 (4.1)	1.15 (0.63–2.10)	0.65
Blind with some function in both eyes†	3/450 (0.7)	2/475 (0.4)	1.57 (0.27–8.96)	0.61
Blind with no useful vision in both eyes†	2/449 (0.4)	4/477 (0.8)	0.54 (0.10–2.96)	0.48
Other abnormal eye finding‡	6/453 (1.3)	12/485 (2.5)	0.55 (0.21–1.46)	0.23
Blind in at least one eye	5/479 (1.0)	8/511 (1.6)	0.67 (0.22–2.02)	0.48
Eye surgery performed§	31/477 (6.5)	67/509 (13.2)	0.53 (0.35–0.78)	0.002

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness and other abnormal eye finding were not adjusted for study center, owing to the small numbers of patients with these characteristics.

† The reference group for relative risk was the group of children with vision that appeared to be normal in both eyes.

‡ Other abnormal eye finding was defined as an abnormality other than a condition requiring corrective lenses but not one severe enough for the child to be considered blind in that eye. Children whose eyes were classified in two different vision categories were included in the other-abnormal-eye-finding category.

§ Reasons for surgery are listed in Table S5 in the Supplementary Appendix.

assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between extremely preterm infants randomly assigned at delivery to early CPAP and those assigned to early intubation with surfactant administration or between infants assigned to lower oxygen saturation and those assigned to higher oxygen saturation. Early CPAP with a limited ventilation strategy can be considered as an alternative to early surfactant treatment, even in infants as immature as those at 24 weeks of gestational age. It is important to consider the

risk of death or neurodevelopmental impairment when deciding on oxygen-saturation targets in extremely preterm infants. Because mortality remained lower in the higher-oxygen-saturation group at the time of follow-up and there were no adverse visual or neurodevelopmental problems, lower oxygen-saturation targets cannot be recommended in these extremely preterm infants.

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

APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Methodology for limited ventilator strategy

CPAP Arm:

NICU management: CPAP infants could be intubated if they met any of the following criteria: an $\text{FiO}_2 > .50$ required to maintain an indicated $\text{SpO}_2 > 88\%$ for one hour, an arterial $\text{PaCO}_2 > 65$ torr documented on a single blood gas within 1 hour prior to intubation, or 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 within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $\text{PaCO}_2 < 65$ torr with a $\text{pH} > 7.20$, an $\text{SpO}_2 > 88\%$ with an $\text{FiO}_2 < 50\%$, a mean airway pressure (MAP) < 10 cm H_2O , ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be extubated within 24 hours of meeting all of the following criteria: $\text{PaCO}_2 < 50$ torr and $\text{pH} > 7.30$, $\text{FiO}_2 \leq .35$ with a $\text{SpO}_2 > 88\%$, a MAP < 8 cm H_2O , ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could 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.¹

Methodology for oximeter blinding strategy

4.1.1 Randomization and Masking, Storing and Assigning Oximeters

Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the 26 - 27 6/7 week gestational age group.... Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO_2 arm of the study. They will be specified as one of the following:

- **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue** or **Orange** OR
- **Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue** or **Orange**.

The **Blue/Orange codes** will designate an assignment to either the **Low (85% - 89%)** or **High (91% -95%)** SpO_2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the

sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form**).

Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know"**. Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO₂) are available to accommodate the delivery. Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.²

Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u>	<u>Higher</u>
			<u>Saturation</u>	<u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) ^δ	849±186	852±193	858±186	844±192
Gestational age (weeks) ^δ	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10 th %) ^ε	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male ^ε	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White ^ε	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black ^ε	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic ^ε	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown ^ε	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation ^ε	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any ^ε	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section ^ε	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only ^ε	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married ^ε	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents ^ε	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < high school degree ^ε	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

Income < \$30,000/year [€]	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language [€]	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP [€]	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD [¶] [€]	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL [€]	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC [€]	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis [€]	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids [€]	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) ^δ	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

^δ Mean ± SD

[€] no./total no.(%)

[¶] At 36 weeks postmenstrual age

*p<0.05, ** p<0.01, ***p<0.001 (Comparison for groups within each intervention arm)

Comparisons adjusted for stratification by center and gestational age and for familial clustering

Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT

<u>24 0/7-25 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07
<u>26 0/7-27 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31

Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS

<u>24 0/7-25 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22
<u>26 0/7-27 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95

Gross motor function level ≥ 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral pal	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78
Hearing impairment	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets

	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

*ARR (Adjusted relative risk)

** (adjusted mean ± standard error)

***(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups

Reason for Eye surgery	Lower N=31	Higher N=67	Total N=98
Retinopathy of Prematurity	26 (84%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)

References

1. **Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010;362:1970-9.**
2. **SUPPORT Manual of Operations, January 4, 2005, Revised March 10, 2005**

From: Gabrio, Jenna
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy.newman@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu; Yvonne Vaucher
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Becky.Brazeel@ucsd.edu; Brenda.Vecchio@ucsd.edu; Cunningham, Meg; Huitema, Carolyn Petrie; Suzanne Sayers; Zaterka-Baxter, Kristin; Lewis-Evans.Amanda@ucsd.edu
Subject: RE: SUPPORT Subcommittee Call - 12/18, Tu, 3:00 PM ET
Date: Tuesday, December 18, 2012 9:17:42 AM

A friendly reminder for today's call.

From: Gabrio, Jenna
Sent: Thursday, December 13, 2012 3:20 PM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy.newman@ucsd.edu; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu; 'Yvonne Vaucher'
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Becky Brazeel'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; 'Suzanne Sayers'; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call - 12/18, Tu, 3:00 PM ET

Dear all,

The SUPPORT subcommittee call to discuss the revised proposal has been scheduled for:

Tuesday, 12/18
3:00 pm ET

Dial:
Within the USA

or

Outside the USA

Then, enter Participant Passcode:

Unfortunately we couldn't find a time that worked for everyone so Wade and Marie will be unable to join. Myriam may also be unable to join but will try to call in.

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750

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From: [Mcbrien, James D](#)
To: ["gbender@wihri.org"](mailto:gbender@wihri.org)
Cc: [Truog, William \(MD\)](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Invited Reviewer Regarding Manuscript Entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" *Sent on Behalf of William E. Truog, MD*
Date: Monday, December 17, 2012 2:44:42 PM
Attachments: [ROP Natural History Study Manuscript \(resend\).doc](#)

The enclosed manuscript entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants", is being sent for internal Neonatal Network Research review. Would you be able to review the manuscript by December 31, 2012? There are no particular guidelines for the review except to look at study design, validity, clarity of results, and appropriateness of interpretation.

Thanks,

Jim

Electronic mail from Children's Mercy Hospitals and Clinics. This communication is intended only for the use of the addressee. It may contain information that is privileged or confidential under applicable law. If you are not the intended recipient or the agent of the recipient, you are hereby notified that any dissemination, copy or disclosure of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the message to Children's Mercy Hospital's Information Security Officer via return electronic mail at informationsecurityofficer@cmh.edu and expunge this communication without making any copies. Thank you for your cooperation.

Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

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Abbreviations:

ELBW – extremely low birth weight (<1000g birth weight)
GA – gestational age
PMA – postmenstrual age
ROP – retinopathy of prematurity
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

Keywords

retinopathy of prematurity, screening, extremely preterm infants

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What's Known on this Subject

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Because earlier treatment is now recommended, updated information regarding the timing of onset of ROP is needed.

What This Study Adds

Our data support the timing of examinations in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. We did not replicate the observation that the onset of ROP is more closely correlated with postmenstrual than chronological age.

Abstract

Objective: To determine if current ROP examination guidelines adequately identify treatable ROP in a contemporary cohort of extremely low gestation infants.

Patients and Methods: Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Inborn infants of 24 ⁰/₇ to 27 ⁶/₇ wks gestational age (GA) with consent prior to delivery were enrolled in 2005-2009. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was a primary outcome for the trial. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

Results: 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had a final ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

Conclusions: Our contemporary data support continued use of the 2006 guidelines. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines^{1,2} are based on natural history data from the CRYO-ROP³ and LIGHT-ROP⁴ studies. The CRYO-ROP study⁵ remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.⁶ Over the past two decades, survival of lower birth weight infants has increased.^{7,8} For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.⁷ The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age. It rarely occurs before 30 weeks postmenstrual age (PMA) or before 4 weeks chronological age. The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.⁴ Based on the results of the ET-ROP study, earlier treatment is now recommended.⁹ With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP, defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP Study¹⁰ and a population-based cohort study of infants born 2004-2007 in Sweden¹¹ reported the age of onset of stages 1, 2, and 3 ROP; the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from the Canadian Neonatal Network reported the age of onset of Type 1 ROP in a cohort of 214 infants \leq 27 weeks gestation;¹² this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort¹³ reported that "No preterm infants required treatment before the 33th postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be

curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 ⁶/₇ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)¹⁴ to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O₂ saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24 ⁰/₇ – 27 ⁶/₇ weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Repeat examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up was curtailed at 55 wks (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for quantiles.¹⁵ Cumulative incidence curves were compared using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-five percent (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular

hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 3. In contrast to prior studies, our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The distributions of PMA of onset of severe ROP is significantly later for ($p < 0.01$ for GA groups 26-27 weeks vs. 24-25 weeks). There is no difference in the distribution of chronological age of onset by GA group.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronological age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop severe ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,⁹ so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies in that the chronological age of ROP onset was not later in lower GA infants, our findings still support the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,³ lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,¹ albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤ 1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.¹⁶ Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP

study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age¹⁷ and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,¹¹ which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al¹² included 23-27 week infants; infants ≤ 25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants > 25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (23-24 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest age of onset of Type 1 ROP is more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA (although 1 infant with unknown age of onset had severe ROP detected on an initial exam at 33 weeks PMA). These findings are consistent with the other recent studies. In the Canadian Network study,¹² the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al¹³ that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronological age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.¹⁸ The SUPPORT Trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants > 27 weeks.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.¹⁸

Conclusion

Current screening guidelines, published in 2006,¹ recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at ≥ 35 weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

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Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP ¹	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA ² [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

¹ Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

² based on Olsen growth curves (Pediatrics, 2010)

Table 2. Risk factors for ROP

Risk Factor	No ROP	Any ROP¹	Severe (Treated or Type 1) ROP
n	353	644	138
Days on supplemental oxygen [median (ISR)]	33 (10, 60)	66 (39, 100)	94 (66, 119)
Late-onset sepsis (+ culture) [(n (%))]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23 ² (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98 ² (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

¹ Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

² missing data for 1 infant

Table 3. Postmenstrual and chronological age of onset¹ [with 95% confidence intervals (CI)] of any stage ROP (among infants with ROP age of onset determined)

ROP type	n	Postmenstrual Age (weeks)								
		min ²	1%	5%	25%	50%	75%	95%	99%	Max ²
Any ROP (95%CI)	635	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP ³ (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

ROP type	n	Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	max
Any ROP (95%CI)	635	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP ³ (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP (95% CI)	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

¹ Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.

² Min = minimum age at which designated severity of ROP was identified; max = maximum age.

³ Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital: n	1	4

Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst exam findings prior to discharge in either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Figure 1. Flow diagram of subjects in the original trial and current analysis

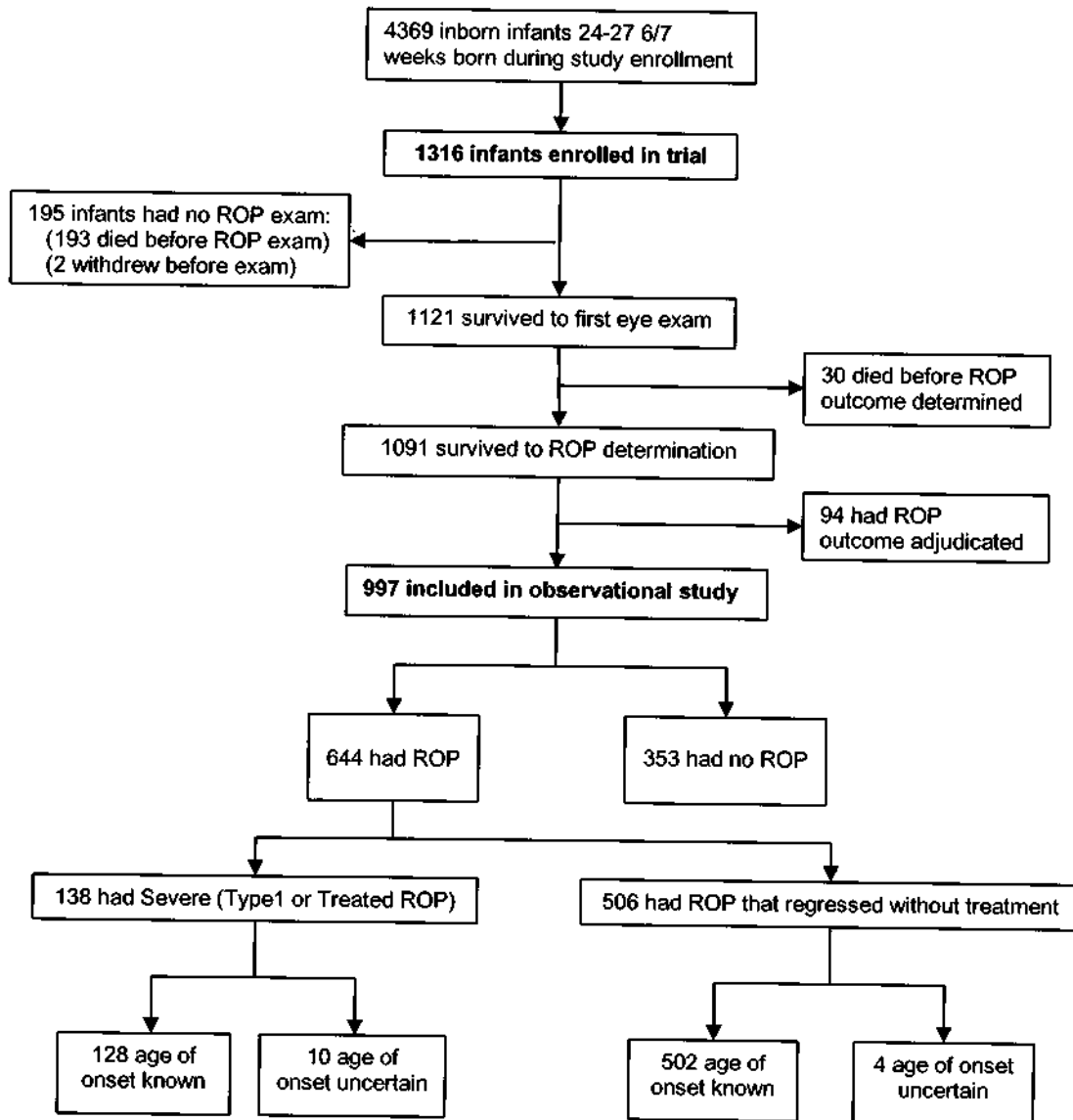


Figure 2. Risk of ROP by gestational age at birth (In completed weeks) among all 1316 infants in SUPPORT Trial

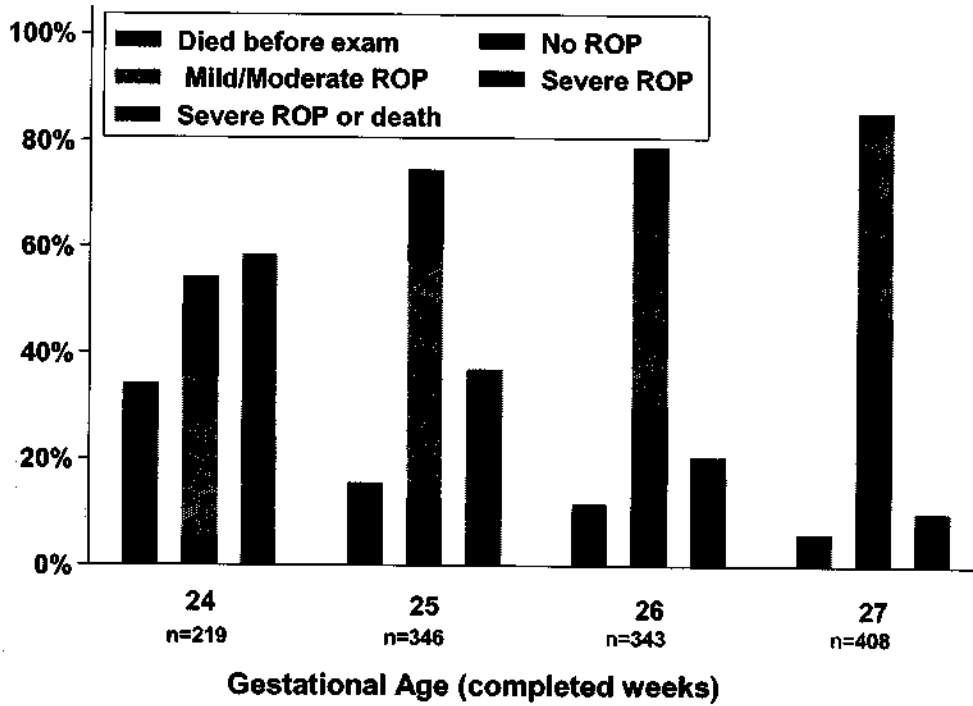


Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals

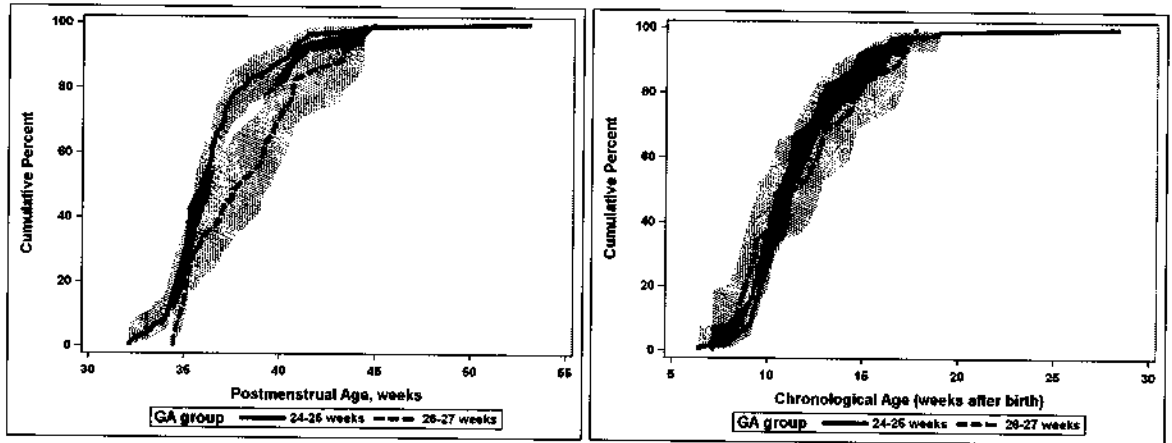
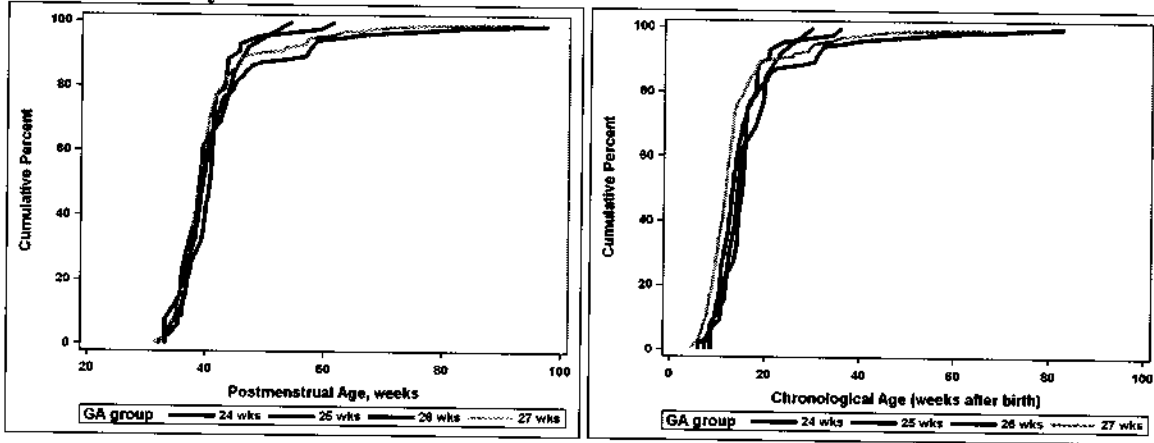
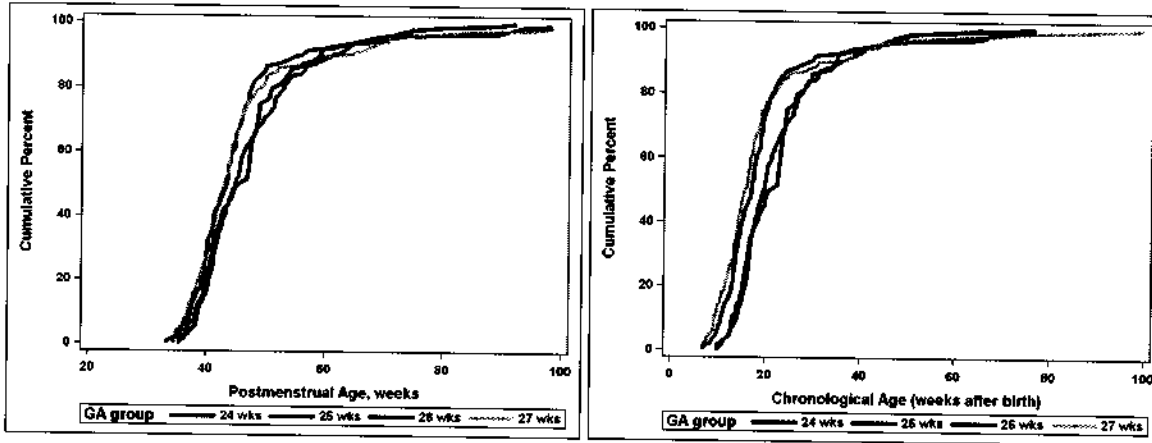


Figure 4. Postmenstrual and chronological age of “favorable outcome” (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

No ROP on any exam



Mild/Moderate ROP



From: McBrien, James, D
To: "Anna Maria Hibbs"
Cc: Truog, William (MD); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Manuscript Entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" *Sent on Behalf of William E. Truog, MD*
Date: Monday, December 17, 2012 11:39:50 AM
Attachments: ROP Natural History Study Manuscript (resend).doc

The enclosed manuscript entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants"; is being sent for internal Neonatal Network Research review. Would you be able to review the manuscript by December 31, 2012? There are no particular guidelines for the review except to look at study design, validity, clarity of results, and appropriateness of interpretation.

Thanks,

Jim

Electronic mail from Children's Mercy Hospitals and Clinics. This communication is intended only for the use of the addressee. It may contain information that is privileged or confidential under applicable law. If you are not the intended recipient or the agent of the recipient, you are hereby notified that any dissemination, copy or disclosure of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the message to Children's Mercy Hospital's Information Security Officer via return electronic mail at informationsecurityofficer@cmh.edu and expunge this communication without making any copies. Thank you for your cooperation.

From: McBrien, James D
To: "Michele Walsh"; "Ron Goldberg"; "Barbara Stoll"; "Abhik Das"; "Krisa Van Meurs"; "Wally Carlo"; "Uday Devaskar"; "Kurt Schibler"; "Ed Bell"; "Kristi Watterberg"; "Barbara Schmidt"; "Pablo Sánchez"; "Kathleen Kennedy"; "Seetha Shankaran"
Cc: Truog, William (MD); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Manuscript Entitled "Evaluating Rebinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" *Sent on Behalf of William E. Truog, MD*
Date: Monday, December 17, 2012 11:39:47 AM
Attachments: ROP Natural History Study Manuscript (resend).doc

Dear Colleagues,

The attached manuscript has been submitted to the Publication Subcommittee for internal review. The manuscript is being sent to you as a member of the NRN Steering Committee as a courtesy. If you wish, you may share comments with the first author. Please do not share the manuscript with others or duplicate.

Thanks

Jim

Electronic mail from Children's Mercy Hospitals and Clinics. This communication is intended only for the use of the addressee. It may contain information that is privileged or confidential under applicable law. If you are not the intended recipient or the agent of the recipient, you are hereby notified that any dissemination, copy or disclosure of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the message to Children's Mercy Hospital's Information Security Officer via return electronic mail at informationsecurityofficer@cmh.edu and expunge this communication without making any copies. Thank you for your cooperation.

From: McBrien, James D
To: "Ed Bell"
Cc: Truog, William (MD); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Manuscript Entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" *Sent on Behalf of William E. Truog, MD*
Date: Monday, December 17, 2012 11:39:32 AM
Attachments: ROP Natural History Study Manuscript (resend).doc

The enclosed manuscript entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants", is being sent for internal Neonatal Network Research review. Would you be able to review the manuscript by **December 31, 2012**? There are no particular guidelines for the review except to look at study design, validity, clarity of results, and appropriateness of interpretation.

Thanks,

Jim

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From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised Preterm infant release
Date: Friday, December 14, 2012 10:12:49 AM

I did share it with them—when I sent it for clearance, and yesterday, when I sent it for finalizing. I'll send the letterhead today—I'm leaving a couple of hours or so for potential after deadline changes from NHLBI.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, December 14, 2012 8:30 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: Revised Preterm infant release

Bob

Can you share the final version with the NHLBI folks or shall I? Also, please send me one with the letterhead so that I can send it to the sites.

Thanks so much!! Also, I will be available for press inquiries—

Dec 21 – office

Dec 22-23 – home (b)(6) or cell (b)(6)

Dec 24 – in office

Dec 25 – home or cell

Dec 26 – in office

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, December 13, 2012 4:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Revised Preterm infant release

FYI. Here's the final version, which I'll distribute on an embargoed basis on the 26th. If you need a letterhead version to share with your coworkers, let me know and I'll send you one.

Thanks.

Bob

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, December 13, 2012 4:52 PM
To: Fritz, Craig (NIH/OD) [E]
Cc: NIH News Clearance (NIH/OD); Striar, Diane (NIH/NHLBI) [E]; Ferrier, Robin (NIH/NHLBI) [E]
Subject: FW: Revised Preterm infant release

Hi Diane and Robin. Please see attached. I received final clearance on this today. (I meant to cc you on this earlier.)

Thanks.

Bob

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, December 13, 2012 4:32 PM
To: Fritz, Craig (NIH/OD) [E]
Cc: NIH News Clearance (NIH/OD)
Subject: Revised Preterm infant release

Please see attached. For distribution Wednesday, December 26, at 5 p.m.

From: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: FW: Revised Preterm infant release
Date: Thursday, December 13, 2012 4:55:30 PM
Attachments: [Final ASPA 0876_20121210_NIH_PR_Premies_Oxygen_Benefit_APPROVED.docx](#)

FYI. Here's the final version, which I'll distribute on an embargoed basis on the 26th. If you need a letterhead version to share with your coworkers, let me know and I'll send you one.

Thanks.
Bob

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, December 13, 2012 4:52 PM
To: Fritz, Craig (NIH/OD) [E]
Cc: NIH News Clearance (NIH/OD); Striar, Diane (NIH/NHLBI) [E]; Ferrier, Robin (NIH/NHLBI) [E]
Subject: FW: Revised Preterm infant release

Hi Diane and Robin. Please see attached. I received final clearance on this today. (I meant to cc you on this earlier.)

Thanks.
Bob

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, December 13, 2012 4:32 PM
To: Fritz, Craig (NIH/OD) [E]
Cc: NIH News Clearance (NIH/OD)
Subject: Revised Preterm infant release

Please see attached. For distribution Wednesday, December 26, at 5 p.m.

From: Gabrio, Jenna
To: alaptook@WIHL.org; [Bradley Yoder](mailto:Bradley.Yoder); adas@rti.org; mgantz@rti.org; [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD); kurt.schibler@cchmc.org; mow3@cwru.edu; MPeralta@PFDS.UAB.EDU; nancy.newman; nfiner@ucsd.edu; Roger.Falx@hsc.utah.edu; [Wallace, Dennis](mailto:Wallace.Dennis); [Wally Carlo, M.D.](mailto:WallyCarlo.M.D.); wrich@ucsd.edu; [Yvonne Vaucher](mailto:Yvonne.Vaucher)
Cc: sharon.gough@hsc.utah.edu; [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer.Stephania@NIH/NICHD); [Becky Brazeel](mailto:Becky.Brazeel); [Brenda Vecchio](mailto:Brenda.Vecchio); [Cunningham, Meg](mailto:Cunningham.Meg); [Gabrio, Jenna](mailto:Gabrio.Jenna); [Huitema, Carolyn Petrie](mailto:Huitema.Carolyn.Petrie); [Suzanne Savers](mailto:Suzanne.Savers); [Zaterka-Baxter, Kristin](mailto:Zaterka-Baxter.Kristin)
Subject: SUPPORT Subcommittee Call - 12/18, Tu, 3:00 PM ET
Date: Thursday, December 13, 2012 3:21:43 PM
Attachments: [Cover letter IH SUPPORT study Dec 2012.doc.doc](#)
[IH in High vs Low sat groups SUPPORT DiFiore.pdf.pdf](#)
[SUPPORT trial proposal - Patterns of IH assoc with mortality REVISED.docx.docx](#)

Dear all,

The SUPPORT subcommittee call to discuss the revised proposal has been scheduled for:

Tuesday, 12/18
3:00 pm ET

Dial:

Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Wade and Marie will be unable to join. Myriam may also be unable to join but will try to call in.

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
Subject: Re: SUPPORT release
Date: Friday, December 07, 2012 5:15:11 PM

Thanks
Rose

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, December 07, 2012 05:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT release

I'm not sure what happened, Rose. When I check my copy on the drive, the change was made.

Maybe I attached it and sent it before the document saved to the drive.

Anyway, I'm going to enter it into Departmental clearance tonight before I leave. I should have approval by Wednesday or Thursday.

Have a good weekend.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, December 05, 2012 10:04 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: SUPPORT release
Importance: High

Bob

See below – this sentence did NOT get changed in the most recent press release – please change as the one in the release is not accurate!! It was accurate in the email you sent so you may have attached the wrong version.

thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]

Sent: Sunday, December 02, 2012 10:22 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: SUPPORT release

Bob

I am working off my BB.

Please change the sentence:

(b)(5)

To the following;

(b)(5)

Can you send me an updated version for one more review?

Thanks

Rose

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, November 30, 2012 03:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT release

Hi Rose. Please see attached. Thanks.

From: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: SUPPORT release
Date: Wednesday, December 05, 2012 10:08:48 AM

Would have sworn I changed it. Will fix when I get back

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, December 05, 2012 10:04 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: SUPPORT release

Bob

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thanks

Rose

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sunday, December 02, 2012 10:22 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: SUPPORT release

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(b)(5)

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Thanks

Rose

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, November 30, 2012 03:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT release

Hi Rose. Please see attached. Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: SUPPORT release
Date: Wednesday, December 05, 2012 10:04:00 AM
Attachments: 2 SUPPORT News Release 01.docx
Importance: High

Bob

See below – this sentence did NOT get changed in the most recent press release – please change as the one in the release is not accurate!! It was accurate in the email you sent so you may have attached the wrong version.

thanks

Rose

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higginsr@mail.nih.gov

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Sent: Sunday, December 02, 2012 10:22 AM
To: Bock, Robert (NIH/NICHD) [E]
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Please change the sentence:

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To the following:

(b)(5)

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Thanks

Rose

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, November 30, 2012 03:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT release

Hi Rose. Please see attached. Thanks.

Page 0913 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0914 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0915 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: [Finer, Neil](#)
To: [Laurencot, Elizabeth](#)
Cc: [Wally Carlo](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Marie Gantz](#); [Abhik Das](#); [Rich, Wade](#); [Myriam Peralta, M.D.](#)
Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)
Date: Tuesday, December 04, 2012 12:44:02 PM

Hi Elizabeth
The change for N.S.N. is in the Appendix of the article, p 2503, NOT the Web Supp
Neil

On 12/4/12 9:41 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org> wrote:

>Dear Neil,

>

>Many thanks for your message. I will send the updated Supp App to the
>Layout Dept. Could you please confirm that the change in affiliation is
>only in the Supp App, i.e., no changes are necessary to the affiliations
>listed in the article?

>

>I'll be in touch tomorrow (Weds) morning if the senior editors have any
>queries for you.

>

>Best,

>Eli

>

>

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

>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]

>Sent: Tuesday, December 04, 2012 12:39 PM

>To: Laurencot, Elizabeth

>Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik
>Das; Rich, Wade; Myriam Peralta, M.D.

>Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)

>

>Hello again Elizabeth

>This process continues to my chagrin

>Please find an altered Web Appendix with all the corrections that I have

>heard about and this will be the final Web Appendix There 1 change

>requested for the manuscript that only involves the Appendix on page

>2503 This is related to an incorrectly noted affiliation.

>The correct wording is below

>

>Appendix p 2503 - Line 5 University, Cleveland (M.C.W., D.E.W.-C, N.S.N.)

>Remove N.S.N. from the beginning of Line 7

>

>This individual works at Cleveland not RTI Sorry for catching this so

>late Thanks again for your patience Neil Finer

>

>

>On 12/4/12 4:32 AM, "Laurencot, Elizabeth"

>><elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>> wrote:

>

>Dear Neil,

>

>Many thanks for your messages. I have marked all the requested changes,
>with one exception: we in the Journal offices are not permitted to make
>any changes to your Supp App file. So, regarding the change to the
>footnote in Table S1, please send me a revised pdf file.

>
>I expect that the senior editors will be sending in their queries and
>comments tomorrow (Weds.) morning. If there is anything that needs your
>attention, I will send the queries to you then; given that the pages are
>due to be finalized on Thursday, I just want to give you a heads-up that
>we will need to hear back from you quickly.

>
>Best,
>Eli

>
>

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

>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>Sent: Tuesday, December 04, 2012 1:00 AM
>To: Laurencot, Elizabeth
>Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das
>Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)

>

>Hi Elizabeth

>I had sent you the correct last sentence of the first paragraph of the
>revised abstract, and I had given you the correct word count I rechecked
>that - 339 words But We had removed the second last sentence and I did
>not indicate that Here is the Introduction of the Abstract as rewritten

>

>"Previous results from our trial of early treatment with continuous
>positive airway pressure (CPAP) versus early surfactant treatment in
>infants showed no significant difference in the outcome of death or
>bronchopulmonary dysplasia. A lower (vs.
>higher) target range of oxygen saturation was associated with a lower
>rate of severe retinopathy but higher mortality. We now report
>longer-term results from our prespecified hypotheses.

>

>We did not make any other changes to the abstract Sorry for the mistake
>which was mine only Be well Neil

>

>

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

>From: Laurencot, Elizabeth [mailto:elaurencot@nejm.org]
>Sent: Monday, December 03, 2012 5:35 AM
>To: Finer, Neil
>Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das
>Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)

>

>Dear Neil,

>

>Somehow we missed the decimal place on the SD for gestational age at
>birth for the higher-oxygen group in Table I. Should this be 1.0?

>

>Best,

>Eli

>

>

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

>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>Sent: Monday, December 03, 2012 8:03 AM
>To: Laurencot, Elizabeth
>Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das
>Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)
>
>These look OK to me
>Let me know if you have any concerns
>Neil
>
>On Dec 3, 2012, at 7:32 AM, "Laurencot, Elizabeth"
><elaurencot@nejm.org<mailto:elaurencot@nejm.org><mailto:elaurencot@nejm.org
>g>> wrote:
>
>Dear Neil,
>
>The revised page proofs for your article went sent to you late Friday
>afternoon. If possible, please take a moment to send me an email
>confirming receipt.
>
>For the most part, the galley changes were made correctly, with a couple
>exceptions (noted below). Also, there are a few other items to be fixed:
>
>We will change the order of the authors Walsh and Gantz, per your request.
>
>Although no one caught this on the galleys, there was an error with the
>footnote marks used in the author list and the front page. Specifically,
>the footnote mark after Dr Dusick should be a dagger, not an asterisk,
>indicating "deceased". The asterisk will go after "Network" at the end of
>the list. Although this is technically "out of order" in terms of how we
>use these footnote marks, it is correct in this instance. Of course, the
>matching marks on the front page must be changed.
>
>In the affiliations, we will move the North Carolina group ahead of the
>Ohio group to match the revised order in the author list.
>
>In the affiliations, the wrong dash was used before "both in Ohio".
>
>In Table 4, a dagger footnote after "Other abnormal eye finding" was
>incorrectly deleted. There should be both the dagger and double dagger
>for this row entry.
>
>Please do read the entire set of proofs carefully and email me a list of
>any corrections you have for the page proofs by 10am (US Eastern)
>Tuesday, December 4 (rather than the 24 hours stated in the letter that
>accompanied the proofs). Also, I would ask that you please send me a list
>of corrections rather than annotating the pdf file.
>
>The editors will be reading your page proofs during this time as well, so
>I will be contacting you with any queries they have (probably Tuesday
>afternoon or Wednesday morning). Please do let me know if you will be
>unavailable via email next week.
>
>I look forward to hearing back from you regarding your page proofs.
>
>Best,
>Eli

>

>

>From: Nejm Article

>Sent: Friday, November 30, 2012 5:06 PM

>To: 'nfiner@ucsd.edu' <mailto:nfiner@ucsd.edu> <mailto:nfiner@ucsd.edu>

>Cc: Laurencot, Elizabeth

>Subject: PDF of Your Article for NEJM

>

>Attached is a PDF file of your article, which is scheduled to be

>published in the Journal.

>

>This file appears in preliminary page format and incorporates changes

>that were made to your galley proofs. Please check it carefully for

>accuracy. Then, please call Eli Laurencot

>(elaurencot@nejm.org <mailto:elaurencot@nejm.org> <mailto:elaurencot@nejm.org

>g>) at 1-800-445-8080 or at 1-617-734-9800 within the next 24 business

>hours. Please do not respond to this e-mail message. We will correct

>errors but can make no other changes at this point.

>

>Please note that this material is confidential and embargoed until

>publication. If you have questions about our embargo policy, please

>contact NEJM Media Relations at 781-434-7847 or at

>Mediasupport@nejm.org <mailto:Mediasupport@nejm.org> <mailto:Mediasupport@nejm.org>

>jm.org>.

>

>To order reprints of your article after publication, please contact the

>Bulk Reprints Department at 1-877-241-7159.

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>

>

>

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>you.

><3vauc_oa1208506.pdf>

><3vauc_supapp.pdf>

>

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From: Finer, Neil
To: Laurencot, Elizabeth
Cc: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Marie Gantz; Abhik Das; Rich, Wade; Myriam Peralta, M.D.
Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)
Date: Tuesday, December 04, 2012 12:39:09 PM
Attachments: SUPPORTWeb Appendix_1204Final[2].pdf

Hello again Elizabeth

This process continues to my chagrin

Please find an altered Web Appendix with all the corrections that I have heard about and this will be the final Web Appendix

There 1 change requested for the manuscript that only involves the Appendix on page 2503

This is related to an incorrectly noted affiliation.

The correct wording is below

Appendix p 2503 - Line 5 University, Cleveland (M.C.W., D.E.W.-C, N.S.N.)
Remove N.S.N. from the beginning of Line 7

This individual works at Cleveland not RTI

Sorry for catching this so late

Thanks again for your patience

Neil Finer

On 12/4/12 4:32 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>> wrote:

Dear Neil,

Many thanks for your messages. I have marked all the requested changes, with one exception: we in the Journal offices are not permitted to make any changes to your Supp App file. So, regarding the change to the footnote in Table S1, please send me a revised pdf file.

I expect that the senior editors will be sending in their queries and comments tomorrow (Weds.) morning. If there is anything that needs your attention, I will send the queries to you then; given that the pages are due to be finalized on Thursday, I just want to give you a heads-up that we will need to hear back from you quickly.

Best,

Eli

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Tuesday, December 04, 2012 1:00 AM
To: Laurencot, Elizabeth
Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das
Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)

Hi Elizabeth

I had sent you the correct last sentence of the first paragraph of the revised abstract, and I had given you the correct word count I rechecked that - 339 words But We had removed the second last sentence and I did not indicate that Here is the Introduction of the Abstract as rewritten

"Previous results from our trial of early treatment with continuous positive airway pressure (CPAP) versus early surfactant treatment in infants showed no significant difference in the outcome of death or bronchopulmonary dysplasia. A lower (vs.

higher) target range of oxygen saturation was associated with a lower rate of severe retinopathy but higher mortality. We now report longer-term results from our prespecified hypotheses.

We did not make any other changes to the abstract Sorry for the mistake which was mine only Be well Neil

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

From: Laurencot, Elizabeth [mailto:elaurencot@nejm.org]
Sent: Monday, December 03, 2012 5:35 AM
To: Finer, Neil
Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das
Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)

Dear Neil,

Somehow we missed the decimal place on the SD for gestational age at birth for the higher-oxygen group in Table 1. Should this be 1.0?

Best,
Eli

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, December 03, 2012 8:03 AM
To: Laurencot, Elizabeth
Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das
Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)

These look OK to me
Let me know if you have any concerns
Neil

On Dec 3, 2012, at 7:32 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>>
<<mailto:elaurencot@nejm.org>>> wrote:

Dear Neil,

The revised page proofs for your article went sent to you late Friday afternoon. If possible, please take a moment to send me an email confirming receipt.

For the most part, the galley changes were made correctly, with a couple exceptions (noted below). Also, there are a few other items to be fixed:

We will change the order of the authors Walsh and Gantz, per your request.

Although no one caught this on the galleys, there was an error with the footnote marks used in the author list and the front page. Specifically, the footnote mark after Dr Dusick should be a dagger, not an asterisk, indicating "deceased". The asterisk will go after "Network" at the end of the list. Although this is technically "out of order" in terms of how we use these footnote marks, it is correct in this instance. Of course, the matching marks on the front page must be changed.

In the affiliations, we will move the North Carolina group ahead of the Ohio group to match the revised order in the author list.

In the affiliations, the wrong dash was used before "both in Ohio".

In Table 4, a dagger footnote after "Other abnormal eye finding" was incorrectly deleted. There should be both the dagger and double dagger for this row entry.

Please do read the entire set of proofs carefully and email me a list of any corrections you have for the page proofs by 10am (US Eastern) Tuesday, December 4 (rather than the 24 hours stated in the letter that accompanied the proofs). Also, I would ask that you please send me a list of corrections rather than annotating the pdf file.

The editors will be reading your page proofs during this time as well, so I will be contacting you with any queries they have (probably Tuesday afternoon or Wednesday morning). Please do let me know if you will be unavailable via email next week.

I look forward to hearing back from you regarding your page proofs.

Best,
Eli

From: Nejm Article
Sent: Friday, November 30, 2012 5:06 PM
To: 'nfiner@ucsd.edu' <<mailto:nfiner@ucsd.edu>> <<mailto:nfiner@ucsd.edu>>
Cc: Laurencot, Elizabeth
Subject: PDF of Your Article for NEJM

Attached is a PDF file of your article, which is scheduled to be published in the Journal.

This file appears in preliminary page format and incorporates changes that were made to your galley proofs. Please check it carefully for accuracy. Then, please call Eli Laurencot (elaurencot@nejm.org <<mailto:elaurencot@nejm.org>> <<mailto:elaurencot@nejm.org>>) at 1-800-445-8080 or at 1-617-734-9800 within the next 24 business hours. Please do not respond to this e-mail message. We will correct errors but can make no other changes at this point.

Please note that this material is confidential and embargoed until publication. If you have questions about our embargo policy, please contact NEJM Media Relations at 781-434-7847 or at Mediasupport@nejm.org <<mailto:Mediasupport@nejm.org>> <<mailto:Mediasupport@nejm.org>>.

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<[3vauc_oa1208506.pdf](#)>

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Investigators

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children’s National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D’Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH, UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

Methodology for limited ventilator strategy

CPAP Arm:

NICU management: CPAP infants could be intubated if they met any of the following criteria: an $FiO_2 > .50$ required to maintain an indicated $SpO_2 > 88\%$ for one hour, an arterial $PaCO_2 > 65$ torr documented on a single blood gas within 1 hour prior to intubation, or 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 within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2 < 65$ torr with a $pH > 7.20$, an $SpO_2 > 88\%$ with an $FiO_2 < 50\%$, a mean airway pressure (MAP) < 10 cm H₂O, ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2 < 50$ torr and $pH > 7.30$, $FiO_2 \leq .35$ with a $SpO_2 > 88\%$, a MAP < 8 cm H₂O, ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could 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.¹

Methodology for oximeter blinding strategy

4.1.1 Randomization and Masking, Storing and Assigning Oximeters

Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the 26 - 27 6/7 week gestational age group.... Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO_2 arm of the study. They will be specified as one of the following:

- **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue** or **Orange** OR
- **Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue** or **Orange**.

The **Blue/Orange** codes will designate an assignment to either the **Low (85% - 89%)** or **High (91% -95%)** SpO_2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the

sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form**).

Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know"**. Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO2) are available to accommodate the delivery. Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.²

Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u> <u>Saturation</u>	<u>Higher</u> <u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) ^δ	849±186	852±193	858±186	844±192
Gestational age (weeks) ^δ	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10 th %) ^ε	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male ^ε	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White ^ε	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black ^ε	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic ^ε	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown ^ε	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation ^ε	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any ^ε	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section ^ε	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only ^ε	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married ^ε	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents ^ε	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education< high school	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

degree [€]				
Income < \$30,000/year [€]	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language [€]	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP [€]	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD [¶] [€]	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL [€]	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC [€]	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis [€]	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids [€]	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) ^δ	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

^δ Mean ± SD

[€] no./total no.(%)

[¶] At 36 weeks postmenstrual age

*p<0.05, ** p<0.01, ***p<0.001 (Comparison for groups within each intervention arm)

Comparisons of neonatal outcomes adjusted for stratification by center and gestational age and for familial clustering

Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT

<u>24 0/7-25 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level \geq 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07
<u>26 0/7-27 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level \geq 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31

Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS

<u>24 0/7-25 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22
<u>26 0/7-27 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22

Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level ≥ 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral pal	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78
Hearing impairment	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets

	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

*ARR (Adjusted relative risk)

** (adjusted mean ± standard error)

***(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups

Reason for Eye surgery	Lower N=31	Higher N=67	Total N=98
Retinopathy of Prematurity	26 (84%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)

References

1. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.

2. SUPPORT Manual of Operations, January 4, 2005, Revised March 10, 2005

From: [Finer, Neil](#)
To: [Gantz, Marie](#)
Cc: [Abhik Das](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: PDF of Your Article for NEJM
Date: Tuesday, December 04, 2012 12:34:39 PM

Many thanks to both of you
Neil

On 12/4/12 9:33 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

>Abhik and I agree that it is not necessarily essential; the change was
>recent and there will probably be other papers coming out that don't
>reflect the reorganization.

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org

>828-254-6255

>

>

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

>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]

>Sent: Tuesday, December 04, 2012 12:30 PM

>To: Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]

>Cc: Vaucher, Yvonne; MPeralta@PEDS.UAB.EDU; WCarlo@peds.uab.edu; Das,

>Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]

>Subject: Re: PDF of Your Article for NEJM

>

>Marie

>Is this an essential change?

>Neil

>

>From: <Gantz>, Marie Gantz <mgantz@rti.org<<mailto:mgantz@rti.org>>>

>Date: Tuesday, December 4, 2012 7:51 AM

>To: Stephanie Archer

><archerst@mail.nih.gov<<mailto:archerst@mail.nih.gov>>>, UCSD Pediatrics

><nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>

>Cc: Yvonne Vaucher <yvaucher@ucsd.edu<<mailto:yvaucher@ucsd.edu>>>,

>"MPeralta@PEDS.UAB.EDU<<mailto:MPeralta@PEDS.UAB.EDU>>"

><MPeralta@PEDS.UAB.EDU<<mailto:MPeralta@PEDS.UAB.EDU>>>, Wally Carlo

><wcarlo@peds.uab.edu<<mailto:wcarlo@peds.uab.edu>>>, Abhik Das

><adas@rti.org<<mailto:adas@rti.org>>>, Wade Rich

><wrich@ucsd.edu<<mailto:wrich@ucsd.edu>>>, Rosemary Higgins

><higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>>

>Subject: RE: PDF of Your Article for NEJM

>

>To clarify, the RTI unit should be changed for both me and Abhik.

>

>Thanks,

>Marie

>

>Marie Gantz, Ph.D.
>Senior Research Statistician
>RTI International
>mgantz@rti.org<mailto:mgantz@rti.org>
>828-254-6255
>
>From: Gantz, Marie
>Sent: Tuesday, December 04, 2012 10:49 AM
>To: 'Archer, Stephanie (NIH/NICHD) [E]';
>'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'
>Cc: 'yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>';
>'MPeralta@PEDS.UAB.EDU<mailto:MPeralta@PEDS.UAB.EDU>';
>'WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>'; Das, Abhik;
>'wrich@ucsd.edu<mailto:wrich@ucsd.edu>'; Higgins, Rosemary (NIH/NICHD)
>[E]
>Subject: RE: PDF of Your Article for NEJM
>Importance: High
>
>I checked over the affiliations on the second page of the article, and
>Nancy Newman is the only incorrect one I saw. I think with the
>reordering of authors she accidentally got moved from Case Western to
>RTI.
>
>Also, RTI recently went through a reorganization, and "Statistics and
>Epidemiology" is no longer a unit. Can we ask NEJM to change that to
>"Social, Statistical, & Environmental Sciences?"
>
>Marie
>
>Marie Gantz, Ph.D.
>Senior Research Statistician
>RTI International
>mgantz@rti.org<mailto:mgantz@rti.org>
>828-254-6255
>
>From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
>Sent: Tuesday, December 04, 2012 10:47 AM
>To: Gantz, Marie; 'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'
>Cc: 'yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>';
>'MPeralta@PEDS.UAB.EDU<mailto:MPeralta@PEDS.UAB.EDU>';
>'WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>'; Das, Abhik;
>'wrich@ucsd.edu<mailto:wrich@ucsd.edu>'; Higgins, Rosemary (NIH/NICHD)
>[E]
>Subject: Re: PDF of Your Article for NEJM
>
>I sent Neil a list of changes for the authors/affiliations and the
>acknowledgements.
>
>
>From: Gantz, Marie [mailto:mgantz@rti.org]
>Sent: Tuesday, December 04, 2012 10:14 AM
>To: Finer, Neil <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>; Archer,
>Stephanie (NIH/NICHD) [E]
>Cc: Vaucher, Yvonne <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>;
>MPeralta@PEDS.UAB.EDU<mailto:MPeralta@PEDS.UAB.EDU>
><MPeralta@PEDS.UAB.EDU<mailto:MPeralta@PEDS.UAB.EDU>>;
>WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>

><WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>; Das, Abhik
><adas@rti.org<mailto:adas@rti.org>>; Rich, Wade
><wrich@ucsd.edu<mailto:wrich@ucsd.edu>>; Higgins, Rosemary (NIH/NICHD)
>[E]
>Subject: RE: PDF of Your Article for NEJM
>
>Neil,
>
>In your email back to NEJM, I did not see mention of the incorrect
>affiliations that are in the "Appendix" section on the second page of
>the article. I know that there is at least one error, as Nancy Newman is
>listed as being from RTI. I have not checked to see if there are other
>errors, but I can do that now if necessary.
>
>Marie
>
>Marie Gantz, Ph.D.
>Senior Research Statistician
>RTI International
>mgantz@rti.org<mailto:mgantz@rti.org>
>828-254-6255
>
>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>Sent: Tuesday, December 04, 2012 9:18 AM
>To: Archer, Stephanie (NIH/NICHD) [E]
>Cc: Gantz, Marie; Finer, Neil; Vaucher, Yvonne;
>'MPeralta@PEDS.UAB.EDU<mailto:MPeralta@PEDS.UAB.EDU>';
>'WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>'; Das, Abhik; Rich,
>Wade; Rosemary (NIH/NICHD) Higgins [E]
>Subject: RE: PDF of Your Article for NEJM
>
>Hi Stephanie
>We do all the changes to the Supplement
>I will get these changed and send back this morning Thanks Neil
>
>From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
>Sent: Tuesday, December 04, 2012 5:19 AM
>To: Finer, Neil
>Subject: Re: PDF of Your Article for NEJM
>
>Julie Ripley at NEJM.
>
>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>Sent: Monday, December 03, 2012 10:59 PM
>To: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PDF of Your Article for NEJM
>
>Hi Stephanie
>Who is Julie?
>Neil
>
>From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
>Sent: Monday, December 03, 2012 12:02 PM
>To: 'mgantz@rti.org<mailto:mgantz@rti.org>'; Finer, Neil; Vaucher,
>Yvonne; 'MPeralta@PEDS.UAB.EDU<mailto:MPeralta@PEDS.UAB.EDU>';
>'WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>';
>'adas@rti.org<mailto:adas@rti.org>'; Higgins, Rosemary (NIH/NICHD) [E];

>Rich, Wade
>Subject: Re: PDF of Your Article for NEJM
>
>Neil,
>
>Did we send Julie the author changes I sent to you last week? It had a
>few changes in it, but maybe she forgot with making the adjustments to
>the author order and getting the signed letters.
>
>From: Gantz, Marie [mailto:mgantz@rti.org]
>Sent: Monday, December 03, 2012 02:15 PM
>To: Finer, Neil <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>; Vaucher,
>Yvonne <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>; Myriam Peralta,
>M.D. <MPeralta@peds.uab.edu<mailto:MPeralta@peds.uab.edu>>; Wally Carlo,
>M.D. <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>; Das, Abhik
><adas@rti.org<mailto:adas@rti.org>>; Higgins, Rosemary (NIH/NICHD) [E];
>Rich, Wade <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>
>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PDF of Your Article for NEJM
>
>The article itself looks OK to me (have yet to check the supplemental
>tables) except the affiliations are still off - I noticed that Nancy
>Newman is listed as being at RTI.
>
>Stephanie - can you please check the affiliations against the
>boilerplate?
>
>The only other minor issue, which is my fault for suggesting the wording
>for the Figure, is that we describe those with an NDI outcome defined as
>having "complete NDI outcome data." Technically, the data only had to be
>complete enough to assign an outcome, which means that if a child met
>one of the NDI criteria it did not matter if another criterion was
>missing. However, I'm OK with leaving as-is if everyone else is.
>
>Marie
>
>Marie Gantz, Ph.D.
>Senior Research Statistician
>RTI International
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>828-254-6255
>
>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>Sent: Friday, November 30, 2012 6:30 PM
>To: Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo, M.D.; Das,
>Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
>Subject: FW: PDF of Your Article for NEJM
>
>FYI
>These look good to me
>Neil
>
>From: Nejm Article [mailto:nejmarticle@mms.org]
>Sent: Friday, November 30, 2012 2:06 PM
>To: Finer, Neil
>Cc: Laurencot, Elizabeth
>Subject: PDF of Your Article for NEJM

- >
- >Attached is a PDF file of your article, which is scheduled to be published in the Journal.
- >
- >This file appears in preliminary page format and incorporates changes that were made to your galley proofs. Please check it carefully for accuracy. Then, please call Eli Laurencot (elaurencot@nejm.org<mailto:elaurencot@nejm.org>) at 1-800-445-8080 or at 1-617-734-9800 within the next 24 business hours. Please do not respond to this e-mail message. We will correct errors but can make no other changes at this point.
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From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PDF of Your Article for NEJM
Date: Tuesday, December 04, 2012 11:38:10 AM

Sure.

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, December 04, 2012 11:38 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Fw: PDF of Your Article for NEJM

FYI- please get their ok as they co-funded the original study

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

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Tuesday, December 04, 2012 11:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]; Zagorski, Nicholas (NIH/NHLBI) [E]
Subject: RE: PDF of Your Article for NEJM

Congrats Rose on the NEJM pub this month, I am copying Nick Zagorski from NHLBI who is the point of contact for coordinating the press release.

It has been great working with you and colleagues at NICHD on this trial,

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sunday, December 02, 2012 10:16 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]
Subject: Fw: PDF of Your Article for NEJM

FYI

We are working on a press release- should have it later this week.

Dec 27 is the publication date.

Thanks for the tremendous support!
Rose

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sunday, December 02, 2012 09:55 AM

To: blaisdellC@mail.nih.gov <blaisdellC@mail.nih.gov>; Bock, Robert (NIH/NICHD) [E]
Subject: FW: PDF of Your Article for NEJM

FYI

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
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301-496-5575
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higginsr@mail.nih.gov

From: Finer, Neil [nfiner@ucsd.edu]
Sent: Friday, November 30, 2012 6:29 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo, M.D.; adas@rti.org; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: FW: PDF of Your Article for NEJM

FYI

These look good to me
Neil

From: Nejm Article [mailto:nejmarticle@mms.org]
Sent: Friday, November 30, 2012 2:06 PM
To: Finer, Neil
Cc: Laurencot, Elizabeth
Subject: PDF of Your Article for NEJM

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Subject: Fw: PDF of Your Article for NEJM
Date: Tuesday, December 04, 2012 11:37:37 AM
Attachments: [3vauc_0a1208506.pdf.pdf](#)

FYI- please get their ok as they co-funded the original study

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

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Tuesday, December 04, 2012 11:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]; Zagorski, Nicholas (NIH/NHLBI) [E]
Subject: RE: PDF of Your Article for NEJM

Congrats Rose on the NEJM pub this month,
I am copying Nick Zagorski from NHLBI who is the point of contact for coordinating the press release.
It has been great working with you and colleagues at NICHD on this trial,

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sunday, December 02, 2012 10:16 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]
Subject: Fw: PDF of Your Article for NEJM

FYI

We are working on a press release- should have it later this week.

Dec 27 is the publication date.

Thanks for the tremendous support!
Rose

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sunday, December 02, 2012 09:55 AM
To: blaisdellC@mail.nih.gov <blaisdellC@mail.nih.gov>; Bock, Robert (NIH/NICHD) [E]
Subject: FW: PDF of Your Article for NEJM

FYI

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH

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301-496-3790 (FAX)
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From: Finer, Neil [nfiner@ucsd.edu]
Sent: Friday, November 30, 2012 6:29 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo, M.D.; adas@rti.org; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: FW: PDF of Your Article for NEJM

FYI
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Neil

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ORIGINAL ARTICLE

Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial

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Neil N. Finer, M.D., Waldemar A. Carlo, M.D., Michele C. Walsh, M.D.,
Marie G. Gantz, Ph.D., Abbot R. Lupton, M.D., Bradley A. Yoder, M.D.,
Roger G. Faix, M.D., Abhik Das, Ph.D., Kurt Schibler, M.D., Wade Rich, R.R.T.,
Nancy S. Newman, R.N., Betty R. Vohr, M.D., Kimberly Yolton, Ph.D.,
Roy J. Heyne, M.D., Deanne E. Wilson-Costello, M.D., Patricia W. Evans, M.D.,
Ricki F. Goldstein, M.D., Michael J. Acarregui, M.D., Ira Adams-Chapman, M.D.,
Athina Pappas, M.D., Susan R. Hintz, M.D., M.S.Epi., Brenda Poindexter, M.D.,
Anna M. Dusick, M.D.,* Elisabeth C. McGowan, M.D., Richard A. Ehrenkranz, M.D.,
Anna Bodnar, M.D., Charles R. Bauer, M.D., Janell Fuller, M.D.,
T. Michael O'Shea, M.D., M.P.H., Gary J. Myers, M.D.,
and Rosemary D. Higgins, M.D., for the SUPPORT Study Group
of the Eunice Kennedy Shriver NICHD Neonatal Research Network†

ABSTRACT

BACKGROUND

Previous results from our trial of early treatment with continuous positive airway pressure (CPAP) versus early surfactant treatment in infants showed no significant difference in the outcome of death or bronchopulmonary dysplasia. A lower (vs. higher) target range of oxygen saturation was associated with a lower rate of severe retinopathy but higher mortality. Our prespecified hypothesis was that early CPAP and a lower target range of oxygen saturation would each decrease the risk of death or neurodevelopmental impairment. We now report longer-term results.

METHODS

Using a 2-by-2 factorial design, we randomly assigned infants born between 24 weeks 0 days and 27 weeks 6 days of gestation to early CPAP with a limited ventilation strategy or early surfactant administration and to lower or higher target ranges of oxygen saturation (85 to 89% or 91 to 95%). The primary composite outcome for the longer-term analysis was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

RESULTS

The primary outcome was determined for 1234 of 1316 enrolled infants (93.8%); 990 of the 1058 surviving infants (93.6%) were evaluated at 18 to 22 months of corrected age. Death or neurodevelopmental impairment occurred in 27.9% of the infants in the CPAP group (173 of 621 infants), versus 29.9% of those in the surfactant group (183 of 613) (relative risk, 0.93; 95% confidence interval [CI], 0.78 to 1.10; $P=0.38$), and in 30.2% of the infants in the lower-oxygen-saturation group (185 of 612), versus 27.5% of those in the higher-oxygen-saturation group (171 of 622) (relative risk, 1.12; 95% CI, 0.94 to 1.32; $P=0.21$). Mortality was increased with the lower-oxygen-saturation target (22.1%, vs. 18.2% with the higher-oxygen-saturation target; relative risk, 1.25; 95% CI, 1.00 to 1.55; $P=0.046$).

CONCLUSIONS

We found no significant differences in the composite outcome of death or neurodevelopmental impairment among extremely premature infants randomly assigned to early CPAP or early surfactant administration and to a lower or higher target range of oxygen saturation. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute; SUPPORT ClinicalTrials.gov number, NCT00233324.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Finer at the University of California, San Diego, Division of Neonatology, 200 W. Arbor Dr., San Diego, CA, 92013, or at nfiner@ucsd.edu.

Drs. Vaucher and Peralta-Carcelen contributed equally to this article.

*Deceased.

†Members of the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network are listed in the Supplementary Appendix, available at NEJM.org.

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EXREMELY PREMATURE INFANTS ARE AT high risk for death and neurosensory or developmental impairment in early childhood.¹⁻³ The risk of neurodevelopmental impairment increases with decreasing gestational age and greater severity of illness. Neurodevelopmental impairment is often a consequence of neonatal complications.⁴⁻¹² Although surfactant administration decreases the risk of death and bronchopulmonary dysplasia, randomized, controlled trials of various respiratory interventions have not shown significant reductions in mortality and morbidity or improvement in developmental outcomes.¹³⁻¹⁷ We previously reported results of the multicenter, randomized, controlled Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), which involved extremely premature infants (from 24 to 27 weeks of gestation); treatment with noninvasive continuous positive airway pressure (CPAP) shortly after birth, as compared with early intubation and surfactant administration, did not reduce rates of death or bronchopulmonary dysplasia or other major morbidity at 36 weeks of postmenstrual age.¹⁸

Although oxygen supplementation is necessary for survival in many preterm infants, several studies have shown that it increases the risk of retinopathy of prematurity,¹⁹ bronchopulmonary dysplasia,^{20,21} periventricular leukomalacia,²² and cerebral palsy.²³ Results from SUPPORT showed no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity among infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) versus a higher range (91 to 95%). However, in the lower-oxygen-saturation group, the risk of retinopathy of prematurity among infants who survived to discharge was decreased (8.6%, vs. 17.9% in the higher-oxygen-saturation group; relative risk, 0.52; 95% confidence interval [CI], 0.37 to 0.73; $P < 0.001$) and the risk of death was increased (19.9% vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; $P = 0.04$).²⁴

We now report the results of our longer-term follow-up of the infants in this study, assessing whether early, noninvasive CPAP with a limited ventilation strategy, as compared with early surfactant administration, and a lower, as compared with higher, target range of oxygen saturation would each decrease the incidence of death be-

fore assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

METHODS

STUDY DESIGN

SUPPORT was a randomized, controlled trial involving 1316 extremely preterm infants (gestational age, 24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009, who were enrolled at delivery at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days). Infants who were part of multiple births were randomly assigned, as a unit, to the same treatment group.

In the delivery room, the infants were randomly assigned to receive either CPAP immediately after delivery with a limited ventilation strategy, as described previously, if subsequent intubation was required, or intubation with surfactant administration within an hour after birth, followed by conventional ventilation.¹⁸ Using a 2-by-2 factorial design, we also randomly assigned participants to a target oxygen-saturation range of 85 to 89% (lower-oxygen-saturation group) or 91 to 95% (higher-oxygen-saturation group); we used pulse oximeters that were specially designed to maintain blinding (see the Supplementary Appendix, available with the full text of this article at NEJM.org).²⁴

The procedures for enrollment, intervention, and data collection have been reported previously.^{18,24} The trial 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. Written informed consent was obtained from the parent or guardian of each child before delivery. Two of the authors employed by RTI International vouch for the accuracy and completeness of the data and analyses reported, and the members of the SUPPORT subcommittee vouch for the fidelity of the trial to the study protocol (see the Supplementary Appendix).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

ASSESSMENTS

At 18 to 22 months of corrected age, surviving infants underwent a comprehensive neurodevelopmental assessment performed by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability. Cognitive function was assessed with the use of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III); scores are assessed relative to a standardized mean (\pm SD) of 100 ± 15 , with higher scores indicating better performance.²⁵ The modified Gross Motor Function Classification System (GMFCS) was used to classify gross-motor performance, with scores ranging from 0 (normal) to 5 (most impaired).²⁶ Moderate-to-severe cerebral palsy was defined as a nonprogressive disorder with abnormal muscle tone in at least one arm or leg that was associated with abnormal control of movement or posture and a GMFCS score of 2 or higher.^{27,28} Assessments of hearing impairment (defined as the inability to understand the oral directions of the examiner and to communicate, with or without hearing amplification) and visual impairment (defined as vision worse than 20/200) were based on examination and parental report.

Certified research staff collected demographic and neonatal-outcome data using standard definitions from the Neonatal Research Network. Demographic and outcome data included gestational age; birth weight; sex; status with respect to multiple gestation; race or ethnic group; and history of medical or surgical necrotizing enterocolitis (modified Bell's stage ≥ 2 , on a scale ranging from 1 to 3, with higher scores indicating greater severity of disease), intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia, late-onset sepsis, retinopathy of prematurity, bronchopulmonary dysplasia (physiological), and use of postnatal glucocorticoids. Socioeconomic variables included health insurance status, maternal marital status, maternal educational level, household income, language spoken at home, and status with respect to whether the child was living with biologic parents. Socioeconomic data were updated during the 18-to-22-month visit; these data were used if data from the neonatal period were not available.

OUTCOMES

The prespecified primary composite outcome for this trial was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age. This composite outcome was selected because infants who died before 18 months of corrected age could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the BSID-III of less than 70, a GMFCS score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment. Other prespecified outcomes at 18 to 22 months of corrected age were death and neurodevelopmental impairment. Exploratory secondary outcomes included the individual components of the neurodevelopmental-impairment assessment, levels of cognitive delay, and a comparison of outcomes within the higher and lower gestational-age strata.

STATISTICAL ANALYSIS

The sample-size calculations were based on Neonatal Research Network data for infants born in the year 2000; the details have been reported previously.^{18,24} Although the sample size for the study was estimated on the basis of hospital outcomes (i.e., death or bronchopulmonary dysplasia for the ventilation intervention, and death or retinopathy of prematurity for the oxygenation intervention), the final sample size was sufficient to detect an absolute reduction of 10 percentage points in the composite outcome of death or neurodevelopmental impairment, with the use of a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% in the surfactant and higher-oxygen-saturation groups and a 15% rate of loss to follow-up, as well as adjustment for familial clustering.

Data were entered on standard forms and were transmitted to RTI International, which stored, managed, and analyzed the data for the study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were performed with the use of chi-square tests for categorical variables and t-tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary

composite outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age could be assigned. 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. The denominator used to calculate the frequency of each outcome was the number of children for whom status with respect to that outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all 18-to-22-month outcomes were adjusted, as prespecified, for gestational-age strata, study center, and familial clustering (because infants who were part of multiple births were assigned to the same treatment group). Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the effect of characteristics that differed between the groups of children with and without follow-up, a sensitivity analysis using multiple imputation was conducted, in which missing values for the primary outcome were imputed on the basis of the treatment assignment, perinatal characteristics, and in-hospital outcomes.²⁹ Two-sided P values of less than 0.05 were considered to indicate statistical significance for all analyses; no adjustments were made for multiple comparisons.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The primary composite outcome of death or neurodevelopmental impairment was determined for 93.8% of the children (1234 of 1316) enrolled in the trial (Fig. 1). A total of 258 children were known to have died before 18 to 22 months of age. Of the 68 children for whom a neurodevelopmental assessment was missing, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment was determined for 98.6% of all children seen (976 of 990); 14 children had an incomplete evaluation that precluded the assignment of a neurodevelopmental-impairment status. The follow-up rate and the mean corrected age at neuro-

developmental assessment were similar for all treatment groups (Table 1).

As compared with the mothers of the 990 children who underwent a neurodevelopmental assessment at 18 to 22 months of corrected age, the mothers of the 68 children who did not undergo an assessment were less likely to be married (47% vs. 31%, $P=0.01$) and more likely to have only public health insurance (52% vs. 69%, $P=0.008$). No other demographic or neonatal characteristics differed significantly between the groups.

The demographic and clinical characteristics of the follow-up population are summarized in Table 1 and in Table S1 in the Supplementary Appendix. Almost all mothers received antenatal glucocorticoids. At follow-up, there were more children who were small for their gestational age and more children with severe retinopathy of prematurity in the higher-oxygen-saturation group than in the lower-oxygen-saturation group. As compared with the surfactant group, children in the CPAP group were more likely to have had necrotizing enterocolitis and less likely to have been exposed to postnatal glucocorticoids. A total of 32% of the infants in the CPAP group were intubated in the delivery room; 65% of the infants in the CPAP group received surfactant with limited ventilation.

PRIMARY OUTCOME

The frequency of the composite outcome of death or neurodevelopmental impairment did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups at 18 to 22 months of corrected age (Tables 2 and 3). Mortality before neonatal discharge accounted for 92% of the overall mortality observed by 18 to 22 months. Mortality did not differ significantly between the CPAP and surfactant groups but remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group. There were no significant differences in the primary outcome between treatment groups in subgroup analyses stratified according to gestational age at birth (Tables S2 and S3 in the Supplementary Appendix). The results of the sensitivity analysis using multiple imputations were virtually identical to the results of the analysis in which missing data were excluded (data not shown). There was no significant interaction be-

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

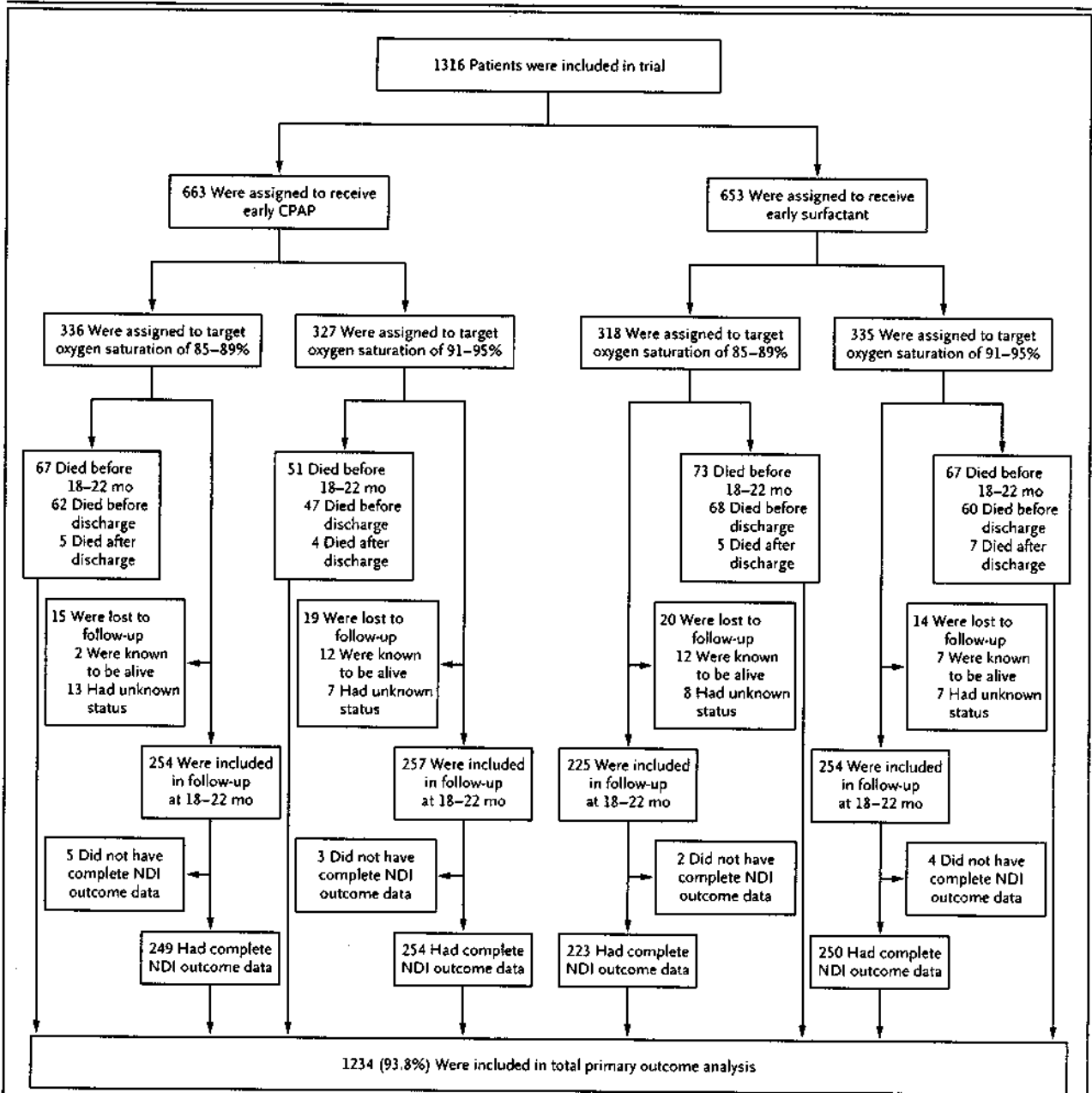


Figure 1. Enrollment, Randomization, and Outcomes.

The primary composite outcome was determined for 93.8% of the enrolled infants. A total of 258 children were known to have died before 18 to 22 months of corrected age. Of the 68 children with a missing neurodevelopmental assessment, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment (NDI) was determined for 98.6% of all children seen; 14 children had an incomplete evaluation that precluded the assignment of NDI status.

tween the two interventions with respect to the composite outcome of death or neurodevelopmental impairment or either of its components ($P > 0.70$ for all comparisons).

OTHER OUTCOMES

The incidences of the individual components of neurodevelopmental impairment (BSID-III cognitive composite score of < 70 , GMFCS score of ≥ 2 ,

Table 1. Demographic and Clinical Characteristics of the Follow-up Cohorts.*

Characteristic	CPAP (N = 511)	Surfactant (N = 479)	Lower Oxygen Saturation (N = 479)	Higher Oxygen Saturation (N = 511)
Birth weight — g	849±186	852±193	858±186	844±192
Gestational age at birth — wk	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age — no. (%)†	23 (4.5)	32 (6.7)	17 (3.5)‡	38 (7.4)
Male sex — no. (%)	256 (50.1)	266 (55.5)	240 (50.1)	282 (55.2)
Multiple birth — no. (%)	138 (27.0)	114 (23.8)	124 (25.9)	128 (25.0)
Maternal use of antenatal glucocorticoids — no. (%)	493 (96.5)	456 (95.2)	462 (96.5)	487 (95.3)
Cesarean section — no. (%)	352 (68.9)	315 (65.8)	332 (69.3)	335 (65.6)
Neonatal outcome — no./total no. (%)§				
Severe retinopathy of prematurity	62/479 (12.9)	58/434 (13.4)	38/442 (8.6)¶	82/471 (17.4)
Bronchopulmonary dysplasia	193/511 (37.8)	187/479 (39.0)	177/479 (37.0)	203/511 (39.7)
Intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia	70/510 (13.7)	46/478 (9.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis	56/511 (11.0)**	30/479 (6.3)	42/479 (8.8)	44/511 (8.6)
Late-onset sepsis or meningitis	167/511 (32.7)	154/479 (32.2)	155/479 (32.4)	166/511 (32.5)
Use of postnatal glucocorticoids	34/508 (6.7)**	55/476 (11.6)	41/477 (8.6)	48/507 (9.5)
Corrected age at follow-up — mo	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

* Plus-minus values are means ±SD. There were no significant between-group differences, except as noted. Additional demographic characteristics of the cohorts are provided in Table S1 in the Supplementary Appendix. CPAP denotes continuous positive airway pressure.

† Infants who were small for gestational age were defined as those with a birth weight in less than the 10th percentile.

‡ P<0.01 for the comparison with the higher-oxygen-saturation group.

§ The comparisons of neonatal outcomes were adjusted for stratification factors (study center and gestational-age group) and familial clustering.

¶ P<0.001 for the comparison with the higher-oxygen-saturation group.

|| Assessment for bronchopulmonary dysplasia was performed at 36 weeks of postmenstrual age.

** P<0.05 for the comparison with the surfactant group.

moderate or severe cerebral palsy, hearing impairment, and blindness) among surviving infants did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups (Tables 2 and 3). Neither were there significant between-group differences in the individual components of neurodevelopmental impairment when the groups were stratified according to gestational age (Tables S2 and S3 in the Supplementary Appendix). However, in the lower-gestational-age stratum, mortality was higher in the surfactant group than in the CPAP group. Although the rates of severe retinopathy of prematurity and eye surgery were higher in the higher-oxygen-saturation group than in the lower-oxygen-saturation group, the rates of bilateral blindness, blindness of at least one eye, and other vision impairment

did not differ significantly between the groups at 18 to 22 months of corrected age (Table 4). There were no significant differences between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups in the rates of the composite outcome of death or individual neurodevelopmental-impairment components (data not shown), mean cognitive composite scores on the BSID-III, or the percentage of infants with cognitive composite scores of less than 80 points or less than 85 points (Table S4 in the Supplementary Appendix). Of the 976 children who were evaluated at 18 to 22 months of corrected age, 583 (60%) had normal status with respect to neuromotor, neurosensory, and cognitive development (with normal cognitive development defined as a BSID-III cognitive composite score of ≥85 points).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

Table 2. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the CPAP and Surfactant Groups.*

Variable	CPAP number/total number (percent)	Surfactant number/total number (percent)	Adjusted Relative Risk (95% CI)	P Value
Primary outcome determined	621/663 (93.7)	613/653 (93.9)	1.00 (0.97–1.03)	0.83
Death or NDI	173/621 (27.9)	183/613 (29.9)	0.93 (0.78–1.10)	0.38
Death before assessment at 18–22 mo of corrected age	118/643 (18.4)	140/638 (21.9)	0.83 (0.67–1.04)	0.10
NDI	55/503 (10.9)	43/473 (9.1)	1.16 (0.79–1.71)	0.44
BSID-III cognitive score <70†	36/502 (7.2)	36/472 (7.6)	0.95 (0.61–1.50)	0.84
GMFCS score ≥2‡	26/511 (5.1)	23/479 (4.8)	0.98 (0.57–1.69)	0.95
Moderate or severe cerebral palsy	21/511 (4.1)	19/479 (4.0)	0.93 (0.51–1.72)	0.82
Bilateral blindness	4/511 (0.8)	7/479 (1.5)	0.53 (0.16–1.78)	0.31
Hearing impairment	17/511 (3.3)	7/479 (1.5)	2.27 (0.96–5.37)	0.06

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic. NDI denotes neurodevelopmental impairment.

† Scores on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), are assessed relative to a standardized mean (\pm SD) of 100 ± 15 , with higher scores indicating better performance.

‡ Gross-motor function was assessed by means of the modified Gross Motor Function Classification System (GMFCS), with scores ranging from 0 to 5 and higher scores indicating greater impairment.

DISCUSSION

In this large, multicenter trial involving very-high-risk, extremely premature infants, we found no significant difference in the primary composite follow-up outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between infants randomly assigned to treatment with early CPAP and those assigned to early intubation and surfactant administration or between those randomly assigned to the lower-oxygen-saturation group and those assigned to the higher-oxygen-saturation group. Mortality did not differ significantly between the CPAP and surfactant groups, and mortality remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group — findings that are consistent with our earlier results.^{18,24} There were no significant differences between the CPAP and surfactant groups or between the higher-oxygen-saturation and lower-oxygen-saturation groups with respect to the frequencies among surviving infants of neurodevelopmental impairment and its components, including severe cognitive impairment (BSID-III

cognitive composite score, <70), moderate or severe cerebral palsy, moderate or severe motor impairment (GMFCS score, ≥2), hearing impairment, and bilateral blindness.

Recent trials have raised concern about using lower target ranges of oxygen saturation because of the possibility of increased mortality among extremely premature infants.^{23,30} In SUPPORT, the risk of death during the initial hospitalization was increased among neonates randomly assigned to the lower-oxygen-saturation group, as compared with those assigned to the higher-oxygen-saturation group, and among neonates in the lowest gestational-age stratum, mortality was increased in the surfactant group as compared with the CPAP group. As previously reported, the causes of death did not differ significantly between the lower-oxygen-saturation and higher-oxygen-saturation groups.²⁴ Although significant differences in mortality persisted at 18 to 22 months of corrected age, these differences largely reflected the differences in mortality before hospital discharge. There are other ongoing studies of this matter that, once completed, could inform decisions.³¹

Severe retinopathy of prematurity may be as-

Table 3. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Primary outcome determined	612/654 (93.6)	622/662 (94.0)	1.00 (0.97–1.03)	0.79
Death or NDI	185/612 (30.2)	171/622 (27.5)	1.12 (0.94–1.32)	0.21
Death before assessment at 18–22 mo of corrected age	140/633 (22.1)	118/648 (18.2)	1.25 (1.00–1.55)	0.046
NDI	45/472 (9.5)	53/504 (10.5)	0.87 (0.60–1.28)	0.49
BSID-III cognitive score <70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58–1.43)	0.69
GMFCS score ≥2	26/479 (5.4)	23/511 (4.5)	1.17 (0.68–2.01)	0.56
Moderate or severe cerebral palsy	20/479 (4.2)	20/511 (3.9)	1.00 (0.54–1.83)	>0.99
Bilateral blindness	5/479 (1.0)	6/511 (1.2)	0.90 (0.28–2.90)	0.86
Hearing impairment	12/479 (2.5)	12/511 (2.3)	1.16 (0.54–2.49)	0.70

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic.

sociated with poor visual outcomes, even with treatment.^{32,33} In this study, infants in the lower-oxygen-saturation group who survived to discharge had a lower incidence of severe retinopathy of prematurity (8.6%, vs. 17.9% in the higher-oxygen-saturation group).²⁴ Although eye surgery was significantly less frequent in the lower-oxygen-saturation group than in the higher-oxygen-saturation group, there were no significant between-group differences with respect to rates of unilateral and bilateral blindness, nystagmus, strabismus, or the use of corrective lenses. We did not collect detailed data on visual function at the 18-to-22-month visit.

The strengths of this study include the large initial sample, which provided sufficient power to detect a clinically significant difference in the prespecified outcome of death or neurodevelopmental impairment, and the high percentage of surviving infants who underwent a comprehensive, standardized neurodevelopmental evaluation at 18 to 22 months of corrected age.

The study also has several limitations. The requirement for antenatal consent, which is associated with enrollment bias, may limit generalizability.^{34,35} In addition, the incidence of neurodevelopmental impairment in extremely premature infants in the present study was substantially lower than that previously reported by the Neonatal Research Network.³⁶ The present study used the BSID-III for cognitive assessment, where-

as previous Neonatal Research Network studies used an earlier edition, the BSID-II. Changes in the test design and standardization between the two editions may account for the lower incidence of neurodevelopmental impairment reported here.³⁶ Although the BSID-III scores in this study were higher than those previously reported for extremely premature infants, there were no significant differences between the treatment groups in this study.

Another limitation is the fact that the reported follow-up results are based on a single visit at 18 to 22 months of corrected age; other disabilities may not be evident until later in childhood. A subcohort of the SUPPORT study will be followed at school age to evaluate the longer-term neurodevelopmental outcome. Also, in comparing several secondary outcomes between pairs of treatments in this factorial-design trial (early CPAP vs. early surfactant treatment and lower vs. higher target ranges of oxygen saturation), we made no adjustments for multiple comparisons; appropriate caution should therefore be used in interpreting the reported results. Finally, differences in the neurodevelopmental outcome may have been blunted by the smaller difference in oxygen saturation between the higher-oxygen-saturation and lower-oxygen-saturation groups than was planned.²⁴

In conclusion, there were no significant differences in the composite outcome of death before

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

Table 4. Visual Outcome at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	number/total number (percent)			
Strabismus	46/478 (9.6)	41/510 (8.0)	1.20 (0.80–1.80)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89–3.69)	0.10
Eyes track 180 degrees	462/476 (97.1)	493/507 (97.2)	1.00 (0.98–1.02)	0.93
Corrective lenses for both eyes†	21/468 (4.5)	20/493 (4.1)	1.15 (0.63–2.10)	0.65
Blind with some function in both eyes†	3/450 (0.7)	2/475 (0.4)	1.57 (0.27–8.96)	0.61
Blind with no useful vision in both eyes†	2/449 (0.4)	4/477 (0.8)	0.54 (0.10–2.96)	0.48
Other abnormal eye finding‡	6/453 (1.3)	12/485 (2.5)	0.55 (0.21–1.46)	0.23
Blind in at least one eye	5/479 (1.0)	8/511 (1.6)	0.67 (0.22–2.02)	0.48
Eye surgery performed§	31/477 (6.5)	67/509 (13.2)	0.53 (0.35–0.78)	0.002

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness and other abnormal eye finding were not adjusted for study center, owing to the small numbers of patients with these characteristics.

† The reference group for relative risk was the group of children with vision that appeared to be normal in both eyes.

‡ Other abnormal eye finding was defined as an abnormality other than a condition requiring corrective lenses but not one severe enough for the child to be considered blind in that eye. Children whose eyes were classified in two different vision categories were included in the other-abnormal-eye-finding category.

§ Reasons for surgery are listed in Table S5 in the Supplementary Appendix.

assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between extremely preterm infants randomly assigned at delivery to early CPAP and those assigned to early intubation with surfactant administration or between infants assigned to lower oxygen saturation and those assigned to higher oxygen saturation. Early CPAP with a limited ventilation strategy can be considered as an alternative to early surfactant treatment, even in infants as immature as those at 24 weeks of gestational age. It is important to consider the

risk of death or neurodevelopmental impairment when deciding on oxygen-saturation targets in extremely preterm infants. Because mortality remained lower in the higher-oxygen-saturation group at the time of follow-up and there were no adverse visual or neurodevelopmental problems, lower oxygen-saturation targets cannot be recommended in these extremely preterm infants.

Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute.

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

APPENDIX

The authors' affiliations are as follows: the Department of Pediatrics, University of California at San Diego, San Diego (Y.E.V., N.N.F., W.R.), and the Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto (S.R.H.) — both in California; the Department of Pediatrics, University of Alabama at Birmingham, Birmingham (M.P.-C., W.A.C.); the Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland (M.C.W., D.E.W.-C.), and the Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati (K.S., K.Y.) — both in Ohio; the Statistics and Epidemiology Unit, RTI International, Research Triangle Park (M.G.G., N.S.N.), the Department of Pediatrics, Duke University, Durham (R.F.G.), and Wake Forest University School of Medicine, Winston-Salem (T.M.O.) — all in North Carolina; the Department of Pediatrics, Women and Infants Hospital, Brown University, Providence, RI (A.R.L., B.R.V.); the Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City (B.A.Y., R.G.E., A.B.); the Statistics and Epidemiology Unit, RTI International, Rockville (A.D.), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda (R.D.H.) — both in Maryland; the Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas (R.J.H.); the Department of Pediatrics, University of Texas Medical School at Houston, Houston (P.W.E.); the Department of Pediatrics, University of Iowa, Iowa City (M.J.A.); the Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta (I.A.-C.); the Department of Pediatrics, Wayne State University, Detroit (A.P.); the Department of Pediatrics, Indiana University School of Medicine, Indianapolis (B.P., A.M.D.); the Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston (E.C.M.); the Department of Pediatrics, Yale University School of Medicine, New Haven, CT (R.A.E.); the University of Miami Miller School of Medicine, Miami (C.R.B.); the University of New Mexico Health Sciences Center, Albuquerque (J.F.); and the Department of Pediatrics, University of Rochester Medical Center, Rochester, NY (G.J.M.).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

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From: [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#); [Zagorski, Nicholas \(NIH/NHLBI\) \[E\]](#)
Subject: RE: PDF of Your Article for NEJM
Date: Tuesday, December 04, 2012 11:36:52 AM
Attachments: [3vauc_0a1208506.pdf.pdf](#)

Congrats Rose on the NEJM pub this month,
I am copying Nick Zagorski from NHLBI who is the point of contact for coordinating the press release.
It has been great working with you and colleagues at NICHD on this trial,

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

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

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Sent: Sunday, December 02, 2012 10:16 AM
To: [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)
Cc: [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#)
Subject: Fw: PDF of Your Article for NEJM

FYI

We are working on a press release- should have it later this week.

Dec 27 is the publication date.

Thanks for the tremendous support!
Rose

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

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Sent: Sunday, December 02, 2012 09:55 AM
To: blaisdellC@mail.nih.gov <blaisdellC@mail.nih.gov>; [Bock, Robert \(NIH/NICHD\) \[E\]](#)
Subject: FW: PDF of Your Article for NEJM

FYI

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and
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301-496-3790 (FAX)
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From: Finer, Neil [nfiner@ucsd.edu]
Sent: Friday, November 30, 2012 6:29 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo, M.D.; adas@rti.org; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: FW: PDF of Your Article for NEJM

FYI
These look good to me
Neil

From: Nejm Article [mailto:nejmarticle@mms.org]
Sent: Friday, November 30, 2012 2:06 PM
To: Finer, Neil
Cc: Laurencot, Elizabeth
Subject: PDF of Your Article for NEJM

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From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Release
Date: Tuesday, December 04, 2012 10:20:43 AM

Gracias.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, December 04, 2012 9:58 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: Release

No problem.

Publication date is Dec 27

From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, December 04, 2012 09:47 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Release

Sure. Don't mean to be a pest, but I realize you're away, and I wanted to make sure you got the revision.

Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, December 04, 2012 9:38 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: Release

It can go through clearance

Thanks

Rose

From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, December 04, 2012 09:37 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Release

OK to put the release into clearance now, or do you have more changes?

Thanks, Rose.

From: [Finer, Neil](#)
To: [Laurencot, Elizabeth](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Marie Gantz](#); [Abhik Das](#); [Vaucher, Yvonne](#); [Myriam Peralta](#); [Wally Carlo](#)
Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)
Date: Monday, December 03, 2012 7:52:05 PM
Importance: High

Hi Lauren

Here are our responses

For the Abstract we have shortened the first paragraph so that the last sentence now reads =
"We now report longer-term results from our prespecified hypotheses."

This word count is now 340.

Somehow we missed the decimal place on the SD for gestational age at birth for the higher-oxygen group in Table 1. Should this be 1.0? Yes Thanks

Table S1 – The footnote should read "Comparisons of neonatal outcomes adjusted for stratification by center and gestational age and for familial clustering"

Please add "neonatal outcomes"

I think these are all of our corrections

Thanks for getting back to us'

Be well

Neil

From: <Laurencot>, Elizabeth <elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>>

Date: Monday, December 3, 2012 4:32 AM

To: UCSD Pediatrics <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>

Subject: FW: PDF of Your Article for NEJM (Vaucher/Finer)

Dear Neil,

The revised page proofs for your article went sent to you late Friday afternoon. If possible, please take a moment to send me an email confirming receipt.

For the most part, the galley changes were made correctly, with a couple exceptions (noted below). Also, there are a few other items to be fixed:

We will change the order of the authors Walsh and Gantz, per your request.

Although no one caught this on the galleys, there was an error with the footnote marks used in the author list and the front page. Specifically, the footnote mark after Dr Dusick should be a dagger, not an asterisk, indicating "deceased". The asterisk will go after "Network" at the end of the list. Although this is technically "out of order" in terms of how we use these footnote marks, it is correct in this instance. Of course, the matching marks on the front page must be changed.

In the affiliations, we will move the North Carolina group ahead of the Ohio group to match the revised order in the author list.

In the affiliations, the wrong dash was used before "both in Ohio".

In Table 4, a dagger footnote after "Other abnormal eye finding" was incorrectly deleted. There should be both the dagger and double dagger for this row entry.

Please do read the entire set of proofs carefully and email me a list of any corrections you have for the page proofs by 10am (US Eastern) Tuesday, December 4 (rather than the 24 hours stated in the letter that accompanied the proofs). Also, I would ask that you please send me a list of corrections rather than annotating the pdf file.

The editors will be reading your page proofs during this time as well, so I will be contacting you with any queries they have (probably Tuesday afternoon or Wednesday morning). Please do let me know if you will be unavailable via email next week.

I look forward to hearing back from you regarding your page proofs.

Best,
Eli

From: Nejm Article
Sent: Friday, November 30, 2012 5:06 PM
To: 'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'
Cc: Laurencot, Elizabeth
Subject: PDF of Your Article for NEJM

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From: [Wally Carlo, M.D.](#)
To: [Walsh, Michele](#); "[Neil Finer](#)" <; [Higgins, Rosemary \(NIH/NICHD\)](#) [E]
Subject: RE: bounced email
Date: Monday, December 03, 2012 5:39:51 PM

Michele:

Thanks so much. I assume the SUPPORT subc will look at this again. I think it is reasonable. My only comment is to make sure that the desaturations are not related to a near-terminal event. I can see how you are trying to address that with the 3 min limit. You may also want to use data from at least a few days before death.

I am in favor of doing further analysis to sort out why babies in the low sat targets die.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
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From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]
Sent: Monday, December 03, 2012 2:10 PM
To: "[Neil Finer](#)" <; Wally Carlo, M.D.; [rose higgins](#)
Subject: bounced email

Trying again: this email was rejected previously.

Hi All:

We have responded to the sub committees prior critique.
Regarding the Intermittent Hypoxia analysis within the support trial.
We would like to submit an R03 application to fund these analyses.
We also attach the PDF of Ms DiFiore's recently published analyses
Of intermittent hypoxia in the CWRU/ UCSD high sat resolution cohort
Which clearly demonstrated an increase in the frequency and severity of
desaturation events in The group randomized to the low saturation environment. Since the
cause/causes of the increased mortality in the low sat group is
still unknown, these exploratory analyses may further inform the
Field, and future studies of saturation management.

Please let us know what next steps are required.
Thank you,

Michele Walsh

Chief Division of Neonatology
Rainbow Babies & Childrens Hospital
Professor of Pediatrics
Case Western Reserve University
11100 Euclid Avenue, Mailstop 6010
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From: [Finer, Neil](#)
To: [Gantz, Marie](#)
Cc: [Wally Carlo](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#)
Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)
Date: Monday, December 03, 2012 4:04:06 PM

Thanks
I will incorporate all of this back to Elizabeth
I am working on The Abstract
Neil

On 12/3/12 1:02 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

>Neil, Eli is correct, this should be 1.0

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org

>828-254-6255

>

>

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

>From: Laurencot, Elizabeth [<mailto:elaurencot@nejm.org>]

>Sent: Monday, December 03, 2012 8:35 AM

>To: 'Finer, Neil'

>Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Gantz, Marie; Das,

>Abhik

>Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)

>

>Dear Neil,

>

>Somehow we missed the decimal place on the SD for gestational age at

>birth for the higher-oxygen group in Table 1. Should this be 1.0?

>

>Best,

>Eli

>

>

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

>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]

>Sent: Monday, December 03, 2012 8:03 AM

>To: Laurencot, Elizabeth

>Cc: Wally Carlo; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das

>Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)

>

>These look OK to me

>Let me know if you have any concerns

>Neil

>

>On Dec 3, 2012, at 7:32 AM, "Laurencot, Elizabeth"

><elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>> wrote:

>

>Dear Neil,

>

>The revised page proofs for your article went sent to you late Friday
>afternoon. If possible, please take a moment to send me an email
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>Best,

>Eli

>

>

>From: Nejm Article

>Sent: Friday, November 30, 2012 5:06 PM

>To: 'nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>'

>Cc: Laurencot, Elizabeth

>Subject: PDF of Your Article for NEJM

>

>Attached is a PDF file of your article, which is scheduled to be
>published in the Journal.

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>email and delete the original message from all computer systems. Thank
>you.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: PDF of Your Article for NEJM
Date: Monday, December 03, 2012 3:53:47 PM

Is this correct???

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

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Monday, December 03, 2012 03:53 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; mgantz@rti.org <mgantz@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>; yvaucher@ucsd.edu <yvaucher@ucsd.edu>; adas@rti.org <adas@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PDF of Your Article for NEJM

I understood from last week that Marie Gantz was following Waldemar Carlo, and on the proof I received it is not thank you.

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, December 03, 2012 2:46 PM
To: Myriam Peralta, M.D.; Wally Carlo, M.D.; 'mgantz@rti.org'; 'nfiner@ucsd.edu'; 'yvaucher@ucsd.edu'; 'adas@rti.org'; 'wrich@ucsd.edu'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PDF of Your Article for NEJM

Can we check the author order again?
Myriam - who is in the incorrect place?

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

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Monday, December 03, 2012 03:44 PM
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Gantz, Marie <mgantz@rti.org>; Finer, Neil <nfiner@ucsd.edu>; Vaucher, Yvonne <yvaucher@ucsd.edu>; Das, Abhik <adas@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PDF of Your Article for NEJM

From: Wally Carlo, M.D.
Sent: Monday, December 03, 2012 1:47 PM
I agree with this. the rest of the PDF looks good as far as I can tell. However the authors order is not corrected in this proof. Thanks.

To: Gantz, Marie; Finer, Neil; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Cc: archerst@mail.nih.gov
Subject: RE: PDF of Your Article for NEJM

I am ok calling it "complete NDI outcome".

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham

Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, December 03, 2012 1:16 PM
To: Finer, Neil; Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Cc: archerst@mail.nih.gov
Subject: RE: PDF of Your Article for NEJM

The article itself looks OK to me (have yet to check the supplemental tables) except the affiliations are still off – I noticed that Nancy Newman is listed as being at RTI.

Stephanie – can you please check the affiliations against the boilerplate?

The only other minor issue, which is my fault for suggesting the wording for the Figure, is that we describe those with an NDI outcome defined as having “complete NDI outcome data.” Technically, the data only had to be complete enough to assign an outcome, which means that if a child met one of the NDI criteria it did not matter if another criterion was missing. However, I’m OK with leaving as-is if everyone else is.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org<mailto:mgantz@rti.org>
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, November 30, 2012 6:30 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: FW: PDF of Your Article for NEJM

FYI
These look good to me
Neil

From: Nejm Article [mailto:nejmarticle@mms.org]
Sent: Friday, November 30, 2012 2:06 PM
To: Finer, Neil
Cc: Laurencot, Elizabeth
Subject: PDF of Your Article for NEJM

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From: Walsh, Michele
To: "Neil Finer" <; "Wally Carlo M.D." <; rose.higgins
Subject: bounced email
Date: Monday, December 03, 2012 3:11:48 PM
Attachments: Cover letter IH SUPPORT study Dec 2012.doc
IH in High vs Low sat groups SUPPORT DiFiore.pdf
SUPPORT trial proposal...Patterns of IH assoc with mortality REVISED.docx

Trying again: this email was rejected previously.

Hi All:

We have responded to the sub committees prior critique.

Regarding the Intermittent Hypoxia analysis within the support trial.

We would like to submit an R03 application to fund these analyses.

We also attach the PDF of Ms DiFiore's recently published analyses

Of intermittent hypoxia in the CWRU/ UCSD high sat resolution cohort

Which clearly demonstrated an increase in the frequency and severity of

desaturation events in The group randomized to the low saturation environment. Since the

cause/causes of the increased mortality in the low sat group is

still unknown, these exploratory analyses may further inform the

Field, and future studies of saturation management.

Please let us know what next steps are required.

Thank you,

Michele Walsh

Chief Division of Neonatology

Rainbow Babies & Childrens Hospital

Professor of Pediatrics

Case Western Reserve University

11100 Euclid Avenue, Mailstop 6010

Cleveland, OH 44106-6010

email: michele.walsh@cwru.edu

Phone: (216) 844-3387

Fax: (216) 844-3380

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From: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: SUPPORT release
Date: Monday, December 03, 2012 1:16:14 PM
Attachments: [2 SUPPORT News Release 01.docx](#)

Here you go, Rose—below and attached.

Embargoed For Release

XXXday, XXX xx, 2012

Time

[*Pub date TBD*]

Contact:

Robert Bock or Marianne Glass Miller

301-496-5133

bockr@mail.nih.gov

(b)(5)



Page 0978 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sunday, December 02, 2012 10:22 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: SUPPORT release

Bob

I am working off my BB.

Please change the sentence:

(b)(5)

To the following;

(b)(5)

Can you send me an updated version for one more review?

Thanks

Rose

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, November 30, 2012 03:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT release

Hi Rose. Please see attached. Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"; "nfiner@ucsd.edu"; "elaurencot@nejm.org"
Cc: "mgantz@rti.org"; "adas@rti.org"
Subject: Re: PDF of Your Article for NEJM (Vaucher/Finer)
Date: Monday, December 03, 2012 8:25:21 AM

Wally
I am fine with this
Thanks
Rose

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

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, December 03, 2012 08:24 AM
To: Finer, Neil <nfiner@ucsd.edu>; Laurencot, Elizabeth <elaurencot@nejm.org>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Marie Gantz <mgantz@rti.org>; Abhik Das <adas@rti.org>
Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)

Neil and All:

I have shortened the abstract. I think it is short enough and we do not miss much.

What do you all think?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, December 03, 2012 7:03 AM
To: Laurencot, Elizabeth
Cc: Wally Carlo, M.D.; Rosemary (NIH/NICHD) Higgins [E]; Marie Gantz; Abhik Das
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Let me know if you have any concerns
Neil

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To: [Finer, Neil](#); [Laurencot, Elizabeth](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Marie Gantz](#); [Abhik Das](#)
Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)
Date: Monday, December 03, 2012 8:24:20 AM
Attachments: [SUPPORT FU shorter abstract.docx](#)

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Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

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<3vauc_supapp.pdf>

BACKGROUND

Previous results from our trial of early treatment with continuous positive airway pressure (CPAP) versus early surfactant treatment in infants showed no significant difference in the outcome of death or bronchopulmonary dysplasia. A lower (vs. higher) target range of oxygen saturation was associated with a lower rate of severe retinopathy but higher mortality. Our prespecified hypothesis was that early CPAP and a lower target range of oxygen saturation would each decrease the risk of death or neurodevelopmental impairment. We now report longer-term results from prespecified hypotheses.

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METHODS

Using a 2-by-2 factorial design, we randomly assigned infants born between 24 weeks 0 days and 27 weeks 6 days of gestation to early CPAP with a limited ventilation strategy or early surfactant administration and to lower or higher target ranges of oxygen saturation (85 to 89% or 91 to 95%). The primary composite outcome for the longer-term analysis was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

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Formatted: Font: (Default) Times New Roman, 12 pt

RESULTS

The primary outcome was determined for 1234 of 1316 enrolled infants (93.8%); 990 of the 1058 surviving infants (93.6%) were evaluated at 18 to 22 months of corrected age. Death or neurodevelopmental impairment occurred in 27.9% of the infants in the CPAP group (173 of 621 infants), versus 29.9% of those in the surfactant group (183 of 613) (relative risk, 0.93; 95% confidence interval [CI], 0.78 to 1.10; $P = 0.38$), and in 30.2% of the infants in the lower-oxygen-saturation group (185 of 612), versus 27.5% of those in the higher-oxygen-saturation group (171 of 622) (relative risk, 1.12; 95% CI, 0.94 to 1.32; $P = 0.21$). Mortality was increased with the lower-oxygen-saturation target (22.1%, vs. 18.2% with the higher-oxygen-saturation target; relative risk, 1.25; 95% CI, 1.00 to 1.55; $P = 0.046$).

CONCLUSIONS

We found no significant differences in the composite outcome of death or neurodevelopmental impairment among extremely premature infants randomly assigned to early CPAP or early surfactant administration and to a lower or higher target range of oxygen saturation. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute; SUPPORT ClinicalTrials.gov number, NCT00233324.)

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From: Finer, Neil
To: Wally Carlo; Marie Gantz; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: PDF of Your Article for NEJM (Vaucher/Finer)
Date: Monday, December 03, 2012 8:02:00 AM

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Date: December 3, 2012, 7:34:36 AM EST
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Subject: RE: PDF of Your Article for NEJM (Vaucher/Finer)

Dear Neil,

One more thing I neglected to mention in my last email. As you can see, the abstract is indeed too long. It must be cut by at least 2 lines and preferably by 3. Dr Drazen and the other senior editors will make suggestions for cutting the length, but if you have preferences or suggestions about what to cut, please let me know.

Best,
Eli

From: Laurencot, Elizabeth
Sent: Monday, December 03, 2012 7:32 AM
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For the most part, the galley changes were made correctly, with a couple exceptions (noted below). Also, there are a few other items to be fixed:

We will change the order of the authors Walsh and Gantz, per your request.

Although no one caught this on the galleys, there was an error with the footnote marks used in the author list and the front page. Specifically, the footnote mark after Dr Dusick should be a dagger, not an asterisk, indicating "deceased". The asterisk will go after "Network" at the end of the list. Although this is technically "out of order" in terms of how we use these footnote marks, it is correct in this instance. Of course, the matching marks on the front page must be changed.

In the affiliations, we will move the North Carolina group ahead of the Ohio group to match the revised order in the author list.

In the affiliations, the wrong dash was used before "both in Ohio".

In Table 4, a dagger footnote after "Other abnormal eye finding" was incorrectly deleted. There should be both the dagger and double dagger for this row entry.

Please do read the entire set of proofs carefully and email me a list of any corrections you have for the page proofs by 10am (US Eastern) Tuesday, December 4 (rather than the 24 hours stated in the letter that accompanied the proofs). Also, I would ask that you please send me a list of corrections rather than annotating the pdf file.

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ORIGINAL ARTICLE

Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial

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ABSTRACT

BACKGROUND

Previous results from our trial of early treatment with continuous positive airway pressure (CPAP) versus early surfactant treatment in infants showed no significant difference in the outcome of death or bronchopulmonary dysplasia. A lower (vs. higher) target range of oxygen saturation was associated with a lower rate of severe retinopathy but higher mortality. Our prespecified hypothesis was that early CPAP and a lower target range of oxygen saturation would each decrease the risk of death or neurodevelopmental impairment. We now report longer-term results.

METHODS

Using a 2-by-2 factorial design, we randomly assigned infants born between 24 weeks 0 days and 27 weeks 6 days of gestation to early CPAP with a limited ventilation strategy or early surfactant administration and to lower or higher target ranges of oxygen saturation (85 to 89% or 91 to 95%). The primary composite outcome for the longer-term analysis was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

RESULTS

The primary outcome was determined for 1234 of 1316 enrolled infants (93.8%); 990 of the 1058 surviving infants (93.6%) were evaluated at 18 to 22 months of corrected age. Death or neurodevelopmental impairment occurred in 27.9% of the infants in the CPAP group (173 of 621 infants), versus 29.9% of those in the surfactant group (183 of 613) (relative risk, 0.93; 95% confidence interval [CI], 0.78 to 1.10; $P=0.38$), and in 30.2% of the infants in the lower-oxygen-saturation group (185 of 612), versus 27.5% of those in the higher-oxygen-saturation group (171 of 622) (relative risk, 1.12; 95% CI, 0.94 to 1.32; $P=0.21$). Mortality was increased with the lower-oxygen-saturation target (22.1%, vs. 18.2% with the higher-oxygen-saturation target; relative risk, 1.25; 95% CI, 1.00 to 1.55; $P=0.046$).

CONCLUSIONS

We found no significant differences in the composite outcome of death or neurodevelopmental impairment among extremely premature infants randomly assigned to early CPAP or early surfactant administration and to a lower or higher target range of oxygen saturation. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute; SUPPORT ClinicalTrials.gov number, NCT00233324.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Finer at the University of California, San Diego, Division of Neonatology, 200 W. Arbor Dr., San Diego, CA, 92013, or at nfiner@ucsd.edu.

Drs. Vaucher and Peralta-Carcelen contributed equally to this article.

*Deceased.

†Members of the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network are listed in the Supplementary Appendix, available at NEJM.org.

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EXTRÊMELY PREMATURE INFANTS ARE AT high risk for death and neurosensory or developmental impairment in early childhood.¹⁻³ The risk of neurodevelopmental impairment increases with decreasing gestational age and greater severity of illness. Neurodevelopmental impairment is often a consequence of neonatal complications.⁴⁻¹² Although surfactant administration decreases the risk of death and bronchopulmonary dysplasia, randomized, controlled trials of various respiratory interventions have not shown significant reductions in mortality and morbidity or improvement in developmental outcomes.¹³⁻¹⁷ We previously reported results of the multicenter, randomized, controlled Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), which involved extremely premature infants (from 24 to 27 weeks of gestation); treatment with noninvasive continuous positive airway pressure (CPAP) shortly after birth, as compared with early intubation and surfactant administration, did not reduce rates of death or bronchopulmonary dysplasia or other major morbidity at 36 weeks of postmenstrual age.¹⁸

Although oxygen supplementation is necessary for survival in many preterm infants, several studies have shown that it increases the risk of retinopathy of prematurity,¹⁹ bronchopulmonary dysplasia,^{20,21} periventricular leukomalacia,²² and cerebral palsy.²³ Results from SUPPORT showed no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity among infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) versus a higher range (91 to 95%). However, in the lower-oxygen-saturation group, the risk of retinopathy of prematurity among infants who survived to discharge was decreased (8.6%, vs. 17.9% in the higher-oxygen-saturation group; relative risk, 0.52; 95% confidence interval [CI], 0.37 to 0.73; $P < 0.001$) and the risk of death was increased (19.9% vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; $P = 0.04$).²⁴

We now report the results of our longer-term follow-up of the infants in this study, assessing whether early, noninvasive CPAP with a limited ventilation strategy, as compared with early surfactant administration, and a lower, as compared with higher, target range of oxygen saturation would each decrease the incidence of death be-

fore assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

METHODS

STUDY DESIGN

SUPPORT was a randomized, controlled trial involving 1316 extremely preterm infants (gestational age, 24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009, who were enrolled at delivery at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days). Infants who were part of multiple births were randomly assigned, as a unit, to the same treatment group.

In the delivery room, the infants were randomly assigned to receive either CPAP immediately after delivery with a limited ventilation strategy, as described previously, if subsequent intubation was required, or intubation with surfactant administration within an hour after birth, followed by conventional ventilation.¹⁸ Using a 2-by-2 factorial design, we also randomly assigned participants to a target oxygen-saturation range of 85 to 89% (lower-oxygen-saturation group) or 91 to 95% (higher-oxygen-saturation group); we used pulse oximeters that were specially designed to maintain blinding (see the Supplementary Appendix, available with the full text of this article at NEJM.org).²⁴

The procedures for enrollment, intervention, and data collection have been reported previously.^{18,24} The trial 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. Written informed consent was obtained from the parent or guardian of each child before delivery. Two of the authors employed by RTI International vouch for the accuracy and completeness of the data and analyses reported, and the members of the SUPPORT subcommittee vouch for the fidelity of the trial to the study protocol (see the Supplementary Appendix).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

ASSESSMENTS

At 18 to 22 months of corrected age, surviving infants underwent a comprehensive neurodevelopmental assessment performed by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability. Cognitive function was assessed with the use of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III); scores are assessed relative to a standardized mean (\pm SD) of 100 ± 15 , with higher scores indicating better performance.²⁵ The modified Gross Motor Function Classification System (GMFCS) was used to classify gross-motor performance, with scores ranging from 0 (normal) to 5 (most impaired).²⁶ Moderate-to-severe cerebral palsy was defined as a nonprogressive disorder with abnormal muscle tone in at least one arm or leg that was associated with abnormal control of movement or posture and a GMFCS score of 2 or higher.^{27,28} Assessments of hearing impairment (defined as the inability to understand the oral directions of the examiner and to communicate, with or without hearing amplification) and visual impairment (defined as vision worse than 20/200) were based on examination and parental report.

Certified research staff collected demographic and neonatal-outcome data using standard definitions from the Neonatal Research Network. Demographic and outcome data included gestational age; birth weight; sex; status with respect to multiple gestation; race or ethnic group; and history of medical or surgical necrotizing enterocolitis (modified Bell's stage ≥ 2 , on a scale ranging from 1 to 3, with higher scores indicating greater severity of disease), intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia, late-onset sepsis, retinopathy of prematurity, bronchopulmonary dysplasia (physiological), and use of postnatal glucocorticoids. Socioeconomic variables included health insurance status, maternal marital status, maternal educational level, household income, language spoken at home, and status with respect to whether the child was living with biologic parents. Socioeconomic data were updated during the 18-to-22-month visit; these data were used if data from the neonatal period were not available.

OUTCOMES

The prespecified primary composite outcome for this trial was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age. This composite outcome was selected because infants who died before 18 months of corrected age could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the BSID-III of less than 70, a GMFCS score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment. Other prespecified outcomes at 18 to 22 months of corrected age were death and neurodevelopmental impairment. Exploratory secondary outcomes included the individual components of the neurodevelopmental-impairment assessment, levels of cognitive delay, and a comparison of outcomes within the higher and lower gestational-age strata.

STATISTICAL ANALYSIS

The sample-size calculations were based on Neonatal Research Network data for infants born in the year 2000; the details have been reported previously.^{18,24} Although the sample size for the study was estimated on the basis of hospital outcomes (i.e., death or bronchopulmonary dysplasia for the ventilation intervention, and death or retinopathy of prematurity for the oxygenation intervention), the final sample size was sufficient to detect an absolute reduction of 10 percentage points in the composite outcome of death or neurodevelopmental impairment, with the use of a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% in the surfactant and higher-oxygen-saturation groups and a 15% rate of loss to follow-up, as well as adjustment for familial clustering.

Data were entered on standard forms and were transmitted to RTI International, which stored, managed, and analyzed the data for the study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were performed with the use of chi-square tests for categorical variables and t-tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary

composite outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age could be assigned. 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. The denominator used to calculate the frequency of each outcome was the number of children for whom status with respect to that outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all 18-to-22-month outcomes were adjusted, as prespecified, for gestational-age strata, study center, and familial clustering (because infants who were part of multiple births were assigned to the same treatment group). Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the effect of characteristics that differed between the groups of children with and without follow-up, a sensitivity analysis using multiple imputation was conducted, in which missing values for the primary outcome were imputed on the basis of the treatment assignment, perinatal characteristics, and in-hospital outcomes.²⁹ Two-sided P values of less than 0.05 were considered to indicate statistical significance for all analyses; no adjustments were made for multiple comparisons.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The primary composite outcome of death or neurodevelopmental impairment was determined for 93.8% of the children (1234 of 1316) enrolled in the trial (Fig. 1). A total of 258 children were known to have died before 18 to 22 months of age. Of the 68 children for whom a neurodevelopmental assessment was missing, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment was determined for 98.6% of all children seen (976 of 990); 14 children had an incomplete evaluation that precluded the assignment of a neurodevelopmental-impairment status. The follow-up rate and the mean corrected age at neuro-

developmental assessment were similar for all treatment groups (Table 1).

As compared with the mothers of the 990 children who underwent a neurodevelopmental assessment at 18 to 22 months of corrected age, the mothers of the 68 children who did not undergo an assessment were less likely to be married (47% vs. 31%, $P=0.01$) and more likely to have only public health insurance (52% vs. 69%, $P=0.008$). No other demographic or neonatal characteristics differed significantly between the groups.

The demographic and clinical characteristics of the follow-up population are summarized in Table 1 and in Table S1 in the Supplementary Appendix. Almost all mothers received antenatal glucocorticoids. At follow-up, there were more children who were small for their gestational age and more children with severe retinopathy of prematurity in the higher-oxygen-saturation group than in the lower-oxygen-saturation group. As compared with the surfactant group, children in the CPAP group were more likely to have had necrotizing enterocolitis and less likely to have been exposed to postnatal glucocorticoids. A total of 32% of the infants in the CPAP group were intubated in the delivery room; 65% of the infants in the CPAP group received surfactant with limited ventilation.

PRIMARY OUTCOME

The frequency of the composite outcome of death or neurodevelopmental impairment did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups at 18 to 22 months of corrected age (Tables 2 and 3). Mortality before neonatal discharge accounted for 92% of the overall mortality observed by 18 to 22 months. Mortality did not differ significantly between the CPAP and surfactant groups but remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group. There were no significant differences in the primary outcome between treatment groups in subgroup analyses stratified according to gestational age at birth (Tables S2 and S3 in the Supplementary Appendix). The results of the sensitivity analysis using multiple imputations were virtually identical to the results of the analysis in which missing data were excluded (data not shown). There was no significant interaction be-

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

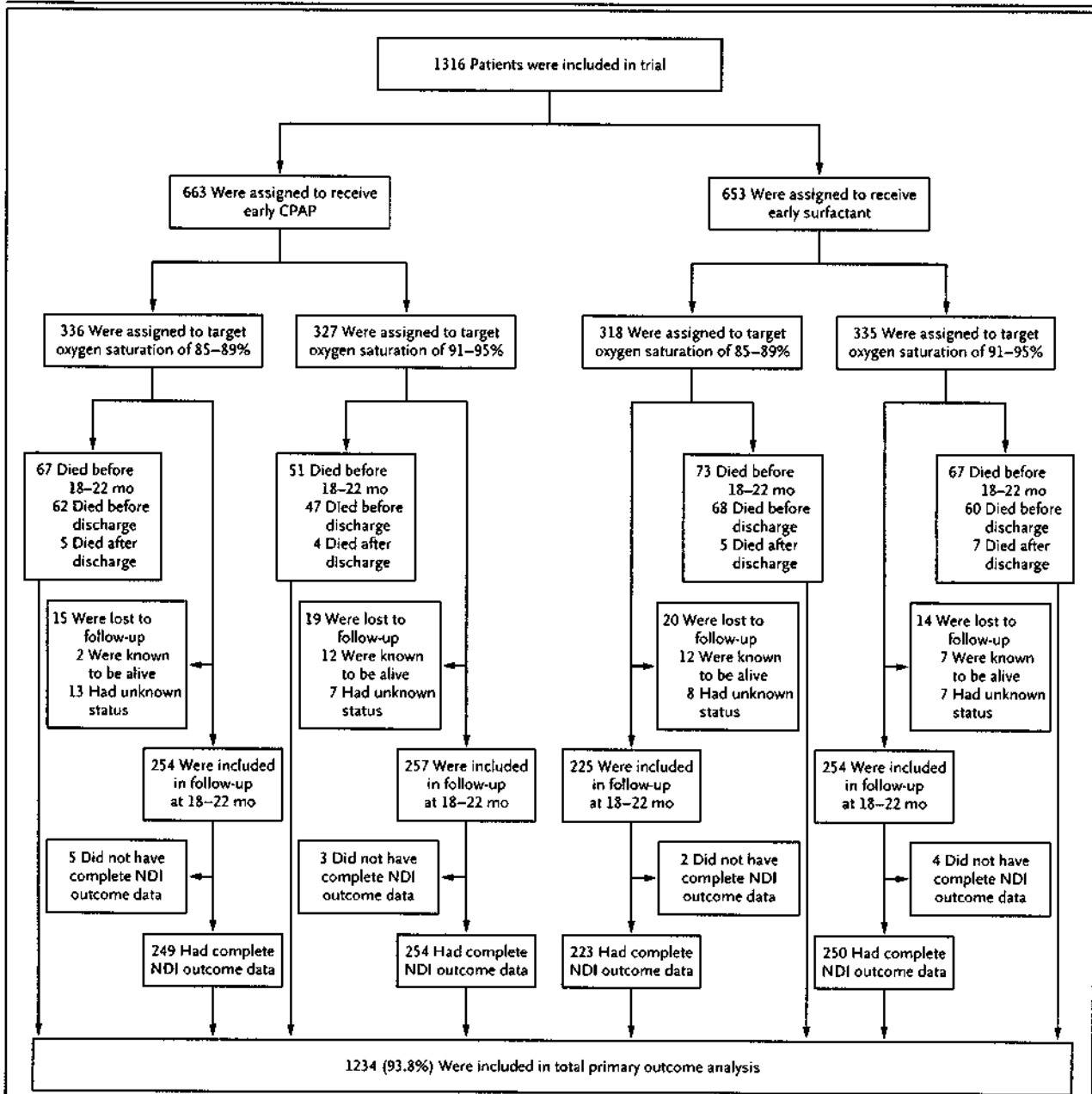


Figure 1. Enrollment, Randomization, and Outcomes.

The primary composite outcome was determined for 93.8% of the enrolled infants. A total of 258 children were known to have died before 18 to 22 months of corrected age. Of the 68 children with a missing neurodevelopmental assessment, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment (NDI) was determined for 98.6% of all children seen; 14 children had an incomplete evaluation that precluded the assignment of NDI status.

tween the two interventions with respect to the composite outcome of death or neurodevelopmental impairment or either of its components ($P>0.70$ for all comparisons).

OTHER OUTCOMES

The incidences of the individual components of neurodevelopmental impairment (BSID-III cognitive composite score of <70 , GMFCS score of ≥ 2 ,

Table 1. Demographic and Clinical Characteristics of the Follow-up Cohorts.*

Characteristic	CPAP (N=511)	Surfactant (N=479)	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=511)
Birth weight — g	849±186	852±193	858±186	844±192
Gestational age at birth — wk	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age — no. (%)†	23 (4.5)	32 (6.7)	17 (3.5)‡	38 (7.4)
Male sex — no. (%)	256 (50.1)	266 (55.5)	240 (50.1)	282 (55.2)
Multiple birth — no. (%)	138 (27.0)	114 (23.8)	124 (25.9)	128 (25.0)
Maternal use of antenatal glucocorticoids — no. (%)	493 (96.5)	456 (95.2)	462 (96.5)	487 (95.3)
Cesarean section — no. (%)	352 (68.9)	315 (65.8)	332 (69.3)	335 (65.6)
Neonatal outcome — no./total no. (%)§				
Severe retinopathy of prematurity	62/479 (12.9)	58/434 (13.4)	38/442 (8.6)¶	82/471 (17.4)
Bronchopulmonary dysplasia	193/511 (37.8)	187/479 (39.0)	177/479 (37.0)	203/511 (39.7)
Intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia	70/510 (13.7)	46/478 (9.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis	56/511 (11.0)**	30/479 (6.3)	42/479 (8.8)	44/511 (8.6)
Late-onset sepsis or meningitis	167/511 (32.7)	154/479 (32.2)	155/479 (32.4)	166/511 (32.5)
Use of postnatal glucocorticoids	34/508 (6.7)**	55/476 (11.6)	41/477 (8.6)	48/507 (9.5)
Corrected age at follow-up — mo	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

* Plus-minus values are means ±SD. There were no significant between-group differences, except as noted. Additional demographic characteristics of the cohorts are provided in Table S1 in the Supplementary Appendix. CPAP denotes continuous positive airway pressure.

† Infants who were small for gestational age were defined as those with a birth weight in less than the 10th percentile.

‡ P<0.01 for the comparison with the higher-oxygen-saturation group.

§ The comparisons of neonatal outcomes were adjusted for stratification factors (study center and gestational-age group) and familial clustering.

¶ P<0.001 for the comparison with the higher-oxygen-saturation group.

|| Assessment for bronchopulmonary dysplasia was performed at 36 weeks of postmenstrual age.

** P<0.05 for the comparison with the surfactant group.

moderate or severe cerebral palsy, hearing impairment, and blindness) among surviving infants did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups (Tables 2 and 3). Neither were there significant between-group differences in the individual components of neurodevelopmental impairment when the groups were stratified according to gestational age (Tables S2 and S3 in the Supplementary Appendix). However, in the lower-gestational-age stratum, mortality was higher in the surfactant group than in the CPAP group. Although the rates of severe retinopathy of prematurity and eye surgery were higher in the higher-oxygen-saturation group than in the lower-oxygen-saturation group, the rates of bilateral blindness, blindness of at least one eye, and other vision impairment

did not differ significantly between the groups at 18 to 22 months of corrected age (Table 4). There were no significant differences between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups in the rates of the composite outcome of death or individual neurodevelopmental-impairment components (data not shown), mean cognitive composite scores on the BSID-III, or the percentage of infants with cognitive composite scores of less than 80 points or less than 85 points (Table S4 in the Supplementary Appendix). Of the 976 children who were evaluated at 18 to 22 months of corrected age, 583 (60%) had normal status with respect to neuromotor, neurosensory, and cognitive development (with normal cognitive development defined as a BSID-III cognitive composite score of ≥85 points).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

Table 2. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the CPAP and Surfactant Groups.*

Variable	CPAP	Surfactant	Adjusted Relative Risk (95% CI)	P Value
	number/total number (percent)			
Primary outcome determined	621/663 (93.7)	613/653 (93.9)	1.00 (0.97–1.03)	0.83
Death or NDI	173/621 (27.9)	183/613 (29.9)	0.93 (0.78–1.10)	0.38
Death before assessment at 18–22 mo of corrected age	118/643 (18.4)	140/638 (21.9)	0.83 (0.67–1.04)	0.10
NDI	55/503 (10.9)	43/473 (9.1)	1.16 (0.79–1.71)	0.44
BSID-III cognitive score <70†	36/502 (7.2)	36/472 (7.6)	0.95 (0.61–1.50)	0.84
GMFCS score ≥2‡	26/511 (5.1)	23/479 (4.8)	0.98 (0.57–1.69)	0.95
Moderate or severe cerebral palsy	21/511 (4.1)	19/479 (4.0)	0.93 (0.51–1.72)	0.82
Bilateral blindness	4/511 (0.8)	7/479 (1.5)	0.53 (0.16–1.78)	0.31
Hearing impairment	17/511 (3.3)	7/479 (1.5)	2.27 (0.96–5.37)	0.06

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic. NDI denotes neurodevelopmental impairment.

† Scores on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), are assessed relative to a standardized mean (\pm SD) of 100 ± 15 , with higher scores indicating better performance.

‡ Gross-motor function was assessed by means of the modified Gross Motor Function Classification System (GMFCS), with scores ranging from 0 to 5 and higher scores indicating greater impairment.

DISCUSSION

In this large, multicenter trial involving very-high-risk, extremely premature infants, we found no significant difference in the primary composite follow-up outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between infants randomly assigned to treatment with early CPAP and those assigned to early intubation and surfactant administration or between those randomly assigned to the lower-oxygen-saturation group and those assigned to the higher-oxygen-saturation group. Mortality did not differ significantly between the CPAP and surfactant groups, and mortality remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group — findings that are consistent with our earlier results.^{18,24} There were no significant differences between the CPAP and surfactant groups or between the higher-oxygen-saturation and lower-oxygen-saturation groups with respect to the frequencies among surviving infants of neurodevelopmental impairment and its components, including severe cognitive impairment (BSID-III

cognitive composite score, <70), moderate or severe cerebral palsy, moderate or severe motor impairment (GMFCS score, ≥2), hearing impairment, and bilateral blindness.

Recent trials have raised concern about using lower target ranges of oxygen saturation because of the possibility of increased mortality among extremely premature infants.^{21,30} In SUPPORT, the risk of death during the initial hospitalization was increased among neonates randomly assigned to the lower-oxygen-saturation group, as compared with those assigned to the higher-oxygen-saturation group, and among neonates in the lowest gestational-age stratum, mortality was increased in the surfactant group as compared with the CPAP group. As previously reported, the causes of death did not differ significantly between the lower-oxygen-saturation and higher-oxygen-saturation groups.²⁴ Although significant differences in mortality persisted at 18 to 22 months of corrected age, these differences largely reflected the differences in mortality before hospital discharge. There are other ongoing studies of this matter that, once completed, could inform decisions.³¹

Severe retinopathy of prematurity may be as-

Table 3. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Primary outcome determined	612/654 (93.6)	622/662 (94.0)	1.00 (0.97–1.03)	0.79
Death or NDI	185/612 (30.2)	171/622 (27.5)	1.12 (0.94–1.32)	0.21
Death before assessment at 18–22 mo of corrected age	140/633 (22.1)	118/648 (18.2)	1.25 (1.00–1.55)	0.046
NDI	45/472 (9.5)	53/504 (10.5)	0.87 (0.60–1.28)	0.49
BSID-III cognitive score <70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58–1.43)	0.69
GMFCS score ≥ 2	26/479 (5.4)	23/511 (4.5)	1.17 (0.68–2.01)	0.56
Moderate or severe cerebral palsy	20/479 (4.2)	20/511 (3.9)	1.00 (0.54–1.83)	>0.99
Bilateral blindness	5/479 (1.0)	6/511 (1.2)	0.90 (0.28–2.90)	0.86
Hearing impairment	12/479 (2.5)	12/511 (2.3)	1.16 (0.54–2.49)	0.70

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic.

sociated with poor visual outcomes, even with treatment.^{32,33} In this study, infants in the lower-oxygen-saturation group who survived to discharge had a lower incidence of severe retinopathy of prematurity (8.6%, vs. 17.9% in the higher-oxygen-saturation group).²⁴ Although eye surgery was significantly less frequent in the lower-oxygen-saturation group than in the higher-oxygen-saturation group, there were no significant between-group differences with respect to rates of unilateral and bilateral blindness, nystagmus, strabismus, or the use of corrective lenses. We did not collect detailed data on visual function at the 18-to-22-month visit.

The strengths of this study include the large initial sample, which provided sufficient power to detect a clinically significant difference in the prespecified outcome of death or neurodevelopmental impairment, and the high percentage of surviving infants who underwent a comprehensive, standardized neurodevelopmental evaluation at 18 to 22 months of corrected age.

The study also has several limitations. The requirement for antenatal consent, which is associated with enrollment bias, may limit generalizability.^{34,35} In addition, the incidence of neurodevelopmental impairment in extremely premature infants in the present study was substantially lower than that previously reported by the Neonatal Research Network.³⁶ The present study used the BSID-III for cognitive assessment, where-

as previous Neonatal Research Network studies used an earlier edition, the BSID-II. Changes in the test design and standardization between the two editions may account for the lower incidence of neurodevelopmental impairment reported here.³⁶ Although the BSID-III scores in this study were higher than those previously reported for extremely premature infants, there were no significant differences between the treatment groups in this study.

Another limitation is the fact that the reported follow-up results are based on a single visit at 18 to 22 months of corrected age; other disabilities may not be evident until later in childhood. A subcohort of the SUPPORT study will be followed at school age to evaluate the longer-term neurodevelopmental outcome. Also, in comparing several secondary outcomes between pairs of treatments in this factorial-design trial (early CPAP vs. early surfactant treatment and lower vs. higher target ranges of oxygen saturation), we made no adjustments for multiple comparisons; appropriate caution should therefore be used in interpreting the reported results. Finally, differences in the neurodevelopmental outcome may have been blunted by the smaller difference in oxygen saturation between the higher-oxygen-saturation and lower-oxygen-saturation groups than was planned.²⁴

In conclusion, there were no significant differences in the composite outcome of death before

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Table 4. Visual Outcome at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.*

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Strabismus	46/478 (9.6)	41/510 (8.0)	1.20 (0.80–1.80)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89–3.69)	0.10
Eyes track 180 degrees	462/476 (97.1)	493/507 (97.2)	1.00 (0.98–1.02)	0.93
Corrective lenses for both eyes†	21/468 (4.5)	20/493 (4.1)	1.15 (0.63–2.10)	0.65
Blind with some function in both eyes†	3/450 (0.7)	2/475 (0.4)	1.57 (0.27–8.96)	0.61
Blind with no useful vision in both eyes†	2/449 (0.4)	4/477 (0.8)	0.54 (0.10–2.96)	0.48
Other abnormal eye finding‡	6/453 (1.3)	12/485 (2.5)	0.55 (0.21–1.46)	0.23
Blind in at least one eye	5/479 (1.0)	8/511 (1.6)	0.67 (0.22–2.02)	0.48
Eye surgery performed§	31/477 (6.5)	67/509 (13.2)	0.53 (0.35–0.78)	0.002

* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness and other abnormal eye finding were not adjusted for study center, owing to the small numbers of patients with these characteristics.

† The reference group for relative risk was the group of children with vision that appeared to be normal in both eyes.

‡ Other abnormal eye finding was defined as an abnormality other than a condition requiring corrective lenses but not one severe enough for the child to be considered blind in that eye. Children whose eyes were classified in two different vision categories were included in the other-abnormal-eye-finding category.

§ Reasons for surgery are listed in Table S5 in the Supplementary Appendix.

assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between extremely preterm infants randomly assigned at delivery to early CPAP and those assigned to early intubation with surfactant administration or between infants assigned to lower oxygen saturation and those assigned to higher oxygen saturation. Early CPAP with a limited ventilation strategy can be considered as an alternative to early surfactant treatment, even in infants as immature as those at 24 weeks of gestational age. It is important to consider the

risk of death or neurodevelopmental impairment when deciding on oxygen-saturation targets in extremely preterm infants. Because mortality remained lower in the higher-oxygen-saturation group at the time of follow-up and there were no adverse visual or neurodevelopmental problems, lower oxygen-saturation targets cannot be recommended in these extremely preterm infants.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica

Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children’s National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D’Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman,

Methodology for limited ventilator strategy

CPAP Arm:

NICU management: CPAP infants could be intubated if they met any of the following criteria: an $\text{FiO}_2 > .50$ required to maintain an indicated $\text{SpO}_2 > 88\%$ for one hour, an arterial $\text{PaCO}_2 > 65$ torr documented on a single blood gas within 1 hour prior to intubation, or 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 within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $\text{PaCO}_2 < 65$ torr with a $\text{pH} > 7.20$, an $\text{SpO}_2 > 88\%$ with an $\text{FiO}_2 < 50\%$, a mean airway pressure (MAP) < 10 cm H_2O , ventilator rate < 20 bpm, an amplitude $< 2\text{X}$ MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be extubated within 24 hours of meeting all of the following criteria: $\text{PaCO}_2 < 50$ torr and $\text{pH} > 7.30$, $\text{FiO}_2 \leq .35$ with a $\text{SpO}_2 > 88\%$, a MAP < 8 cm H_2O , ventilator rate < 20 bpm, an amplitude $< 2\text{X}$ MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could 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.¹

Methodology for oximeter blinding strategy

4.1.1 Randomization and Masking, Storing and Assigning Oximeters

Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the 26 - 27 6/7 week gestational age group.... Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO_2 arm of the study. They will be specified as one of the following:

- **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue or Orange** OR
- **Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue or Orange**.

The **Blue/Orange** codes will designate an assignment to either the **Low (85% - 89%)** or **High (91% -95%)** SpO_2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the

sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form**).

Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know"**. Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO₂) are available to accommodate the delivery. Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.²

Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u>	<u>Higher</u>
			<u>Saturation</u>	<u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) ^δ	849±186	852±193	858±186	844±192
Gestational age (weeks) ^δ	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10 th %) ^ε	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male ^ε	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White ^ε	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black ^ε	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic ^ε	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown ^ε	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation ^ε	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any ^ε	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section ^ε	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only ^ε	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married ^ε	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents ^ε	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < high school degree ^ε	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

Income < \$30,000/year [€]	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language [€]	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP [€]	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD [¶] [€]	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL [€]	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC [€]	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis [€]	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids [€]	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) ^δ	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

^δ Mean ± SD

[€] no./total no.(%)

[¶] At 36 weeks postmenstrual age

*p<0.05, ** p<0.01, ***p<0.001 (Comparison for groups within each intervention arm)

Comparisons adjusted for stratification by center and gestational age and for familial clustering

Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT

<u>24 0/7-25 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07
<u>26 0/7-27 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31

Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS

<u>24 0/7-25 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22
<u>26 0/7-27 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95

Gross motor function level ≥ 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral pal	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78
Hearing impairment	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets

	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

*ARR (Adjusted relative risk)

** (adjusted mean ± standard error)

***(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups

Reason for Eye surgery	Lower N=31	Higher N=67	Total N=98
Retinopathy of Prematurity	26 (84%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)

References

1. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
2. SUPPORT Manual of Operations, January 4, 2005, Revised March 10, 2005

From: Finer, Neil
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Gantz, Marie; adas@rti.org; Rich, Wade; Higgins, Rosemary (NIH/NICHD) (E); Vaucher, Yvonne
Subject: FW: Vaucher/Finer page proofs
Date: Friday, November 30, 2012 6:56:05 PM

FYI

From: Laurencot, Elizabeth [mailto:elaurencot@nejm.org]
Sent: Friday, November 30, 2012 12:44 PM
To: Finer, Neil
Subject: Vaucher/Finer page proofs

Dear Neil,

The revised page proofs for your article are scheduled to be sent to you later this afternoon. If possible, when they arrive, please take a moment to send me an email confirming receipt.

On Monday morning, I will review the page proofs against the changes that were marked on the galleys and will check in with you if I notice any incorrect items. Please do read the entire set of proofs carefully and email me a list of any corrections you have for the page proofs by 10am (US Eastern) Tuesday, December 4 (rather than the 24 hours stated in the standard letter that accompanies the proofs). Also, I would ask that you please send me a list of corrections rather than annotating the pdf file.

The editors will be reading your page proofs during this time as well, so I will be contacting you with any queries they have (probably Tuesday afternoon or Wednesday morning). Please do let me know if you will be unavailable via email next week.

I look forward to hearing back from you regarding your page proofs.

Best,
Eli

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From: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: SUPPORT release
Date: Friday, November 30, 2012 3:43:12 PM
Attachments: [2 SUPPORT News Release 01.docx](#)

Hi Rose. Please see attached. Thanks.

Page 1022 of 2000

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(b)(5)

of the Freedom of Information and Privacy Act

Page 1023 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1024 of 2000

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(b)(5)

of the Freedom of Information and Privacy Act

From: Ripley, Julie
To: Higoins, Rosemary (NIH/NICHD) [E]
Subject: RE: nejm permission
Date: Friday, November 30, 2012 10:53:36 AM

We have all the letters now, Rose.

Thanks very much for your help!

Best,
Julie

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

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Friday, November 30, 2012 10:51 AM
To: Ripley, Julie
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: nejm permission

HI Julie: OK- my fax says went through just now Sent to 617 739 9864 Prior was to 781 207 6529 Just to be safe, here also is a scanned version.
Hope one of these 3 makes it to you.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

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From: P47J [mailto:p47j@uhhs.com]
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Subject: nejm permission

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From: Ripley, Julie
To: "Walsh, Michele"
Cc: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: nejm permission
Date: Friday, November 30, 2012 10:53:34 AM

Perfect, thanks very much.

Best,
Julie

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

From: Walsh, Michele [mailto:Michele.Walsh@UHHospitals.org]
Sent: Friday, November 30, 2012 10:51 AM
To: Ripley, Julie
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: nejm permission

Hi Julie: OK- my fax says went through just now Sent to 617 739 9864 Prior was to 781 207 6529 Just to be safe, here also is a scanned version.
Hope one of these 3 makes it to you.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

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

From: P47J [mailto:p47j@uhhs.com]
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To: Walsh, Michele
Subject: nejm permission

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From: [Wally Carlo, M.D.](#)
To: [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [nfiner@ucsd.edu](#); [yvaucher@ucsd.edu](#); [Das, Abhik](#); [Myriam Peralta, M.D.](#); [wrich@ucsd.edu](#)
Subject: RE: NEJM Publication Date for #12-08506
Date: Friday, November 30, 2012 10:05:15 AM

AGREE!

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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-----Original Message-----

From: [Gantz, Marie \[mailto:mgantz@rti.org\]](mailto:mgantz@rti.org)
Sent: Friday, November 30, 2012 9:04 AM
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [nfiner@ucsd.edu](#); [yvaucher@ucsd.edu](#); [Wally Carlo, M.D.](#); [Das, Abhik](#); [Myriam Peralta, M.D.](#); [wrich@ucsd.edu](#)
Subject: RE: NEJM Publication Date for #12-08506

Great news, and great work, everyone!

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#) [<mailto:higginsr@mail.nih.gov>]
Sent: Thursday, November 29, 2012 8:11 PM
To: '[nfiner@ucsd.edu](#)'; '[yvaucher@ucsd.edu](#)'; '[wcarlo@peds.uab.edu](#)'; [Das, Abhik](#); [Gantz, Marie](#); '[mperalta@peds.uab.edu](#)'; '[wrich@ucsd.edu](#)'
Subject: Re: NEJM Publication Date for #12-08506

Please send the final galleys once you have them.
Congratulations to all!

Rose

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

From: [Finer, Neil \[mailto:nfiner@ucsd.edu\]](#)
Sent: Thursday, November 29, 2012 07:05 PM

To: Vaucher, Yvonne <yvaucher@ucsd.edu>; Wally Carlo <wcarlo@peds.uab.edu>; Abhik Das <adas@rti.org>; Marie Gantz <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHID) [E]; Myriam Peralta <MPeralta@peds.uab.edu>; Rich. Wade <wrich@ucsd.edu>
Subject: FW: NEJM Publication Date for #12-08506

FYI

I have put Yvonne as the contact for the media frenzy!! I will be in Europe Merry Christmas!!

Neil

From: "mediasupport@nejm.org<mailto:mediasupport@nejm.org>" <mediasupport@nejm.org<mailto:mediasupport@nejm.org>>
Date: Thursday, November 29, 2012 2:00 PM
To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Subject: NEJM Publication Date for #12-08506

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[\[http://images.nejm.org/CDF/email/nejm_logo.gif\]](http://images.nejm.org/CDF/email/nejm_logo.gif) <<http://content.nejm.org/>>

Dear Dr. Finer,

Your Original Article will appear in the December 27, 2012 issue of the New England Journal of Medicine (NEJM). This information is confidential. There is a press embargo on the contents of the issue until 5:00 PM ET on Wednesday December 26, 2012.

On Friday, December 21, 2012 the content of the December 27, 2012 issue will made available to reporters who have agreed to respect our embargo. We will send you a PDF file of the final copy of your article and any associated articles on Thursday evening, Dec 20, 2012.

Once they receive the content, reporters may wish to contact you for an interview. Please let us know how you would like them to contact you during the week prior to publication by filling out the "Points of Contact" form here<<https://cdl.nejm.org/misc/media/AuthorPoc.aspx?POCID=0091FEE1-9F6E-4E03-B774-C294508D8976>>. Note the information is not saved until you receive a confirmation screen.

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If you would like to share this information with your academic institution's press office, you may do so. Please be sure they have the proper embargo date and time.

Please let us know if you have any questions.

Sincerely yours,

Jennifer Zeis
Media Relations
The New England Journal of Medicine
781-434-7847
mediasupport@nejm.org<<mailto:mediasupport@nejm.org>>

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The New England Journal of Medicine • 860 Winter Street • Waltham, MA 02451 • USA

From: Ripley, Julie
To: Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh (mcw3@cwru.edu)
Subject: RE: FINER change of authorship form2
Date: Friday, November 30, 2012 9:54:53 AM
Attachments: FINER change of authorship form2.doc

Hi Dr. Walsh,

Would you be able to sign the attached letter and send it back to me today?

Thank you,
Julie

Editorial Assistant
New England Journal of Medicine

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 27, 2012 4:30 PM
To: Michele Walsh (mcw3@cwru.edu); golds005@mc.duke.edu; Michael.Acarregui@providence.org; Adams-Chapman, Ira; Charlie Bauer (cbauer@med.miami.edu)
Cc: Ripley, Julie
Subject: FINER change of authorship form2
Importance: High

Hi

Please sign the attached letter and return it to Julie Ripley (on email cc line) at NEJM as soon as possible.

Thanks
Rose

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Jeffrey M. Drazen, MD
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School
10 Shattuck Street
Boston, MA 02115

RE: NEJM MS ID #12-08506

STATEMENT OF AUTHORSHIP CHANGE

We hereby allow a change in the order of authors for "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" from:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

to:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Gantz, Marie; Walsh, Michele; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

Sincerely,

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NEJM Publication Date for #12-08506
Date: Friday, November 30, 2012 9:38:12 AM

I should have it for you today, Rose. I won't commit to it definitely, because we have the Director's podcast today, and the 50th on Wednesday, but soon.

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, November 29, 2012 8:14 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: NEJM Publication Date for #12-08506

Bob

The scheduled date is 12/27. Please send me a draft of the press release (or let me know if you want me to draft it).

Thanks for your help!

Rose

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, November 29, 2012 07:05 PM
To: Vaucher, Yvonne <yvaucher@ucsd.edu>; Wally Carlo <wcarlo@peds.uab.edu>; Abhik Das <adas@rti.org>; Marie Gantz <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta <MPeralta@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>
Subject: FW: NEJM Publication Date for #12-08506

FYI

I have put Yvonne as the contact for the media frenzy!! (b)(6) Merry Christmas!!

Neil

From: "mediasupport@nejm.org<mailto:mediasupport@nejm.org>"
<mediasupport@nejm.org<mailto:mediasupport@nejm.org>>
Date: Thursday, November 29, 2012 2:00 PM
To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Subject: NEJM Publication Date for #12-08506

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http://images.nejm.org/CDF/email/nejm_logo.gif <<http://content.nejm.org/>>

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have agreed to respect our embargo. We will send you a PDF file of the final copy of your article and any associated articles on Thursday evening, Dec 20, 2012.

Once they receive the content, reporters may wish to contact you for an interview. Please let us know how you would like them to contact you during the week prior to publication by filling out the "Points of Contact" form here<<https://cd.nejm.org/misc/media/AuthorPoc.aspx?POCID=0091FEE1-9F6E-4E03-B774-C294508D8976>>. Note the information is not saved until you receive a confirmation screen.

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If you would like to share this information with your academic institution's press office, you may do so. Please be sure they have the proper embargo date and time.

Please let us know if you have any questions.

Sincerely yours,

Jennifer Zeis
Media Relations
The New England Journal of Medicine
781-434-7847
mediasupport@nejm.org<<mailto:mediasupport@nejm.org>>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re: NEJM Publication Date for #12-08506
Date: Friday, November 30, 2012 9:01:31 AM

I even offered to write it!

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

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Friday, November 30, 2012 07:44 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NEJM Publication Date for #12-08506

We had to put pressure on Bob and would up doing a lot of editing- so keep it on.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, November 29, 2012 8:14 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: NEJM Publication Date for #12-08506

Bob

The scheduled date is 12/27. Please send me a draft of the press release (or let me know if you want me to draft it).

Thanks for your help!

Rose

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Thursday, November 29, 2012 07:05 PM
To: Vaucher, Yvonne <yvaucher@ucsd.edu>; Wally Carlo <wcarlo@peds.uab.edu>; Abhik Das <adas@rti.org>; Marie Gantz <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta <MPeralta@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>
Subject: FW: NEJM Publication Date for #12-08506

FYI

I have put Yvonne as the contact for the media frenzy!! (b)(6)

Merry Christmas!!

Neil

From: "mediasupport@nejm.org" <<mailto:mediasupport@nejm.org>>
<mediasupport@nejm.org> <<mailto:mediasupport@nejm.org>>>
Date: Thursday, November 29, 2012 2:00 PM
To: UCSD Pediatrics <nfiner@ucsd.edu> <<mailto:nfiner@ucsd.edu>>>
Subject: NEJM Publication Date for #12-08506

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[http://images.nejm.org/CDF/email/nejm_logo.gif] <<http://content.nejm.org/>>

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Once they receive the content, reporters may wish to contact you for an interview. Please let us know how you would like them to contact you during the week prior to publication by filling out the "Points of Contact" form here<<https://cdf.nejm.org/misc/media/AuthorPoc.aspx?POCID=0091FEE1-9F6E-4E03-B774-C294508D8976>>. Note the information is not saved until you receive a confirmation screen.

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Please let us know if you have any questions.

Sincerely yours,

Jennifer Zeis
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Michele.Walsh@UHhospitals.org"; Archer, Stephanie (NIH/NICHD) [E]; "Michele.walsh@cwru.edu"
Cc: "Nancy.Newman@UHhospitals.org"
Subject: Re: FINER change of authorship form2
Date: Thursday, November 29, 2012 5:08:08 PM

Thanks so much

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Thursday, November 29, 2012 05:05 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Michele.walsh@cwru.edu <Michele.walsh@cwru.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Newman, Nancy <Nancy.Newman@UHhospitals.org>
Subject: RE: FINER change of authorship form2

Sent again today.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Wednesday, November 28, 2012 12:01 PM
To: Michele Walsh (Michele.walsh@cwru.edu)
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Newman, Nancy
Subject: RE: FINER change of authorship form2

Hi Michele,

I just checked with Julie at NEJM. Neither she nor I received your form. Did you fax or email it? If it is available in your office, could Nancy or someone else re-send it? Attached is the revised form that was sent out November 20th.

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 28, 2012 11:14 AM

To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: FINER change of authorship form2

Can you forward to julie Ripley?

From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]
Sent: Wednesday, November 28, 2012 11:03 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FINER change of authorship form2

Sent last week out of town today also copied to stephanie

Sent with Good (www.good.com)

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

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, November 28, 2012 09:34 AM Eastern Standard Time
To: Michele Walsh (mcw3@cwru.edu)
Subject: FW: FINER change of authorship form2

Michele –
Please send to NEJM asap
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 27, 2012 4:30 PM
To: Michele Walsh (mcw3@cwru.edu); gold005@mc.duke.edu; Michael.Acarregui@providence.org;
Adams-Chapman, Ira; Charlie Bauer (cbauer@med.miami.edu)
Cc: jripley@nejm.org
Subject: FINER change of authorship form2
Importance: High

Hi

Please sign the attached letter and return it to Julie Ripley (on email cc line) at NEJM as soon as possible.

Thanks
Rose

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From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: December 10
Date: Thursday, November 29, 2012 1:29:25 PM

OK. I don't have much time between the November podcast (tomorrow) and the December podcast on the 10th. At this point, I'm just inquiring about who's going to be around.

Have a good trip.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, November 29, 2012 1:28 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: December 10

NO

I am (b)(6) I am here on Dec 13 and beyond. We don't have a publication date yet

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, November 29, 2012 1:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: December 10

Rose, are you here on December 10th at 9? I'm lining up potential podcast guests and it's possible your study will be published by then.

From: [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#)
Subject: RE:
Date: Wednesday, November 28, 2012 3:11:45 PM

Thanks Rose

Look forward to the "final" draft

And pub in (NEJM?)

Your communications office can communicate with ours re: press release

Not sure we will need to add comment, but leave it up to the communications offices?

--cb

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 28, 2012 3:05 PM
To: [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)
Cc: [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#)
Subject: RE:

Yes, Neil Finer is the main contact person and he added it – see the attached email.

ROse

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)
Sent: Wednesday, November 28, 2012 3:03 PM
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#)
Subject: RE:

Hi Rose,

Can you ensure that NHLBI support is mentioned in this manuscript?

Given the base support of the cohort.

Thanks, Carol

Carol J. Blaisdell M.D.

Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 28, 2012 2:32 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE:

NHLBI funded the main trial. We are planning a press release.
Thanks
ROse

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, November 28, 2012 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:

Thanks for this Rose. Let me know if you are doing any press release so we can coordinate.
Was this not also funded by NHLBI?
Cannot remember how we cited NHLBI with the original manuscripts of the primary outcomes

Page 2

(b)(5)

(b)(5)

Might want to clarify....

CONCLUSIONS

38 We found no significant differences in the compo39
site outcome of death or neurodevelopmental im40
pairment among extremely premature infants ran41
domly assigned to early CPAP or early surfactant
42 administration and to a lower or higher target
43 range of oxygen saturation. (Funded by the Eunice
44 Kennedy Shriver National Institute of Child Health
45 and Human Development; SUPPORT Clinical-
46 Trials.gov number, NCT00233324.)

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 28, 2012 2:24 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject:

Carol

Here is the most recent galley proofs for the SUPPORT follow up paper. We should have another version by the end of the week which I will forward to you. We don't have a publication date as of yet.

Thanks for all the support with this!
rose

From: Ripley, Julie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Wednesday, November 28, 2012 1:46:46 PM

Hi Rose-

Just Michele Walsh.

Thanks very much.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 28, 2012 1:43 PM
To: Ripley, Julie
Subject: FW: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2

Hi Julie –

Can you let me know if you are missing any of these now?

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Janell Fuller [mailto:JaFuller@salud.unm.edu]
Sent: Wednesday, November 28, 2012 1:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2

Attached is the signed changed authorship.

Thank you,

Annie Chavez on behalf of Janell Fuller, MD

Janell Fuller, MD
Associate Professor of Pediatrics
Division Chief of Neonatology
Medical Director, Special Care Nurseries
Medical Director, Transport and Practitioner Services
University of New Mexico Children's Hospital
MSC10 5590
1 University of New Mexico
Albuquerque NM 87131-0001
505-272-6409
jfuller@salud.unm.edu

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 11/28/2012 7:32 AM >>>

Janell - Please submit ASAP!

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 27, 2012 4:32 PM
To: 'Janell Fuller'; jripley@nejm.org
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Janell

You will need to sign this updated version of the letter.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Janell Fuller [<mailto:jaFuller@salud.unm.edu>]
Sent: Monday, November 26, 2012 2:32 PM
To: jripley@nejm.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Change in authorship order - New England Journal of Medicine 12-08506.R2

Hello

Please find my change in authorship order page attached.

Janell

Janell Fuller, MD
Associate Professor of Pediatrics
Division Chief of Neonatology
Medical Director, Transport and Practitioner Services
University of New Mexico Children's Hospital
MSC10 5590
1 University of New Mexico
Albuquerque NM 87131-0001
505-272-6409
jfuller@salud.unm.edu

>>> <jripley@nejm.org> 11/20/2012 8:59 AM >>>

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

I have been notified that you would like to change the order of the authors of the above manuscript. Our Deputy

Editor has approved the change, but we will also need documentation that each of you approve the change. I've attached a letter detailing this change; please review it to ensure the new author order is correct (or revise as necessary), and then each of you should sign it. You can each sign one letter, or if necessary you may return separate letters. The signed letter should be sent back to me via email or fax (781-207-6529). If you could attend to this promptly, we'd greatly appreciate it, as we do not want this to cause a delay in the publication of your manuscript.

Thank you!

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "jripley@nejm.org"
Subject: FW: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Wednesday, November 28, 2012 1:42:00 PM
Attachments: 20121128105322546.pdf

Hi Julie –

Can you let me know if you are missing any of these now?

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Janell Fuller [<mailto:JaFuller@salud.unm.edu>]
Sent: Wednesday, November 28, 2012 1:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2

Attached is the signed changed authorship.

Thank you,

Annie Chavez on behalf of Janell Fuller, MD

Janell Fuller, MD
Associate Professor of Pediatrics
Division Chief of Neonatology
Medical Director, Special Care Nurseries
Medical Director, Transport and Practitioner Services
University of New Mexico Children's Hospital
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1 University of New Mexico

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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 11/28/2012 7:32 AM >>>

Janell - Please submit ASAP!
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 27, 2012 4:32 PM
To: 'Janell Fuller'; jripley@nejm.org
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Janell

You will need to sign this updated version of the letter.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Janell Fuller [<mailto:JaFuller@salud.unm.edu>]
Sent: Monday, November 26, 2012 2:32 PM
To: jripley@nejm.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Change in authorship order - New England Journal of Medicine 12-08506.R2

Hello

Please find my change in authorship order page attached.

Janell

Janell Fuller, MD
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>>> <jripley@nejm.org> 11/20/2012 8:59 AM >>>

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

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Thank you!

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine

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<http://www.nejm.org>

Jeffrey M. Drazen, MD
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School
10 Shattuck Street
Boston, MA 02115

RE: NEJM MS ID #12-08506

STATEMENT OF AUTHORSHIP CHANGE

We hereby allow a change in the order of authors for "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" from:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

to:

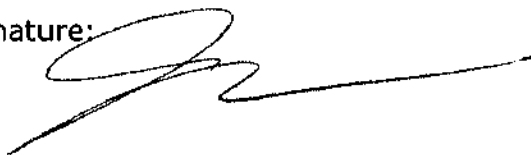
Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Gantz, Marie; Walsh, Michele; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

Sincerely,

Date: 11/27/12

Printed Name: Janell Fuller, MD

Signature:



From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov)
To: triplev@nejm.org
Subject: FW: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Wednesday, November 28, 2012 9:53:00 AM
Attachments: [20121126122350901_2.pdf](#)

Dr. Fuller's form

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Janell Fuller [<mailto:JaFuller@salud.unm.edu>]
Sent: Wednesday, November 28, 2012 9:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Janell Fuller
Subject: Re: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2

Dr. Higgins - Attached is the signed document. Please let us know if you need anything more.

Annie Chavez on behalf of Janell Fuller, MD

Janell Fuller, MD
Associate Professor of Pediatrics
Division Chief of Neonatology
Medical Director, Special Care Nurseries
Medical Director, Transport and Practitioner Services
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Janell! - Please submit ASAP!

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 27, 2012 4:32 PM
To: 'Janell Fuller'; jripley@nejm.org
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Janell

You will need to sign this updated version of the letter.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Janell Fuller [<mailto:JaFuller@salud.unm.edu>]
Sent: Monday, November 26, 2012 2:32 PM
To: jripley@nejm.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Change in authorship order - New England Journal of Medicine 12-08506.R2

Hello

Please find my change in authorship order page attached.

Janell

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Associate Professor of Pediatrics
Division Chief of Neonatology
Medical Director, Transport and Practitioner Services
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1 University of New Mexico
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>>> <jripley@nejm.org> 11/20/2012 8:59 AM >>>

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Dear Dr. Finer and Co-authors:

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Julie Ripley
Editorial Assistant

New England Journal of Medicine
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Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: [Janell Fuller](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); jripley@nejm.org
Cc: [Janell Fuller](#)
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Wednesday, November 28, 2012 9:50:24 AM

Sorry Dr. Higgins, I just saw this updated version. I have printed and will ask Dr. Fuller to sign when she comes in today and send it to you. Please ignore my previous email to you this AM.

Annie on behalf of Janell Fuller, MD

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 11/27/2012 2:32 PM >>>

Janell

You will need to sign this updated version of the letter.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Subject: Re: Change in authorship order - New England Journal of Medicine 12-08506.R2

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<http://www.nejm.org>

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: "Ricki Goldstein, M.D."
Cc: [Ronald Goldberg, M.D.](#)
Subject: RE: FINER change of authorship form2
Date: Wednesday, November 28, 2012 9:45:00 AM

When was this done – I spoke to Julie Ripley in the last hour and she didn't have it??

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ricki Goldstein, M.D. [<mailto:ricki.goldstein@duke.edu>]
Sent: Wednesday, November 28, 2012 9:37 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald Goldberg, M.D.
Subject: RE: FINER change of authorship form2

It has already been done.

Ricki

Ricki F. Goldstein
Professor of Pediatrics
Director, High-Risk Infant Follow-up Program and
Special Infant Care Clinic
Division of Neonatal-Perinatal Medicine
Duke University Medical Center
919-681-6024
ricki.goldstein@duke.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Wednesday, November 28, 2012 9:33 AM
To: Ricki Goldstein, M.D.
Cc: Ronald Goldberg, M.D.
Subject: FW: FINER change of authorship form2
Importance: High

Ricki-

Please submit this to NEJM asap-I also left a phone message.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 27, 2012 4:30 PM
To: Michele Walsh (mcw3@cwru.edu); golds005@mc.duke.edu; Michael.Acarregui@providence.org;
Adams-Chapman, Ira; Charlie Bauer (cbauer@med.miami.edu)
Cc: jripley@nejm.org
Subject: FINER change of authorship form2
Importance: High

Hi

Please sign the attached letter and return it to Julie Ripley (on email cc line) at NEJM as soon as possible.

Thanks

Rose

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Michele Walsh \(mcw3@cwru.edu\)](#)
Subject: FW: FINER change of authorship form2
Date: Wednesday, November 28, 2012 9:33:00 AM
Attachments: [FINER change of authorship form2.doc](#)
Importance: High

Michele –
Please send to NEJM asap
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 27, 2012 4:30 PM
To: [Michele Walsh \(mcw3@cwru.edu\)](#); [golds005@mc.duke.edu](#); [Michael.Acarregui@providence.org](#); [Adams-Chapman, Ira](#); [Charlie Bauer \(cbauer@med.miami.edu\)](#)
Cc: jripley@nejm.org
Subject: FINER change of authorship form2
Importance: High

Hi
Please sign the attached letter and return it to Julie Ripley (on email cc line) at NEJM as soon as possible.

Thanks
Rose

From: Ripley, Julie
To: "Ravelo, Elisabeth"
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Bauer, Charles R
Subject: RE: FINER change of authorship form2- Charles R. Bauer, M.D.
Date: Wednesday, November 28, 2012 9:23:35 AM

Thank you!

From: Ravelo, Elisabeth [mailto:ERavelo@med.miami.edu]
Sent: Wednesday, November 28, 2012 8:53 AM
To: Ripley, Julie
Cc: 'higginsr@mail.nih.gov'; Bauer, Charles R
Subject: FINER change of authorship form2- Charles R. Bauer, M.D.
Importance: High

Dear Ms. Ripley,

Please see attached Dr. Bauer's change of authorship form. Thank you!

Best,

Lis



Elisabeth Ravelo, B.A.
Administrative Assistant to Charles R. Bauer, M.D.
Conference Coordinator
University of Miami-Miller School of Medicine
Division of Neonatology
(305) 243-5508
(305) 243-3501 FAX

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Adams-Chapman, Ira"
Subject: RE: FINER change of authorship form2
Date: Wednesday, November 28, 2012 8:28:00 AM

Ira-

There is no signature on this – they need an ink signature and fax is ok – please resend to NEJM>

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Adams-Chapman, Ira [mailto:iadamsc@emory.edu]
Sent: Tuesday, November 27, 2012 9:53 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FINER change of authorship form2

Hi Rose,
My admin was supposed to fax this previously - sorry for the delay.
Here is a scanned copy.
Thanks,
Ira

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, November 27, 2012 4:30 PM
To: Michele Walsh (mcw3@cwru.edu); gold005@mc.duke.edu; Michael.Acarregui@providence.org;
Adams-Chapman, Ira; Charlie Bauer (cbauer@med.miami.edu)
Cc: jripley@nejm.org
Subject: FINER change of authorship form2

Hi
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Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Janell Fuller"; jripley@nejm.org
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 27, 2012 4:32:00 PM
Attachments: [FINER change of authorship form2.doc](#)

Janell

You will need to sign this updated version of the letter.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

I have been notified that you would like to change the order of the authors of the above manuscript. Our Deputy Editor has approved the change, but we will also need documentation that each of you approve the change. I've attached a letter detailing this change; please review it to ensure the new author order is correct (or revise as necessary), and then each of you should sign it. You can each sign one letter, or if necessary you may return separate letters. The signed letter should be sent back to me via email or fax (781-207-6529). If you could attend to this promptly, we'd greatly appreciate it, as we do not want this to cause a delay in the publication of your manuscript.

Thank you!

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: Ripley, Julie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Authorship change for SUPPORT paper
Date: Tuesday, November 27, 2012 4:28:04 PM
Attachments: FINER change of authorship form2.doc

Hi Rose,

Missing forms from:

Michele Walsh
Ricki Goldstein
Michael Acarregui
Ira Adams-Chapman
Charles Bauer
Janell Filler

Thanks for your help!

Best,
Julie

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 26, 2012 12:20 PM
To: Ripley, Julie
Subject: RE: Authorship change for SUPPORT paper

Julie

Can you let me know if you have received all of the forms? If you are missing any, let me know and I can try to get folks to send them to you.

Thanks for your help
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ripley, Julie [mailto:jripley@nejm.org]
Sent: Tuesday, November 20, 2012 3:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Authorship change for SUPPORT paper

Thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 20, 2012 2:30 PM
To: Ripley, Julie
Cc: Archer, Stephanie (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: Authorship change for SUPPORT paper

Julie – Here is my authorship letter with signature.
Thanks for your help
Rose

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From: Laurencot, Elizabeth
To: "Finer, Neil"
Cc: Wally Carlo (wcarlo@peds.uab.edu); Rich, Wade; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Subject: RE: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 2:18:38 PM

Dear Neil,

Many thanks!

I will check in with you again once I see that your page proofs have been sent out on Friday.

Best,
Eli

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Tuesday, November 27, 2012 2:16 PM
To: Laurencot, Elizabeth
Cc: Wally Carlo (wcarlo@peds.uab.edu); Rich, Wade; Vaucher, Yvonne; Rosemary Higgins; Das, Abhik; Gantz, Marie
Subject: Re: Vaucher/Finer OA galleys

These look OK Eli
Neil

On 11/27/12 10:34 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org> wrote:

>Dear Neil,
>
>It turns out that there was still a bit of tweaking to do on the
>footnotes in Table 4. What we'd like to do is use the following
>sentence (marked as the dagger and applied as already shown on the table):
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>vision that appeared to be normal in both eyes."
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>Will this work?
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>And finally, just a slight edit on page 7, lines 53-56:
>"There was no significant interaction between the two interventions
>with respect to the composite outcome of death or neurodevelopmental
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>OK?

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>I look forward to your reply. Many thanks!

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>

>Thanks for all your help

>Be well

>Neil

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>On 11/27/12 9:36 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org> wrote:

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>>Dear Dr Finer,

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>>Wonderful --- many thanks for hashing through all these details on the
>>galleys.

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>>I will pass along your galley proofs for approval. If there are
>>additional queries for you that arise during that process, I will send
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>>That would be acceptable to us

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>>>"Children whose eyes were classified in two different vision

>>>categories were included in the other-abnormal-eye-finding group."

>>>

>>>OK?

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>>>Many thanks,

>>>Eli

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>>>Our preferred wording differs a little and is below We have clarified

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>>>useful vision), wearing or having a prescription for corrective

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>>>>you see fit.

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>>>>Best,

>>>>Eli

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>>>>I hope these responses are adequate

>>>>Regards

>>>>Neil Finer

>>>>

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From: [Finer, Neil](#)
To: [Marie Gantz](#)
Cc: [Wally Carlo](#); [Higgins, Rosemary \(NIH/NICHD\) \(E\)](#); [Abhik Das](#); [Vaucher, Yvonne](#)
Subject: FW: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 1:38:57 PM

Are you OK with this wording about relative risk??
Neil

On 11/27/12 10:34 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org> wrote:

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>Eli
>
>
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>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
>Sent: Tuesday, November 27, 2012 12:38 PM
>To: Laurencot, Elizabeth
>Cc: Wally Carlo (wcarlo@peds.uab.edu); Rich, Wade; Vaucher, Yvonne;
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>>>>>Subject: Re: Vaucher/Finer OA galley

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To: "Laurencot, Elizabeth"; "Finer, Neil"
Cc: Wally Carlo (wcarlo@peds.uab.edu); Rich, Wade; Vaucher, Yvonne; Das, Abhik; Gantz, Marie
Subject: RE: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 12:40:00 PM

Ok
Thanks for getting back to me so quickly
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Laurencot, Elizabeth [mailto:elaurencot@nejm.org]
Sent: Tuesday, November 27, 2012 12:40 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'
Cc: Wally Carlo (wcarlo@peds.uab.edu); Rich, Wade; Vaucher, Yvonne; Das, Abhik; Gantz, Marie
Subject: RE: Vaucher/Finer OA galleys

Dear Rose,

I'm sorry, I don't have that specific information for you. You should soon be receiving email from the Media Relations Department with specific publication and embargo-date information.

Best,
Eli

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 27, 2012 12:38 PM
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Subject: RE: Vaucher/Finer OA galleys

Thanks for your help - do you have a tentative publication date as of yet?

Thanks
ROse

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
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higginsr@mail.nih.gov

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>>prescribed corrective lenses, or other abnormality defined as "child
>>has an other abnormality affecting that eye other than a condition

>>requiring corrective lenses but the impairment is not severe enough
>>for the child to be considered blind in that eye."

>>

>>I hope these responses are adequate

>>Regards

>>Neil Finer

>>

>>

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From: Finer, Neil
To: Wally Carlo, M.D.
Cc: Rich, Wade; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [F]; Das, Abhik; Gantz, Marie
Subject: Re: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 12:38:40 PM

I hope we are done (but I doubt it!)
Be well
Neil

From: "<Wally Carlo>", Wally Carlo <wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>>
Date: Tuesday, November 27, 2012 9:36 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Cc: Wade Rich <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>, Yvonne Vaucher <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>, Rosemary Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, Abhik Das <adas@rti.org<mailto:adas@rti.org>>, Marie Gantz <mgantz@rti.org<mailto:mgantz@rti.org>>
Subject: RE: Vaucher/Finer OA galleys

Great job, Neil. Thx so much.

Wally

-----Original message-----

From: "Laurencot, Elizabeth" <elaurencot@nejm.org<mailto:elaurencot@nejm.org>>
To: "'Finer, Neil'"; <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Cc: "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>, "Rich, Wade" <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>, "Vaucher, Yvonne" <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>, Rosemary Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, "Das, Abhik" <adas@rti.org<mailto:adas@rti.org>>, "Gantz, Marie" <mgantz@rti.org<mailto:mgantz@rti.org>>
Sent: Tue, Nov 27, 2012 17:33:31 GMT+00:00
Subject: RE: Vaucher/Finer OA galleys

Dear Dr Finer,

Thank you for your revisions. It looks good, although I need to note that, per style, we would adjust the final phrasing as:

(b)(4)

OK?

Many thanks,
Eli

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Tuesday, November 27, 2012 12:29 PM
To: Laurencot, Elizabeth
Cc: Wally Carlo (wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>); Rich, Wade; Vaucher, Yvonne; Rosemary Higgins; Das, Abhik; Gantz, Marie
Subject: Re: Vaucher/Finer OA galleys

Hello Elizabeth

Our preferred wording differs a little and is below We have clarified that this is both eyes

"Findings were compared against vision that appeared normal in both eyes. Categories included blindness (with some functional vision or with no useful vision), wearing or having a prescription for corrective lenses, or other abnormality, defined as an abnormality other than a condition requiring corrective lenses but not one severe enough for the child to be considered blind in that eye. Children whose eyes were in two different vision categories are in the other abnormal eye finding group."

Please let me know if this is acceptable Thanks Neil Finer On 11/27/12 8:44 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>> wrote:

>Dear Dr Finer,

>

>We are getting close to being finished here. The table footnote needs
>to be revised to include the info you provided below. OK to revise as:

>

>Findings were compared against vision that appeared normal. Categories
>included blindness (with some functional vision or with no useful
>vision), wearing or having a prescription for corrective lenses, or
>other abnormality, defined as an abnormality other than a condition
>requiring corrective lenses but not one severe enough for the child to
>be considered blind in that eye.

>

>Please let me know if this phrasing will work, or please revise as you
>see fit.

>

>Best,

>Eli

>

>

>

>

>

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

>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]

>Sent: Tuesday, November 27, 2012 11:19 AM

>To: Laurencot, Elizabeth

>Cc: Wally Carlo (wcarlo@peds.uab.edu<<mailto:wcarlo@peds.uab.edu>>); Rich, Wade; Vaucher, Yvonne;

>Rosemary Higgins; Das, Abhik; Gantz, Marie

>Subject: Re: Vaucher/Finer OA galleys

>

>

>Table - correct as you stated We define normal vision "if vision
>appears normal." The other possible categories are blindness (with some
>functional vision or with no useful vision), wears or was prescribed
>corrective lenses, or other abnormality defined as "child has an other
>abnormality affecting that eye other than a condition requiring
>corrective lenses but the impairment is not severe enough for the child
>to be considered blind in that eye."

>

>I hope these responses are adequate

>Regards

>Neil Finer

>

>

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From: Finer, Neil
To: Laurencot, Elizabeth
Cc: Wally Carlo (wcarlo@peds.uab.edu); Rich, Wade; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) (E); Das, Abhik; Gantz, Marie
Subject: Re: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 11:19:54 AM

Hello Elizabeth

A75-A76

The statement about no adverse visual or ND problems is correct

A77 - Thank you this should be added there as well

Table - correct as you stated

We define normal vision "if vision appears normal." The other possible categories are blindness (with some functional vision or with no useful vision), wears or was prescribed corrective lenses, or other abnormality defined as "child has an other abnormality affecting that eye other than a condition requiring corrective lenses but the impairment is not severe enough for the child to be considered blind in that eye."

I hope these responses are adequate

Regards

Neil Finer

On 11/27/12 6:46 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org> wrote:

>Dear Dr Finer,

>

>Thank you for your replies regarding these items. There are just two

>items that need more attention at this time. Please see items below

>preceded by ****.

>

>1. A75-A76- We would like to change the last 2 sentences in this

>manuscript to read as follows starting at Line 50, page 10

(b)(4)

> Yes

>This wording change would be acceptable if preferred

>

>**** Also, please confirm accuracy of statement that there were (b)(4)

(b)(4)

or

>please clarify.

>

>A77 - Please add "and the National Heart Lung and Blood Institute" Line

>2 Page 11

>This change will also need to be made to page 2, line 45. OK

>

>

>2. Table 4 looks fine to us...The query about (b)(4) appears OK to us

>Sorry, sometimes the queries in tables are not formatted or lined up
>correctly.
>The third query (Please clarify) is regarding the second footnote. ??
>Currently says (b)(4) This is
>correct as stated

>
>****Although it is correct, it is not clear what you mean. What does
>"normal" refer to here, or how is it defined?

>
>If you could please reply by noon today, that would be most helpful. The
>galleys are due to be finalized early this afternoon. Many thanks for
>your attention to these details.

>
>Best,
>Elizabeth

>
>
>
>

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

>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>Sent: Tuesday, November 27, 2012 8:59 AM
>To: Laurencot, Elizabeth
>Cc: Wally Carlo (wcarlo@peds.uab.edu); Rich, Wade; Vaucher, Yvonne;
>Rosemary Higgins; Das, Abhik; Gantz, Marie
>Subject: FW: Vaucher/Finer OA galleys

>
>Hello Elizabeth
>Here are our responses
>I hope they are acceptable
>Regards
>Neil Finer

>
>

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

>From: Laurencot, Elizabeth [mailto:elaurencot@nejm.org]
>Sent: Wednesday, November 21, 2012 7:54 AM
>To: Finer, Neil
>Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade;
>Vaucher, Yvonne
>Subject: RE: Vaucher/Finer OA galleys

>
>

>Dear Dr Finer,
>
>Many thanks for your clear replies and corrections on the galley proofs.
>There are several items that need additional discussion. Please see the
>attached file; my replies are in blue font.

>
>

>If you could possibly respond to these items by noon on Tuesday, Nov 27,
>that would be most helpful.
>
>Thank you, and I wish you a Happy Thanksgiving!

>
>

>Best,
>Elizabeth

>
>

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

>From: Finer, Neil [mailto:nfiner@ucsd.edu]

>Sent: Monday, November 19, 2012 6:05 PM

>To: Laurencot, Elizabeth

>Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade;

>Vaucher, Yvonne

>Subject: Re: Vaucher/Finer OA galley

>Importance: High

>

>Hello Elizabeth

>Please find attached our response to your queries for the proofs of the

>SUPPORT Neurodevelopmental Outcome paper.

>I believe that we answered all the questions and corrected some errors

>that we discovered Let me know if there are any further questions Thanks

>for the opportunity to review the galley Be well Neil Finer for all

>authors

>

>

>From: <Laurencot>, Elizabeth

><elaurencot@nejm.org<mailto:elaurencot@nejm.org>>

>Date: Friday, November 16, 2012 6:35 AM

>To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>Subject: FW: Vaucher/Finer OA galley

>

>Dear Dr Finer,

>

>Attached is a copy of your galley proofs (identical to the copy just

>sent).

>

>After you have reviewed the galley, the fastest process is to send me an

>e-mail with answers to the numbered queries as well as any changes you

>have, and then we can go over anything that we still have questions about.

>

>Please record your responses to all of the queries in a simple email or

>Word file and indicate changes as "Page 2, line 17, change 'xxxx' to

>'yyyy'. (Please do not annotate the pdf file, which can be quite

>cumbersome on both ends.)

>

>Please send me your corrections and responses to all the queries on the

>galley proofs by noon (US Eastern) on Tuesday, November 20. Please note

>that it is likely that I will be sending follow-up emails to you next

>Tuesday and Wednesday; please do let me know if you will not be available.

>

>In the meantime, if you could please drop me a note confirming receipt of

>the galley proofs, that would be most helpful.

>

>Thanks in advance.

>

>Best,

>Elizabeth

>

>Elizabeth Laurencot

>Manuscript Editor

>New England Journal of Medicine

>617-487-6547

>elaurencot@nejm.org<mailto:elaurencot@nejm.org>

>

>

>From: NEJM Galleys
>Sent: Friday, November 16, 2012 9:31 AM
>To: 'nfiner@ucsd.edu' <<mailto:nfiner@ucsd.edu>>
>Subject: Vaucher/Finer OA galleys

>

>PLEASE DO NOT REPLY TO THIS E-MAIL

>

>AUTHOR: Vaucher/Finer
>MANUSCRIPT EDITOR: Elizabeth Laurençot
>(elaurencot@nejm.org <<mailto:elaurencot@nejm.org>>); 800-445-8080 or
>617-734-9800

>

>Please check the attached galley proofs of your article. It is important
>that we receive your changes by noon on Tuesday, November 20.

>

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>charge at the Adobe Web site
>(http://www.adobe.com/products/acrobat/readermain.html).

>

>TO RESPOND BY E-MAIL: If your corrections and your responses to the
>queries are straightforward, we encourage you to respond by e-mail. Send
>your corrections to the manuscript editor named above.

>

>TO RESPOND BY TELEPHONE: If your changes require discussion or if you
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>Mediasupport@nejm.org <<mailto:Mediasupport@nejm.org>>.

>

>Thank you.

>

>

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From: [Laurencot, Elizabeth](#)
To: "Finer, Neil"
Cc: [Wally Carlo \(wcarlo@peds.uab.edu\)](#); [Rich, Wade](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#); [Gantz, Marie](#)
Subject: RE: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 9:13:44 AM

Dear Dr Finer,

I will start reviewing these replies this morning and will let you know if anything else needs more discussion.

Best,
Eli

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Tuesday, November 27, 2012 8:59 AM
To: Laurencot, Elizabeth
Cc: [Wally Carlo \(wcarlo@peds.uab.edu\)](#); [Rich, Wade](#); [Vaucher, Yvonne](#); [Rosemary Higgins](#); [Das, Abhik](#); [Gantz, Marie](#)
Subject: FW: Vaucher/Finer OA galleys

Hello Elizabeth
Here are our responses
I hope they are acceptable
Regards
Neil Finer

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

From: Laurencot, Elizabeth [<mailto:elaurencot@nejm.org>]
Sent: Wednesday, November 21, 2012 7:54 AM
To: Finer, Neil
Cc: [Rosemary Higgins](#); [Wally Carlo](#); [Abhik Das](#); [Marie Gantz](#); [Rich, Wade](#); [Vaucher, Yvonne](#)
Subject: RE: Vaucher/Finer OA galleys

Dear Dr Finer,

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If you could possibly respond to these items by noon on Tuesday, Nov 27, that would be most helpful.

Thank you, and I wish you a Happy Thanksgiving!

Best,
Elizabeth

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Monday, November 19, 2012 6:05 PM
To: Laurencot, Elizabeth
Cc: [Rosemary Higgins](#); [Wally Carlo](#); [Abhik Das](#); [Marie Gantz](#); [Rich, Wade](#); [Vaucher, Yvonne](#)
Subject: Re: Vaucher/Finer OA galleys

Importance: High

Hello Elizabeth

Please find attached our response to your queries for the proofs of the SUPPORT Neurodevelopmental Outcome paper.

I believe that we answered all the questions and corrected some errors that we discovered. Let me know if there are any further questions. Thanks for the opportunity to review the galleys. Be well. Neil Finer for all authors.

From: <Laurencot>, Elizabeth <elaurencot@nejm.org<mailto:elaurencot@nejm.org>>
Date: Friday, November 16, 2012 6:35 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Subject: FW: Vaucher/Finer OA galleys

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Thanks in advance.

Best,
Elizabeth

Elizabeth Laurençot
Manuscript Editor
New England Journal of Medicine
617-487-6547
elaurencot@nejm.org<mailto:elaurencot@nejm.org>

From: NEJM Galleys
Sent: Friday, November 16, 2012 9:31 AM
To: 'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'
Subject: Vaucher/Finer OA galleys

PLEASE DO NOT REPLY TO THIS E-MAIL

AUTHOR: Vaucher/Finer
MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<mailto:elaurencot@nejm.org>); 800-445-8080 or 617-734-9800

Please check the attached galley proofs of your article. It is important that we receive your changes by noon on Tuesday, November 20.

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From: [Finer, Neil](#)
To: [Wally Carlo, M.D.](#); [Stenson, Ben](#); "Val GebSKI"; [Schmidt, Barbara \(Neonatology\)](#); [Kylie Hunter](#); [Peter Graham Davis](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; [Brian Darlow](#); [Henry Halliday](#); [n.marlow@ucl.ac.uk](#); [Colin Morley](#); [Christian Poets](#); [John Simes](#); [Robin Whyte](#); [peter.brocklehurst@npeu.ox.ac.uk](#); [Lorrie Costantini](#); [adas@rti.org](#); [Lex Doyle](#); [Ed Juszczak](#); [Robin Roberts](#); [William Tarnow Mordj](#); [win.tin@stees.nhs.uk](#)
Cc: [Lisa Askie](#); [Jenny Chow](#); [Thalia Hambides](#)
Subject: RE: NeOProm meeting/teleconference - Hot Topics 2012
Date: Tuesday, November 27, 2012 9:11:05 AM

Ben's point is well taken

We have all the data in SUPPORT for on or off oxygen

Our analyses did include all time and then just on oxygen

For the NeoProm it will be important to determine if each study has the information to know when the infant was on or off oxygen.

Neil

From: [Wally Carlo, M.D. \[mailto:WCarlo@peds.uab.edu\]](mailto:WCarlo@peds.uab.edu)
Sent: Tuesday, November 27, 2012 4:14 AM
To: [Stenson, Ben](#); "Val GebSKI"; [Schmidt, Barbara \(Neonatology\)](#); [Kylie Hunter](#); [Peter Graham Davis](#); [Finer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; [Brian Darlow](#); [Henry Halliday](#); [n.marlow@ucl.ac.uk](#); [Colin Morley](#); [Christian Poets](#); [John Simes](#); [Robin Whyte](#); [peter.brocklehurst@npeu.ox.ac.uk](#); [Lorrie Costantini](#); [adas@rti.org](#); [Lex Doyle](#); [Ed Juszczak](#); [Robin Roberts](#); [William Tarnow Mordj](#); [win.tin@stees.nhs.uk](#)
Cc: [Lisa Askie](#); [Jenny Chow](#); [Thalia Hambides](#)
Subject: RE: NeOProm meeting/teleconference - Hot Topics 2012

I agree with Ben. We observed the same in SUPPORT. Our approach was to analyze saturations data and outcomes only while on oxygen supplementation.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: [Stenson, Ben \[mailto:Ben.Stenson@nhslothian.scot.nhs.uk\]](mailto:Ben.Stenson@nhslothian.scot.nhs.uk)
Sent: Tuesday, November 27, 2012 3:44 AM
To: "Val GebSKI"; [Schmidt, Barbara \(Neonatology\)](#); [Kylie Hunter](#); [Peter Graham Davis](#); [nfiner@ucsd.edu](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; [Brian Darlow](#); [Henry Halliday](#); [n.marlow@ucl.ac.uk](#); [Colin Morley](#); [Christian Poets](#); [John Simes](#); [Robin Whyte](#); [peter.brocklehurst@npeu.ox.ac.uk](#); [Wally Carlo, M.D.](#); [Lorrie Costantini](#); [adas@rti.org](#); [Lex Doyle](#); [Ed Juszczak](#); [Robin Roberts](#); [William Tarnow Mordj](#); [win.tin@stees.nhs.uk](#)
Cc: [Lisa Askie](#); [Jenny Chow](#); [Thalia Hambides](#)
Subject: RE: NeOProm meeting/teleconference - Hot Topics 2012

Dear Val

An analysis related to saturation patterns need to consider whether or not the infant was receiving supplemental oxygen at the time.

We may be interested in the relationship between both relative hyperoxia and relative hypoxia on outcomes.

If an infant is breathing air then high sats do not necessarily indicate likely hyperoxia. That is why we had the oxygen logs to determine when the infants were or were not receiving oxygen. An analysis confined to time breathing oxygen would be important.

Low sats are likely to be associated with relative hypoxia whether the infant was breathing air or supplemental oxygen. An analysis of all time on the intervention would also therefore be important.

Kind regards

Ben

From: Val GebSKI [mailto:Val@ctc.usyd.edu.au]

Sent: 26 November 2012 22:52

To: Schmidt, Barbara (Neonatology); Kylie Hunter; Peter Graham Davis; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Brian Darlow; Henry Halliday; n.marlow@ucl.ac.uk; Colin Morley; Christian Poets; John Simes; Robin Whyte; peter.brocklehurst@npeu.ox.ac.uk; WCarlo@peds.uab.edu; Lorrie Costantini; adas@rti.org; Lex Doyle; Ed Juszczak; Robin Roberts; Stenson, Ben; William Tarnow Mordi; win.tin@stees.nhs.uk

Cc: Lisa Askie; Jenny Chow; Thalia Hambides

Subject: RE: NeOProm meeting/teleconference - Hot Topics 2012

Hi Barbra ... we did not intend to discuss the SAP.

We just want to bend down if & how we should do an analysis adjusting for oxygen given - we may not be able to do this globally if we all haven't collected the oxygen saturation in a consistent manner. Your thoughts are most welcome

Kind regards

Val

Val GebSKI (hon)FRANZCR

Professor and Director, Biostatistics and Research Methodology

NHMRC Clinical Trials Centre, University of Sydney

Postal : Locked Bag 77, Camperdown NSW 1450, AUSTRALIA

Delivery : Level 5 Medical Foundation Building, 92-94 Parramatta Rd, Camperdown, NSW, 2050

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P: +61 (0) 2 9562 5000 (reception)

M: +61 (0) 412 309 967

F : +61 (0)2 9565 1863

E : val@ctc.usyd.edu.au

From: Schmidt, Barbara (Neonatology) [barbara.schmidt@uphs.upenn.edu]

Sent: Tuesday, 27 November 2012 9:27 AM

To: Kylie Hunter; Peter Graham Davis; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Brian Darlow; Henry Halliday; n.marlow@ucl.ac.uk; Colin Morley; Christian Poets; John Simes; Robin Whyte; peter.brocklehurst@npeu.ox.ac.uk; WCarlo@peds.uab.edu; Lorrie Costantini; adas@rti.org; Lex Doyle; Val GebSKI; Ed Juszczak; Robin Roberts; ben.stenson@luht.scot.nhs.uk; William Tarnow Mordi; win.tin@stees.nhs.uk

Cc: Lisa Askie; Jenny Chow; Thalia Hambides

Subject: RE: NeOProm meeting/teleconference - Hot Topics 2012

Thanks, Kylie. Just one immediate comment:

Since basically all of our trial statisticians will be unable to join this meeting – either in person or by phone – I suggest that we not table item # 3 on your agenda (Statistical Analysis Plan). We won't be able to have a meaningful discussion without our statistical colleagues.

Till Sunday
Barbara

From: Kylie Hunter [mailto:kylie.hunter@ctc.usyd.edu.au]
Sent: Monday, November 26, 2012 5:17 PM
To: 'Peter Graham Davis'; nfiner@ucsd.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; Schmidt, Barbara (Neonatology); 'Brian Darlow'; 'Henry Halliday'; 'n.marlow@ucl.ac.uk'; 'Colin Morley'; 'Christian Poets'; John Simes; 'Robin Whyte'; 'peter.brocklehurst@npeu.ox.ac.uk'; 'WCarlo@peds.uab.edu'; 'Lorrie Costantini'; 'adas@rti.org'; 'Lex Doyle'; Val Gebski; 'Ed Juszcak'; 'Robin Roberts'; 'ben.stenson@luht.scot.nhs.uk'; William Tarnow Mordi; 'win.tin@stees.nhs.uk'
Cc: Lisa Askie; Jenny Chow; Thalia Hambides
Subject: NeOProm meeting/teleconference - Hot Topics 2012

Dear NeOProm Collaborators,

In preparation for the NeOProm meeting/teleconference to be held in conjunction with Hot Topics, please find attached:

1. The agenda (including dial-in details for those joining by teleconference)
2. Minutes of previous meeting at PAS in April 2012
3. Update on trials
4. Latest draft of the statistical analysis plan
5. Weighted analysis document prepared by Val Gebski
6. International Teleconferencing Access Numbers (in case yours is not included in the agenda)

Date and time details of the meeting/teleconference are as follows:

Location	Date/Time
Washington DC, USA	Sun Dec 2, 3:30 – 4:45pm
Ontario, Canada	Sun Dec 2, 3:30 – 4:45pm
Nova Scotia, Canada	Sun Dec 2, 4:30 – 5:45pm
United Kingdom	Sun Dec 2, 8:30 – 9:45pm
Tuebingen, Germany	Sun Dec 2, 9:30 – 10:45pm
Sydney/Melbourne, Aus	Mon Dec 3, 7:30 – 8:45am
Christchurch, NZ	Mon Dec 3, 9:30 – 10:45am

Kind regards,
Kylie

KYLIE HUNTER | Systematic Reviews Project Officer

NHMRC Clinical Trials Centre

THE UNIVERSITY OF SYDNEY

L6 Medical Foundation Building | 92-94 Parramatta Rd | Camperdown | NSW | 2050

T +61 2 9562 5031 | F +61 2 9565 1863

E kylie.hunter@ctc.usyd.edu.au | W www.ctc.usyd.edu.au

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From: [Finer, Neil](mailto:Finer_Neil)
To: elaurencot@nejm.org
Cc: [Wally Carlo \(wcarlo@peds.uab.edu\)](mailto:wcarlo@peds.uab.edu); [Rich, Wade](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#); [Gantz, Marie](#)
Subject: FW: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 8:59:52 AM
Attachments: [Vaucher SUPPORT FU CPAP PAPER Reply to Editors Nov 21 2012.docx](#)

Hello Elizabeth
Here are our responses
I hope they are acceptable
Regards
Neil Finer

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

From: Laurencot, Elizabeth [<mailto:elaurencot@nejm.org>]
Sent: Wednesday, November 21, 2012 7:54 AM
To: Finer, Neil
Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade; Vaucher, Yvonne
Subject: RE: Vaucher/Finer OA galleys

Dear Dr Finer,

Many thanks for your clear replies and corrections on the galley proofs. There are several items that need additional discussion. Please see the attached file; my replies are in blue font.

If you could possibly respond to these items by noon on Tuesday, Nov 27, that would be most helpful.

Thank you, and I wish you a Happy Thanksgiving!

Best,
Elizabeth

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Monday, November 19, 2012 6:05 PM
To: Laurencot, Elizabeth
Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade; Vaucher, Yvonne
Subject: Re: Vaucher/Finer OA galleys
Importance: High

Hello Elizabeth

Please find attached our response to your queries for the proofs of the SUPPORT Neurodevelopmental Outcome paper.

I believe that we answered all the questions and corrected some errors that we discovered. Let me know if there are any further questions. Thanks for the opportunity to review the galleys. Be well. Neil Finer for all authors

From: <Laurencot>, Elizabeth <elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>>
Date: Friday, November 16, 2012 6:35 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>
Subject: FW: Vaucher/Finer OA galleys

Dear Dr Finer,

Attached is a copy of your galley proofs (identical to the copy just sent).

After you have reviewed the galleys, the fastest process is to send me an e-mail with answers to the numbered queries as well as any changes you have, and then we can go over anything that we still have questions about.

Please record your responses to all of the queries in a simple email or Word file and indicate changes as "Page 2, line 17, change 'xxxx' to 'yyyy'". (Please do not annotate the pdf file, which can be quite cumbersome on both ends.)

Please send me your corrections and responses to all the queries on the galley proofs by noon (US Eastern) on Tuesday, November 20. Please note that it is likely that I will be sending follow-up emails to you next Tuesday and Wednesday; please do let me know if you will not be available.

In the meantime, if you could please drop me a note confirming receipt of the galley proofs, that would be most helpful.

Thanks in advance.

Best,
Elizabeth

Elizabeth Laurençot
Manuscript Editor
New England Journal of Medicine
617-487-6547
elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>

From: NEJM Galleys
Sent: Friday, November 16, 2012 9:31 AM
To: 'nfiner@ucsd.edu'<<mailto:nfiner@ucsd.edu>>
Subject: Vaucher/Finer OA galleys

PLEASE DO NOT REPLY TO THIS E-MAIL

AUTHOR: Vaucher/Finer
MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>); 800-445-8080 or 617-734-9800

Please check the attached galley proofs of your article. It is important that we receive your changes by noon on Tuesday, November 20.

TO READ THE GALLEYS: You will need Adobe Acrobat Reader software (version 4.0 or later) to view these files. Acrobat Reader is available free of charge at the Adobe Web site (<http://www.adobe.com/products/acrobat/readermain.html>).

TO RESPOND BY E-MAIL: If your corrections and your responses to the queries are straightforward, we encourage you to respond by e-mail. Send your corrections to the manuscript editor named above.

TO RESPOND BY TELEPHONE: If your changes require discussion or if you have already made arrangements to go over your galleys by telephone, please call one of the numbers listed above; if you cannot reach your manuscript editor, ask to speak with another manuscript editor in the department. For calls from outside the United States, we will pay the telephone charges; have the operator bill us. Our switchboard is open Monday through Friday from 8:30 to 5:00 Eastern time.

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Bock, Robert \(NIH/NICHD\) \[E\]](#)
Subject: FW: Vaucher/Finer OA galleys
Date: Tuesday, November 27, 2012 8:23:00 AM
Attachments: [4Vauc_0a1208506.pdf](#)
[Response to NEJM for SUPPORT Follow up.docx](#)
Importance: High

Bob - Do you have a draft of the press release?? This may come out within the next 3-5 weeks.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, November 19, 2012 8:32 AM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: Vaucher/Finer OA galleys
Importance: High

Bob

Here are the penultimate galleys for the upcoming NEJM SUPPORT Follow Up paper - can you send me a draft of the press release?? I don't yet have a publication date but likely in the next 3-6 weeks.

Thanks for your help

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Sunday, November 18, 2012 9:40 PM
To: Finer, Neil; Vaucher, Yvonne; mperalta@peds.uab.edu; wcarlo@peds.uab.edu
Cc: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Vaucher/Finer OA galleys

Hi Everyone

Yvonne and I have gone through all your suggestions and corrected any other errors

Please review before I send back to editor and send me your OK or changes to the response MANY THANKS FOR ALL OF YOUR RAPID REPLIES' HAVE A GREAT THANKSGIVING Be well Neil and Yvonne

From: NEJM Galleys <NejmGalleys@mms.org<<mailto:NejmGalleys@mms.org>>>
Date: Friday, November 16, 2012 6:31 AM
To: Neil Finer <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>
Subject: Vaucher/Finer OA galleys

PLEASE DO NOT REPLY TO THIS E-MAIL

AUTHOR: Vaucher/Finer
MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>); 800-445-8080 or 617-734-9800

Please check the attached galley proofs of your article. It is important that we receive your changes by noon on Tuesday, November 20.

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TO RESPOND BY E-MAIL: If your corrections and your responses to the queries are straightforward, we encourage you to respond by e-mail. Send your corrections to the manuscript editor named above.

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: jripley@nejm.org
Cc: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Subject: FW: FW: Revised form - New England Journal of Medicine 12-08506.R2
Date: Monday, November 26, 2012 2:56:00 PM
Attachments: [PEvans - Change Authorship.pdf](#)

From Dr. Patricia Evans

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Patricia Evans [<mailto:pwildermd@gmail.com>]
Sent: Monday, November 26, 2012 2:53 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Revised form - New England Journal of Medicine 12-08506.R2

Please let me know if this is what you need.

All the best,

Patricia

On Mon, Nov 26, 2012 at 8:06 AM, Higgins, Rosemary (NIH/NICHD) [E]
<higginsr@mail.nih.gov> wrote:
Here you go
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
[301-435-7909](tel:3014357909)
[301-496-5575](tel:3014965575)
[301-496-3790](tel:3014963790) (FAX)
higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of
jripley@nejm.org

Sent: Tuesday, November 20, 2012 1:33 PM

To: nfiner@ucsd.edu

Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu;
michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org;
Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org;
kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org;
kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; drfjcmd@aol.com;
Patricia.W.Evans@uth.tmc.edu; gold005@mc.duke.edu; michael.acarregui@providence.org;
iadamsc@emory.edu; apappas@med.wayne.edu; schintz@stanford.edu; hpoindex@iupui.edu;
adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org;
richard.ehrenkranz@yale.edu; annabodnar.ab@gmail.com; cbauer@peds.med.miami.edu;
jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins,
Rosemary (NIH/NICHD) [E]; pandrhiggins@aol.com

Subject: Revised form - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

Dr. Higgins brought to my attention that the letter I sent had the wrong order of the authors. I have fixed this in the attached letter. Please use this one, and I apologize for the inconvenience if you've already sent a signed letter as you will have to send again.

Thank you,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

Jeffrey M. Drazen, MD
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School
10 Shattuck Street
Boston, MA 02115

RE: NEJM MS ID #12-08506

STATEMENT OF AUTHORSHIP CHANGE

We hereby allow a change in the order of authors for "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" from:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

to:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Gantz, Marie; Walsh, Michele; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

Sincerely,

Date: 11/26/2012

Printed Name: Patricia W. Evans

Signature: 

From: [Janell Fuller](#)
To: jripley@nejm.org
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Monday, November 26, 2012 2:32:40 PM
Attachments: [Fuller-author change NEJM.pdf](#)

Hello

Please find my change in authorship order page attached.

Janell

Janell Fuller, MD
Associate Professor of Pediatrics
Division Chief of Neonatology
Medical Director, Transport and Practitioner Services
University of New Mexico Children's Hospital
MSC10 5590
1 University of New Mexico
Albuquerque NM 87131-0001
505-272-6409
jafuller@salud.unm.edu

>>> <jripley@nejm.org> 11/20/2012 8:59 AM >>>

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

I have been notified that you would like to change the order of the authors of the above manuscript. Our Deputy Editor has approved the change, but we will also need documentation that each of you approve the change. I've attached a letter detailing this change; please review it to ensure the new author order is correct (or revise as necessary), and then each of you should sign it. You can each sign one letter, or if necessary you may return separate letters. The signed letter should be sent back to me via email or fax (781-207-6529). If you could attend to this promptly, we'd greatly appreciate it, as we do not want this to cause a delay in the publication of your manuscript.

Thank you!

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Ripley, Julie"
Subject: RE: Authorship change for SUPPORT paper
Date: Monday, November 26, 2012 12:19:00 PM

Julie

Can you let me know if you have received all of the forms? If you are missing any, let me know and I can try to get folks to send them to you.

Thanks for your help

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ripley, Julie [mailto:jripley@nejm.org]
Sent: Tuesday, November 20, 2012 3:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Authorship change for SUPPORT paper

Thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 20, 2012 2:30 PM
To: Ripley, Julie
Cc: Archer, Stephanie (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: Authorship change for SUPPORT paper

Julie – Here is my authorship letter with signature.

Thanks for your help

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: pwildermd@gmail.com
Subject: FW: Revised form - New England Journal of Medicine 12-08506.R2
Date: Monday, November 26, 2012 9:06:00 AM
Attachments: [FINER-change-of-authorship-form2.doc](#)

Here you go
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 1:33 PM
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu;
michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu;
roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu;
BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; drfjcmd@aol.com;
Patricia.W.Evans@uth.tmc.edu; gold005@mc.duke.edu; michael.acarregui@providence.org;
iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpointindex@iupui.edu;
adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu;
annabodnar.ab@gmail.com; cbauer@peds.med.miami.edu; jfuller@salud.unm.edu; moshea@wfubmc.edu;
gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; pandrhiggins@aol.com
Subject: Revised form - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

Dr. Higgins brought to my attention that the letter I sent had the wrong order of the authors. I have fixed this in the attached letter. Please use this one, and I apologize for the inconvenience if you've already sent a signed letter as you will have to send again.

Thank you,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115

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From: [Vaucher, Yvonne](mailto:Yvonne.Vaucher@ucsd.edu)
To: elaurencot@nejm.org
Cc: [Vaucher, Yvonne](mailto:Yvonne.Vaucher@ucsd.edu); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Rosemary.Higgins@nih.gov)
Subject: Re: Vaucher/Finer OA galleys
Date: Saturday, November 24, 2012 9:16:02 AM
Attachments: [YEv.jpg](#)

Dear Elizabeth,

Attached is my attestation concerning authorship.
Thanks for all your help.

Yvonne Vaucher

On 11/24/12 5:32 AM, "Vaucher, Yvonne" <yvaucher@ucsd.edu> wrote:

>

>

>On 11/21/12 7:54 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org> wrote:

>

>>Dear Dr Finer,

>>

>>Many thanks for your clear replies and corrections on the galley proofs.

>>There are several items that need additional discussion. Please see the

>>attached file; my replies are in blue font.

>>

>>If you could possibly respond to these items by noon on Tuesday, Nov 27,

>>that would be most helpful.

>>

>>Thank you, and I wish you a Happy Thanksgiving!

>>

>>Best,

>>Elizabeth

>>

>>

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

>>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]

>>Sent: Monday, November 19, 2012 6:05 PM

>>To: Laurencot, Elizabeth

>>Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade;

>>Vaucher, Yvonne

>>Subject: Re: Vaucher/Finer OA galleys

>>Importance: High

>>

>>Hello Elizabeth

>>Please find attached our response to your queries for the proofs of the

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>>I believe that we answered all the questions and corrected some errors

>>that we discovered Let me know if there are any further questions Thanks

>>for the opportunity to review the galleys Be well Neil Finer for all

>>authors

>>

>>

>>From: <Laurencot>, Elizabeth

>><elaurencot@nejm.org<mailto:elaurencot@nejm.org>>

>>Date: Friday, November 16, 2012 6:35 AM

>>To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>>Subject: FW: Vaucher/Finer OA galleys

>>

>>Dear Dr Finer,

>>

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>>sent).

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>>

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>>the galley proofs, that would be most helpful.

>>

>>Thanks in advance.

>>

>>Best,

>>Elizabeth

>>

>>Elizabeth Laurençot

>>Manuscript Editor

>>New England Journal of Medicine

>>617-487-6547

>>elaurencot@nejm.org<mailto:elaurencot@nejm.org>

>>

>>

>>From: NEJM Galleys

>>Sent: Friday, November 16, 2012 9:31 AM

>>To: 'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'

>>Subject: Vaucher/Finer OA galleys

>>

>>PLEASE DO NOT REPLY TO THIS E-MAIL

>>

>>AUTHOR: Vaucher/Finer

>>MANUSCRIPT EDITOR: Elizabeth Laurençot

>>(elaurencot@nejm.org<mailto:elaurencot@nejm.org>); 800-445-8080 or

>>617-734-9800

>>

>>Please check the attached galley proofs of your article. It is important
>>that we receive your changes by noon on Tuesday, November 20.
>>
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>>
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>>queries are straightforward, we encourage you to respond by e-mail. Send
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>>
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>>
>>Thank you.

>>
>>
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>>you.

>

Jeffrey M. Drazen, MD
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School
10 Shattuck Street
Boston, MA 02115

RE: NEJM MS ID #12-08506

STATEMENT OF AUTHORSHIP CHANGE

We hereby allow a change in the order of authors for "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" from:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

to:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Gantz, Marie; Walsh, Michele; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

Sincerely,

Date: 11/22/12

Printed Name: Yvonne Vaucher

Signature:

A handwritten signature in black ink, appearing to be 'Yvonne Vaucher', written over a horizontal line. The signature is stylized and cursive.

From: [Finer, Neil](#)
To: [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]
Cc: [Wally Carlo](#); [Das, Abhik](#); [Rich, Wade](#); [Vaucher, Yvonne](#)
Subject: RE: Vaucher/Finer OA galleys
Date: Friday, November 23, 2012 6:16:39 PM

Thanks Marie
Neil

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

From: Gantz, Marie [<mailto:mgantz@rti.org>]
Sent: Friday, November 23, 2012 12:39 PM
To: Finer, Neil; Rosemary Higgins
Cc: Wally Carlo; Das, Abhik; Rich, Wade; Vaucher, Yvonne
Subject: RE: Vaucher/Finer OA galleys

Neil, I agree with your responses. I am fine with saying eye findings "were as compared against normal." This was a multi-category variable and all categories were compared against the normal category. As you say, the "other abnormal findings" were those not specified in other categories.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Wednesday, November 21, 2012 10:01 PM
To: Rosemary Higgins
Cc: Wally Carlo; Das, Abhik; Gantz, Marie; Rich, Wade; Vaucher, Yvonne
Subject: RE: Vaucher/Finer OA galleys

Hi Everyone

I am on service for Thanksgiving week so I am late getting to this I have responded to these queries Please, if you have a chance - look these over and see if you agree Marie and Wally The comment about Eye findings "Findings were as compared against normal"

Are you OK with this

Can we say this differently

I assume we mean that these were other abnormal eye findings not specified in the previous categories

OK Have a Good Thanksgiving

Send me a note when you can if you agree to what I have written Neil

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

From: Laurencot, Elizabeth [<mailto:elaurencot@nejm.org>]
Sent: Wednesday, November 21, 2012 7:54 AM
To: Finer, Neil
Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade; Vaucher, Yvonne
Subject: RE: Vaucher/Finer OA galleys

Dear Dr Finer,

Many thanks for your clear replies and corrections on the galley proofs. There are several items that need additional discussion. Please see the attached file; my replies are in blue font.

If you could possibly respond to these items by noon on Tuesday, Nov 27, that would be most helpful.

Thank you, and I wish you a Happy Thanksgiving!

Best,
Elizabeth

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Monday, November 19, 2012 6:05 PM
To: Laurencot, Elizabeth
Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade; Vaucher, Yvonne
Subject: Re: Vaucher/Finer OA galleys
Importance: High

Hello Elizabeth

Please find attached our response to your queries for the proofs of the SUPPORT Neurodevelopmental Outcome paper.

I believe that we answered all the questions and corrected some errors that we discovered. Let me know if there are any further questions. Thanks for the opportunity to review the galleys. Be well. Neil Finer for all authors.

From: <Laurencot>, Elizabeth <elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>>
Date: Friday, November 16, 2012 6:35 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>
Subject: FW: Vaucher/Finer OA galleys

Dear Dr Finer,

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Elizabeth

Elizabeth Laurençot
Manuscript Editor
New England Journal of Medicine
617-487-6547

elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>

From: NEJM Galleys
Sent: Friday, November 16, 2012 9:31 AM
To: 'nfiner@ucsd.edu'<<mailto:nfiner@ucsd.edu>>
Subject: Vaucher/Finer OA galleys

PLEASE DO NOT REPLY TO THIS E-MAIL

AUTHOR: Vaucher/Finer
MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>); 800-445-8080 or 617-734-9800

Please check the attached galley proofs of your article. It is important that we receive your changes by noon on Tuesday, November 20.

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TO RESPOND BY E-MAIL: If your corrections and your responses to the queries are straightforward, we encourage you to respond by e-mail. Send your corrections to the manuscript editor named above.

TO RESPOND BY TELEPHONE: If your changes require discussion or if you have already made arrangements to go over your galleys by telephone, please call one of the numbers listed above; if you cannot reach your manuscript editor, ask to speak with another manuscript editor in the department. For calls from outside the United States, we will pay the telephone charges; have the operator bill us. Our switchboard is open Monday through Friday from 8:30 to 5:00 Eastern time.

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Thank you.

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From: [Finer, Neil](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Wally Carlo](#); [Abhik Das](#); [Marie Gantz](#); [Rich, Wade](#); [Vaucher, Yvonne](#)
Subject: RE: Vaucher/Finer OA galley
Date: Wednesday, November 21, 2012 10:01:30 PM
Attachments: [Vaucher SUPPORT FU CPAP PAPER Reply to Editors Nov 21 2012.docx](#)

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Please, if you have a chance - look these over and see if you agree
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Neil

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

From: Laurencot, Elizabeth [<mailto:elaurencot@nejm.org>]
Sent: Wednesday, November 21, 2012 7:54 AM
To: Finer, Neil
Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade; Vaucher, Yvonne
Subject: RE: Vaucher/Finer OA galley

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AUTHOR: Vaucher/Finer
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: Scan from a Xerox WorkCentre
Date: Wednesday, November 21, 2012 12:53:10 PM

Who knows! Just keep them in a file and I will check with Julie Ripley on monday for the missing ones.

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

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, November 21, 2012 12:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Scan from a Xerox WorkCentre

Thanks. I assume he faxed it to NEJM too?

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 21, 2012 12:43 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Scan from a Xerox WorkCentre

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

From: 4b07Xerox@mail.nih.gov [mailto:4b07Xerox@mail.nih.gov]
Sent: Wednesday, November 21, 2012 06:16 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Scan from a Xerox WorkCentre

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Device Name: B6100R4B07XEROX7665

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From: [Laurencot, Elizabeth](#)
To: "Finer, Neil"
Cc: [Higgins, Rosemary \(NIH/NICHD\) \(E\)](#); [Wally Carlo](#); [Abhik Das](#); [Marie Gantz](#); [Rich, Wade](#); [Vaucher, Yvonne](#)
Subject: RE: Vaucher/Finer OA galley
Date: Wednesday, November 21, 2012 10:54:17 AM
Attachments: [SUPPORT galley - ed reply.docx](#)

Dear Dr Finer,

Many thanks for your clear replies and corrections on the galley proofs. There are several items that need additional discussion. Please see the attached file; my replies are in blue font.

If you could possibly respond to these items by noon on Tuesday, Nov 27, that would be most helpful.

Thank you, and I wish you a Happy Thanksgiving!

Best,
Elizabeth

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Monday, November 19, 2012 6:05 PM
To: Laurencot, Elizabeth
Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade; Vaucher, Yvonne
Subject: Re: Vaucher/Finer OA galley
Importance: High

Hello Elizabeth

Please find attached our response to your queries for the proofs of the SUPPORT Neurodevelopmental Outcome paper.

I believe that we answered all the questions and corrected some errors that we discovered. Let me know if there are any further questions. Thanks for the opportunity to review the galley proofs. Be well, Neil Finer for all authors.

From: <Laurencot>, Elizabeth <elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>>
Date: Friday, November 16, 2012 6:35 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>
Subject: FW: Vaucher/Finer OA galley

Dear Dr Finer,

Attached is a copy of your galley proofs (identical to the copy just sent).

After you have reviewed the galley proofs, the fastest process is to send me an e-mail with answers to the numbered queries as well as any changes you have, and then we can go over anything that we still have questions about.

Please record your responses to all of the queries in a simple email or Word file and indicate changes as "Page 2, line 17, change 'xxxx' to 'yyyy'". (Please do not annotate the pdf file, which can be quite cumbersome on both ends.)

Please send me your corrections and responses to all the queries on the galley proofs by noon (US Eastern) on Tuesday, November 20. Please note that it is likely that I will be sending follow-up emails to you next Tuesday and Wednesday; please do let me know if you will not be available.

In the meantime, if you could please drop me a note confirming receipt of the galley proofs, that would be most

helpful.

Thanks in advance.

Best,
Elizabeth

Elizabeth Laurençot
Manuscript Editor
New England Journal of Medicine
617-487-6547
elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>

From: NEJM Galleys
Sent: Friday, November 16, 2012 9:31 AM
To: 'nfiner@ucsd.edu'<<mailto:nfiner@ucsd.edu>>
Subject: Vaucher/Finer OA galleys

PLEASE DO NOT REPLY TO THIS E-MAIL

AUTHOR: Vaucher/Finer
MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>); 800-445-8080 or 617-734-9800

Please check the attached galley proofs of your article. It is important that we receive your changes by noon on Tuesday, November 20.

TO READ THE GALLEYS: You will need Adobe Acrobat Reader software (version 4.0 or later) to view these files. Acrobat Reader is available free of charge at the Adobe Web site (<http://www.adobe.com/products/acrobat/readermain.html>).

TO RESPOND BY E-MAIL: If your corrections and your responses to the queries are straightforward, we encourage you to respond by e-mail. Send your corrections to the manuscript editor named above.

TO RESPOND BY TELEPHONE: If your changes require discussion or if you have already made arrangements to go over your galleys by telephone, please call one of the numbers listed above; if you cannot reach your manuscript editor, ask to speak with another manuscript editor in the department. For calls from outside the United States, we will pay the telephone charges; have the operator bill us. Our switchboard is open Monday through Friday from 8:30 to 5:00 Eastern time.

Please note that this material is confidential and embargoed until publication. If you have questions about our embargo policy, please contact NEJM Media Relations at 781-434-7847 or at Mediasupport@nejm.org<<mailto:Mediasupport@nejm.org>>.

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Page 1149 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 1150 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 1151 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]; "nfiner@ucsd.edu"; "richard.ehrenkranz@yale.edu"
Subject: Re: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Wednesday, November 21, 2012 8:42:11 AM

This should be ok as many folks are away.

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

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, November 21, 2012 08:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer (nfiner@ucsd.edu) <nfiner@ucsd.edu>
Subject: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2

FYI

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

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Tuesday, November 20, 2012 9:37 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Stephanie:

I am away this week-back in the office on Monday Nov 26th. I will fax it to the NEJM then.
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Tuesday, November 20, 2012 11:46 AM
To: 'Pappas, Athina'; nfiner@ucsd.edu; 'yvaucher@ucsd.edu'; 'mperalta@peds.uab.edu'; 'wcarlo@peds.uab.edu'; 'michele.walsh@cwru.edu'; 'mgantz@rti.org'; 'alaptook@wihri.org'; 'Bradley.yoder@hsc.utah.edu'; 'roger.faix@hsc.utah.edu'; 'adas@rti.org'; 'kurt.schibler@cchmc.org'; 'wrich@ucsd.edu'; 'nxs5@cwru.edu'; 'BVohr@wihri.org'; 'kimberly.yolton@cchmc.org'; 'roy.heyne@utsouthwestern.edu'; '(b)(6)@aol.com'; 'Patricia.W.Evans@uth.tmc.edu'; 'gold005@mc.duke.edu'; 'michael.acarregui@providence.org'; 'iadamsc@emory.edu'; Athina Pappas (apappas@med.wayne.edu); 'srhintz@stanford.edu'; 'bpoindex@iupui.edu'; 'adusick@pediatrics.wisc.edu'; 'emcgowan@tuftsmedicalcenter.org'; Ehrenkranz, Richard; '(b)(6)@gmail.com'; 'cbauer@peds.med.miami.edu'; 'jafuller@salud.unm.edu'; 'moshea@wfubmc.edu'; 'gary_myers@urmc.rochester.edu'; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

You should all have received the email below from NEJM about the SUPPORT FU paper. Please sign and fax/email the attached form to NEJM directly. Please also send a CC Rose and I so that we can keep track of whose

paperwork is still outstanding.

Thank you,

Stephanie

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

From: Pappas, Athina [mailto:apappas@med.wayne.edu]
Sent: Tuesday, November 20, 2012 11:42 AM
To: nfiner@ucsd.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2

Would you like us to sign individually and fax or e-mail to NEJM?

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 11:00 AM
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu;
mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org;
kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org;
roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu;
michael.acarregui@providence.org; iadamsc@emory.edu; Pappas, Athina; shintz@stanford.edu;
bpointex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org;
richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu;
moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; higginsr@mail.nih.gov; (b)(6)@aol.com
Subject: Change in authorship order - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

I have been notified that you would like to change the order of the authors of the above manuscript. Our Deputy Editor has approved the change, but we will also need documentation that each of you approve the change. I've attached a letter detailing this change; please review it to ensure the new author order is correct (or revise as necessary), and then each of you should sign it. You can each sign one letter, or if necessary you may return separate letters. The signed letter should be sent back to me via email or fax (781-207-6529). If you could attend to this promptly, we'd greatly appreciate it, as we do not want this to cause a delay in the publication of your manuscript.

Thank you!

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: Ripley, Julie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Authorship change for SUPPORT paper
Date: Tuesday, November 20, 2012 3:05:32 PM

Thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 20, 2012 2:30 PM
To: Ripley, Julie
Cc: Archer, Stephanie (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject: Authorship change for SUPPORT paper

Julie – Here is my authorship letter with signature.
Thanks for your help
Rose

This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: ["triplej@neim.org"](mailto:triplej@neim.org)
Cc: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); nfiner@ucsd.edu
Subject: Authorship change for SUPPORT paper
Date: Tuesday, November 20, 2012 2:29:00 PM
Attachments: [Scan001.PDF](#)

Julie – Here is my authorship letter with signature.
Thanks for your help
Rose

Jeffrey M. Drazen, MD
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School
10 Shattuck Street
Boston, MA 02115

RE: NEJM MS ID #12-08506

STATEMENT OF AUTHORSHIP CHANGE

We hereby allow a change in the order of authors for "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" from:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

to:

Vaucher, Yvonne; Peralta Carcelen, Myriam; Finer, Neil; Carlo, Waldemar; Gantz, Marie; Walsh, Michele; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

Sincerely,

Date:

11/20/2012

Printed Name:

Rosemary D. Higgins

Signature:

R Higgins

From: Ripley, Julie
To: "Gantz, Marie"
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Revised form - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 1:43:26 PM

Thanks!

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

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, November 20, 2012 1:43 PM
To: Ripley, Julie
Cc: higginsr@mail.nih.gov; archerst@mail.nih.gov
Subject: RE: Revised form - New England Journal of Medicine 12-08506.R2

Here is my signed letter.

Thanks,
Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 1:33 PM
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu;
michele.walsh@cwru.edu; Gantz, Marie; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu;
roger.faix@hsc.utah.edu; Das, Abhik; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu;
BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com;
Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org;
iadams@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu;
adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu;
(b)(6)@gmail.com; cbaucr@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu;
gary_myers@urmc.rochester.edu; higginsr@mail.nih.gov; (b)(6)@aol.com
Subject: Revised form - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

Dr. Higgins brought to my attention that the letter I sent had the wrong order of the authors. I have fixed this in the attached letter. Please use this one, and I apologize for the inconvenience if you've already sent a signed letter as you will have to send again.

Thank you,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Revised form - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 1:36:00 PM

Whew!!

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, November 20, 2012 1:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised form - New England Journal of Medicine 12-08506.R2

The order matches what I have in the boilerplate.

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 20, 2012 1:33 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Revised form - New England Journal of Medicine 12-08506.R2

Can you make sure she has it right??

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 1:33 PM
To: nfiner@ucsd.edu

Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu;
michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu;
roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu;
BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com;
Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org;
iadams@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu;
adusick@pediatrics.wisc.edu; emogowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu;
(b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu;
gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
Subject: Revised form - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

Dr. Higgins brought to my attention that the letter I sent had the wrong order of the authors. I have fixed this in the attached letter. Please use this one, and I apologize for the inconvenience if you've already sent a signed letter as you will have to send again.

Thank you,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: pwildermd@gmail.com
Subject: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 1:30:00 PM
Importance: High

FYI - look for a new letter with Yvonne listed as the first author

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 20, 2012 1:29 PM
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; [\[\(b\)\(6\)\]@aol.com](mailto:[(b)(6)]@aol.com); Patricia.W.Evans@uth.tmc.edu; gold005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpointex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; [\[\(b\)\(6\)\]@gmail.com](mailto:[(b)(6)]@gmail.com); cbauer@peds.med.miami.edu; jfuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; [\[\(b\)\(6\)\]@aol.com](mailto:[(b)(6)]@aol.com); Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2
Importance: High

Hi All,

I just talked to Julie Ripley who had put Neil as the first author in the letter for authorship[order change- Neil is third (he was listed as first as he is the corresponding author and the system at NEJM automatically listed him first).

A new letter is coming in your email from Julie - please print it out, sign and scan or fax back to NEJM.

Sorry for the trouble!!

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909

301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 11:00 AM
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu;
mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org;
kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org;
roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu;
michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu;
bpointex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org;
richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu;
moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E];
(b)(6)@aol.com
Subject: Change in authorship order - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

I have been notified that you would like to change the order of the authors of the above manuscript. Our Deputy Editor has approved the change, but we will also need documentation that each of you approve the change. I've attached a letter detailing this change; please review it to ensure the new author order is correct (or revise as necessary), and then each of you should sign it. You can each sign one letter, or if necessary you may return separate letters. The signed letter should be sent back to me via email or fax (781-207-6529). If you could attend to this promptly, we'd greatly appreciate it, as we do not want this to cause a delay in the publication of your manuscript.

Thank you!

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: Ripley, Julie
To: "Dr. Athina Pappas"
Cc: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 12:37:48 PM

Thanks!

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

From: Dr. Athina Pappas [mailto:apappas@med.wayne.edu]
Sent: Tuesday, November 20, 2012 12:18 PM
To: Ripley, Julie
Cc: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial.

Please see attached letter.

Kindest regards,

Athina Pappas, MD
Assistant Professor of Pediatrics
Neonatal-Perinatal Medicine
Director, Developmental Assessment Clinic, Children's Hospital of Michigan Wayne State University School of Medicine
Phone: 313-745-5638 Fax: 313-745-5867

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 11:00 AM
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; drfjcmd@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; annabodnar.ab@gmail.com; cbauer@peds.med.miami.edu; jfuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; higginsr@mail.nih.gov; pandrhiggins@aol.com
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Fax: (617) 739-9864
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From: Ripley, Julie
To: "Michael O'Shea"
Cc: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 12:09:22 PM

Thanks!

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

From: Michael O'Shea [mailto:moshea@wakehealth.edu]
Sent: Tuesday, November 20, 2012 11:50 AM
To: Ripley, Julie
Cc: archerst@mail.nih.gov; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Thank you.
It is attached.
Mike

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

From: Ripley, Julie [mailto:jripley@nejm.org]
Sent: Tuesday, November 20, 2012 11:35 AM
To: Michael O'Shea
Cc: nfiner@ucsd.edu
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Thanks; However, it needs to be signed in pen.

Best,
Julie

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

From: Michael O'Shea [mailto:moshea@wakehealth.edu]
Sent: Tuesday, November 20, 2012 11:11 AM
To: Ripley, Julie
Cc: nfiner@ucsd.edu
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2

Dear Ms. Ripley,

Attached please find the signed letter for T. Michael O'Shea

Thank you

Michael O'Shea, MD, MPH
Professor of Pediatrics
Wake Forest School of Medicine

phone (336)-716-4663
FAX (336)-716-2525
email moshea@wakehealth.edu

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com

[mailto:onbehalfofjripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org

Sent: Tuesday, November 20, 2012 11:00 AM

To: nfiner@ucsd.edu

Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.chrenkranz@yale.edu; (b)(6)@gmail.com; cbaucr@peds.med.miami.edu; jafuller@salud.unm.edu; Michael O'Shea; gary_myers@urmc.rochester.edu; higginsr@mail.nih.gov; (b)(6)@aol.com

Subject: Change in authorship order - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

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From: Rich, Wade
To: jripley@nejm.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 11:55:17 AM
Attachments: FINER-change-of-authorship-form (3).doc

Signature from Rich, W.

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 8:00 AM
To: Finer, Neil
Cc: Vaucher, Yvonne; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@echmc.org; Rich, Wade; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@echmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emegowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; higginsr@mail.nih.gov; (b)(6)@aol.com
Subject: Change in authorship order - New England Journal of Medicine 12-08506.R2

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer and Co-authors:

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Julie Ripley
Editorial Assistant

New England Journal of Medicine
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Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

Jeffrey M. Drazen, MD
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School
10 Shattuck Street
Boston, MA 02115

RE: NEJM MS ID #12-08506

STATEMENT OF AUTHORSHIP CHANGE

We hereby allow a change in the order of authors for "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" from:

Finer, Neil; Vaucher, Yvonne; Peralta Carcelen, Myriam; Carlo, Waldemar; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

to:

Finer, Neil; Vaucher, Yvonne; Peralta Carcelen, Myriam; Carlo, Waldemar; Gantz, Marie; Walsh, Michele; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Das, Abhik; Schibler, Kurt; Rich, Wade; Newman, Nancy; Vohr, Betty; Yolton, Kimberly; Heyne, Roy; Wilson-Costello, Deanne; Evans, Patricia; Goldstein, Ricki; Acarregui, Michael; Adams-Chapman, Ira; Pappas, Athina; Hintz, Susan; Poindexter, Brenda; Dusick, Anna; McGowan, Elisabeth; Ehrenkranz, Richard; Bodnar, Anna; Bauer, Charles; Fuller, Janell; O'Shea, T.; Myers, Gary; Higgins, Rosemary

Sincerely,

Date: 11/20/2012

Printed Name: Wade Rich

Signature:

A handwritten signature in black ink, appearing to read "Wade Rich", written over a white background.

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

Date:

Printed Name:

Signature:

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD)
To: "Susan Hintz"; das Das
Cc: [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer.Stephanie@NIH/NICHD); Jenna Gabrio; Kris Zaterka
Subject: RE: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 11:38:00 AM

Thanks for being so prompt!

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Susan Hintz [<mailto:srhintz@stanford.edu>]
Sent: Tuesday, November 20, 2012 11:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; das Das
Cc: Archer, Stephanie (NIH/NICHD) [E]; Jenna Gabrio; Kris Zaterka
Subject: Fwd: Change in authorship order - New England Journal of Medicine 12-08506.R2

Rose, Abhik, et al -

I have signed and returned the document below to the Fax as described in the body of the fax.

Let me know if you need it too

Susan

Begin forwarded message:

From: jripley@nejm.org
Date: November 20, 2012 7:59:36 AM PST
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu, mperalta@peds.uab.edu, wcarlo@peds.uab.edu,
michele.walsh@cwru.edu, mgantz@rti.org, alaptook@wihri.org,
Bradley.yoder@hsc.utah.edu, roger.faix@hsc.utah.edu, adas@rti.org,
kurt.schibler@cchmc.org, wrich@ucsd.edu, nxs5@cwru.edu,
BVohr@wihri.org, kimberly.yolton@cchmc.org,
roy.heyne@utsouthwestern.edu, [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com),
Patricia.W.Evans@uth.tmc.edu, gold005@mc.duke.edu,

michael.acarregui@providence.org, iadamsc@emory.edu,
apappas@med.wayne.edu, srhinz@stanford.edu, bpoindex@iupui.edu,
adusick@pediatrics.wisc.edu, emcgowan@tuftsmedicalcenter.org,
richard.ehrenkranz@yale.edu, (b)(6)@gmail.com,
cbauer@peds.med.miami.edu, jafuller@salud.unm.edu,
moshea@wfubmc.edu, gary_myers@urmc.rochester.edu,
higginsr@mail.nih.gov, (b)(6)@aol.com

**Subject: Change in authorship order - New England Journal of
Medicine 12-08506.R2**

Re: 12-08506.R2 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry
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Editorial Assistant

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(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: Ripley, Julie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: change of authorship form
Date: Tuesday, November 20, 2012 11:19:08 AM

Thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 20, 2012 11:18 AM
To: Ripley, Julie
Cc: nfiner@ucsd.edu; Archer, Stephanie (NIH/NICHD) [E]
Subject: change of authorship form

Julie – Here is my letter.

Thanks for your help
Rose Higgins

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: pwiklermd@gmail.com
Subject: FW: Change in authorship order - New England Journal of Medicine 12-08506.R2
Date: Tuesday, November 20, 2012 11:06:00 AM
Attachments: [FINER-change-of-authorship-form.doc](#)

Patricia

We re-ordered the NEJM authors - can you sign the attached letter and fax or email back asap??

Happy Thanksgiving - hope you are doing well.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[<mailto:mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com>] On Behalf Of jripley@nejm.org
Sent: Tuesday, November 20, 2012 11:00 AM
To: nfiner@ucsd.edu
Cc: yvaucher@ucsd.edu; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com); Patricia.W.Evans@uth.tmc.edu; gold05@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com); cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com)
Subject: Change in authorship order - New England Journal of Medicine 12-08506.R2

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Thank you!

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Editorial Assistant

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Fax: (617) 739-9864
<http://www.nejm.org>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"
Cc: Wally Carlo; Vaucher, Yvonne; Marie Gantz; Abhik Das; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Vaucher/Finer OA galleys
Date: Tuesday, November 20, 2012 10:12:00 AM
Attachments: Boilerplate, SUPPORT FU Combined paper, 2012-04-06.docx

This looks like the most recent one I can find -
Was this what went in to NEJM??

We can get everyone to send us a note stating they are ok with the authorship if needed.

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

CDBPM, NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]

Sent: Tuesday, November 20, 2012 10:07 AM

To: Higgins, Rosemary (NIH/NICHD) [E]

Cc: Wally Carlo; Vaucher, Yvonne; Marie Gantz; Abhik Das

Subject: FW: Vaucher/Finer OA galleys

Rose,

To my knowledge, we did not produce the actual list of authors, nor did we change it.

I cannot explain the order that was created in this submission Is that something that Stephanie does?

Do you want to poll all the authors to approve the change that we have recommended?

Thanks

Neil

On 11/20/12 5:44 AM, "Laurencot, Elizabeth" <elaurencot@nejm.org> wrote:

>Dear Dr Finer,

>

>Just a quick note regarding your first requested change:

>

>Any change to the author list requires the approval of the Deputy

>Editor for your article, as well as agreement from all authors. The

>DE's office will be in touch with you regarding obtaining that

>agreement. In the meantime, we will need to leave it as-is; we can make

>the change on the page proofs if necessary.

>

>Best,

>Elizabeth

>

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

>From: Finer, Neil [mailto:nfiner@ucsd.edu]

>Sent: Monday, November 19, 2012 6:05 PM

>To: Laurencot, Elizabeth

>Cc: Rosemary Higgins; Wally Carlo; Abhik Das; Marie Gantz; Rich, Wade;

>Vaucher, Yvonne

>Subject: Re: Vaucher/Finer OA galley

>Importance: High

>

>Hello Elizabeth

>Please find attached our response to your queries for the proofs of the

>SUPPORT Neurodevelopmental Outcome paper.

>I believe that we answered all the questions and corrected some errors

>that we discovered Let me know if there are any further questions

>Thanks for the opportunity to review the galley Be well Neil Finer for

>all authors

>

>

>From: <Laurencot>, Elizabeth

><elaurencot@nejm.org<mailto:elaurencot@nejm.org>>

>Date: Friday, November 16, 2012 6:35 AM

>To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>Subject: FW: Vaucher/Finer OA galley

>

>Dear Dr Finer,

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>Thanks in advance.

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>Best,

>Elizabeth

>

>Elizabeth Laurencot

>Manuscript Editor

>New England Journal of Medicine

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>elaurencot@nejm.org<mailto:elaurencot@nejm.org>

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>From: NEJM Galleys
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>To: 'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'
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>AUTHOR: Vaucher/Finer
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Outcome of extremely preterm infants in a trial to receive early CPAP vs. surfactant and two different oxygen saturation targets

Yvonne E. Vaucher, MD MPH^{1*}; Myriam Peralta-Carcelen, MD MPH^{2*}; Neil N. Finer, MD¹; Waldemar A. Carlo, MD²; Marie G. Gantz, PhD³; Michele C. Walsh, MD MS⁴; Abbot R. Laptook, MD⁵; Bradley A. Yoder, MD⁶; Roger G. Faix, MD⁶; Abhik Das, PhD⁷; Kurt Schibler, MD⁸; Wade Rich, RRT¹; Nancy S. Newman, RN⁴; Betty R. Vohr, MD⁵; Kimberly Yolton, PhD⁸; Roy J. Heyne, MD⁹; Deanne E. Wilson-Costello, MD⁴; Patricia W. Evans, MD¹⁰; Ricki F. Goldstein, MD¹¹; Michael J. Acarregui, MD¹²; Ira Adams-Chapman, MD¹³; Athina Pappas, MD¹⁴; Susan R. Hintz, MD MS Epi¹⁵; [REDACTED] Anna M. Dusick, MD FAAP¹⁶; Elisabeth C. McGowan, MD¹⁷; Richard A. Ehrenkranz, MD¹⁸; Anna Bodnar, MD⁶; Charles R. Bauer, MD¹⁹; Janell Fuller, MD²⁰; T. Michael O'Shea, MD MPH²¹; Gary J. Myers, MD²²; Rosemary D. Higgins, MD²³ for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Comment [swa1]: Center Authors start here

* Both authors contributed equally to this study.

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Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Comment [swa2]:
Recruitment: 2004-2009
FU: 2006-2011

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Subject: RE: Vaucher/Finer OA galleys
Date: Tuesday, November 20, 2012 8:08:05 AM

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "nfiner@ucsd.edu"
Subject: Re: Vaucher/Finer OA galleys
Date: Monday, November 19, 2012 5:40:41 PM

Yes, please

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, November 19, 2012 05:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Vaucher/Finer OA galleys

Rose

Did you want to acknowledge the support of NHLBI in this manuscript?- it was not indicated in the Appendix
Neil

On 11/19/12 7:42 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

>Yes
>Thanks
>Rose
>
>Rosemary D. Higgins, MD
>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research
>Network
>Pregnancy and Perinatology Branch
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>301-435-7909
>301-496-5575
>301-496-3790 (FAX)
>higginsr@mail.nih.gov

>

>

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

>>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>>Sent: Monday, November 19, 2012 10:29 AM
>>To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher,
>>Yvonne; Myriam Peralta, M.D.
>>Cc: Rich, Wade; adas@rti.org
>>Subject: Re: Vaucher/Finer OA galleys

>

>>Is everyone OK with Wally's suggestion?

>>Neil

>

>>On 11/19/12 7:17 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

>

>>All:

>>

>>I propose we change the last sentence on the paper to two sentences as follows:

>>

>>"It is important to weigh the mortality and neurodevelopmental outcomes at 18 to 22 months of corrected age when deciding on oxygen-saturation targets in extremely preterm infants. As mortality remained lower in the higher oxygen saturation group at the time of follow up and there were no adverse visual or neurodevelopmental problems, lower oxygen saturation targets cannot be recommended in these extremely preterm infants."

>>

>>The first sentence is modified from Dr. Drazen's sentence. The second is modified from what we had said initially.

>>

>>Wally

>>

>>Wally Carlo, M.D.

>>Edwin M. Dixon Professor of Pediatrics

>>University of Alabama at Birmingham

>>Director, Division of Neonatology

>>Director, Newborn Nurseries

>>1700 6th Avenue South

>>176F Suite 9380R

>>Birmingham, AL 35233-7335

>>Phone: 205 934 4680

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>>Cell: 205 (b)(6)

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>>

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

>>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

>>Sent: Monday, November 19, 2012 9:04 AM

>>To: Wally Carlo, M.D.; 'Finer, Neil'; Vaucher, Yvonne; Myriam Peralta, M.D.

>>Cc: Rich, Wade; adas@rti.org

>>Subject: RE: Vaucher/Finer OA galleys

>>

>>These are suggestions - we should say what we want and see what Dr.

>>Drazen says!!

>>

>>Rosemary D. Higgins, MD

>>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal

>>Research Network Pregnancy and Perinatology Branch CDBPM, NIH

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>>

>>

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

>>From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

>>Sent: Monday, November 19, 2012 9:20 AM

>>To: Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; Vaucher, Yvonne;

>>Myriam Peralta, M.D.

>>Cc: Rich, Wade; adas@rti.org

>>Subject: RE: Vaucher/Finer OA galleys

>>

>>Rose:

>>

>>Thanks for bringing this up.

>>

>>I am not so happy with the wording for the O2 saturations. I should
>>have raised the issue.

>>

>>We had said "However, as mortality remained lower in the higher oxygen
>>saturation group at the time of follow up and there were no adverse
>>visual or neurodevelopmental problems, lower oxygen saturation targets
>>cannot be recommended in these extremely preterm infants."

>>

>>The message now is so much softer even though this is the most
>>important effect we found on long term outcomes.

>>

>>It says now "It is important to weigh the lower mortality and similar
>>rates of neurodevelopmental impairment and major adverse visual
>>outcomes at 18 to 22 months of corrected age in the higher-oxygen
>>saturation group, as compared with the lower oxygen-saturation group,
>>when deciding on oxygen-saturation targets in extremely preterm infants."

>>

>>We could change it to: "It is important to weigh the mortality and
>>neurodevelopmental outcomes at 18 to 22 months of corrected age when
>>deciding on oxygen-saturation targets in extremely preterm infants. As
>>mortality remained lower in the higher oxygen saturation group at the
>>time of follow up and there were no adverse visual or
>>neurodevelopmental problems, lower oxygen saturation targets cannot be
>>recommended in these extremely preterm infants."

>>

>>Wally

>>

>>

>>

>>Wally Carlo, M.D.

>>Edwin M. Dixon Professor of Pediatrics

>>University of Alabama at Birmingham

>>Director, Division of Neonatology

>>Director, Newborn Nurseries

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>>

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

>>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

>>Sent: Monday, November 19, 2012 7:31 AM

>>To: 'Finer, Neil'; Vaucher, Yvonne; Myriam Peralta, M.D.; Wally Carlo,
>>M.D.

>>Cc: Rich, Wade; Abhik Das (adas@rti.org)

>>Subject: RE: Vaucher/Finer OA galleys

>>
>>Neil and everyone - sorry for the delay as I had trouble accessing
>>files while travelling- I am fine with all of the changes - Is everyone
>>ok with Dr. Drazen's final statement in the discussion regarding choice
>>of dsaturation targets??
>>
>>Also - can we get the supplementary appendix that will be posted on
>>line
>>- we need to make sure that this is accurate as well.
>>
>>Thanks to everyone and congratulations!!
>>Do we have a publication date as of yet?
>>
>>Rose
>>
>>Rosemary D. Higgins, MD
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>>-----Original Message-----
>>From: Finer, Neil [mailto:nfiner@ucsd.edu]
>>Sent: Sunday, November 18, 2012 9:40 PM
>>To: Finer, Neil; Vaucher, Yvonne; mperalta@peds.uab.edu;
>>wcarlo@peds.uab.edu
>>Cc: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
>>Subject: FW: Vaucher/Finer OA galleys
>>
>>Hi Everyone
>>Yvonne and I have gone through all your suggestions and corrected any
>>other errors
>>
>>Please review before I send back to editor and send me your OK or
>>changes to the response MANY THANKS FOR ALL OF YOUR RAPID REPLIES' HAVE
>>A GREAT THANKSGIVING Be well Neil and Yvonne
>>
>>From: NEJM Galleys <NejmGalleys@mms.org<mailto:NejmGalleys@mms.org>>
>>Date: Friday, November 16, 2012 6:31 AM
>>To: Neil Finer <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
>>Subject: Vaucher/Finer OA galleys
>>
>>PLEASE DO NOT REPLY TO THIS E-MAIL
>>
>>AUTHOR: Vaucher/Finer
>>MANUSCRIPT EDITOR: Elizabeth Laurençot
>>(elaurencot@nejm.org<mailto:elaurencot@nejm.org>); 800-445-8080 or
>>617-734-9800
>>
>>Please check the attached galley proofs of your article. It is
>>important that we receive your changes by noon on Tuesday, November 20.

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Cc: nfiner@ucsd.edu
Subject: SUPPORT Publications
Date: Monday, November 19, 2012 2:35:00 PM

Stephanie

Can you send Neil and I a complete list of all published SUPPORT papers? The NEOPROM folks would like this for an update. Please do NOT include the main FU paper as that is under NEJM embargo.

Thanks

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Jean Lowe (jlowe@salud.unm.edu)
Subject: FW: Object permanence manuscript
Date: Monday, November 19, 2012 11:08:00 AM
Attachments: Lowe Early working memory SUPPORT CB JL 111512.docx

Steph - did this go through clearance?

If so, it can be submitted. I checked with Bill Truog and he said that the reviews are done.

Thanks

Rose

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

From: (b)(6)@gmail.com [mailto:(b)(6)@gmail.com] On Behalf Of Jean Lowe
Sent: Friday, November 16, 2012 12:31 AM
To: Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]; Carla M. Bann; Kristi Watterberg; Andrea Duncan; Janell Fuller
Subject: Object permanence manuscript

Hi

After a month of waiting I got back one review. I incorporated those suggestions and others from the co-authors and hope to submit next week to Journal of Pediatrics.

I am attaching the revised manuscript.

Please can you get this back to me by Monday so I can submit before Thanksgiving holidays.

Thanks

Jean

--

Jean Lowe Ph.D.
Developmental Specialist
Associate Professor

505-(b)(6) cell
505-272-3946 office
jrlowe@unm.edu

>>

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Early working memory as a racially and ethnically neutral measure of outcome in extremely preterm children at 18-22 months

Jean R. Lowe, PhD¹; Andrea Freeman Duncan, MD¹; Carla M. Bann, PhD²; Janell Fuller, MD¹; Susan R. Hintz, MD MS Epi³; Abhik Das, PhD⁴; Rosemary D. Higgins, MD⁵ Kristi L. Watterberg, MD¹ for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Reprint Requests: Please address reprint requests to Jean Lowe Ph.D.

Disclosures: The coauthors have no conflicts of interests relevant to this manuscript.

Running Title: Early working memory in preterm

Key Words: Working memory, prematurity, development

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⁵ *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD

ABSTRACT

Objective

This study evaluated the relationship of early working memory as measured by object permanence test items to the cognitive and language scores on the BSID-III at 18-22 months corrected age in a large cohort of children born extremely preterm.

Study Design

Extremely preterm toddlers (540) who were part of the NICHD Neonatal Research Network SUPPORT multi-center study were evaluated at 18-22 months corrected age. Logistic regression models were conducted to compare object permanence scores derived from the Bayley Developmental Scales by race/ethnicity and maternal education, controlling for medical covariates.

Results

There were no significant differences in object permanence mastery and scores among the treatment groups after controlling for medical and social variables, including maternal education and race/ethnicity. Males and children with ROP and BPD were less likely to demonstrate object permanence mastery and had lower object permanence scores. Children who attained object permanence mastery had significantly higher BSID-III cognitive and language scores after controlling for medical and socio-economic factors.

Conclusions

Our measure of object permanence is free of influence from race, ethnic and socio-economic factors. Adding this simple task to our current clinical practice would allow us to detect early executive function difficulties in young children.

INTRODUCTION

Executive function is a critical element of neurodevelopment in humans, and encompasses working memory, inhibition, and cognitive flexibility^{1,2}. Difficulties with executive function have been found in infants born preterm as early as 8 to 18 months, independent of maternal education and cognitive skills³. Early working memory, an integral component of executive function, requires the ability to selectively attend to information that is important while simultaneously inhibiting interfering information, and mediates a wide range of activities requiring reasoning and planning⁴. Woodward et al (2005) found that 2-year-olds born preterm had more problems encoding new information into working memory, than term infants⁵. Children born extremely preterm continue to exhibit difficulties in cognition, inhibition, and perceptual-motor skills in kindergarten compared to peers born full term⁶. Difficulty with executive function persists into school age, especially in the areas of response inhibition, planning, and verbal and spatial working memory skills^{7,8,9,10}. The Bayley Scales of Infant and Toddler Development^{11,12,13} are used to determine cognitive function in extremely preterm children prior to the age of 42 months, though these scores have been found to be poor predictors of school-age function¹⁴. We have previously reported differences among racial/ethnic groups on the Bayley Scales of Infant and Toddler Development –II¹² not explained by socioeconomic status or maternal education¹⁵, with white children having significantly higher mental developmental index than Hispanic or Black children. However, we found that measures of object permanence were similar among these groups as well as across income levels¹⁵, suggesting that object permanence may be a culturally neutral measure of early executive function.

The objective of the current study was to evaluate the relationship of early working memory as measured by object permanence test items to the cognitive and language scores on the BSID-III in a large cohort of children born extremely preterm at 18-22 months corrected age who had been enrolled in an randomized, multicenter trial in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN). We hypothesized that object permanence would not be affected by maternal education or race/ethnicity, in contrast to BSID-III cognitive and language scores and that object permanence scores would correlate significantly with performance on the BSID-III cognitive and language scores.

METHODS

Study Population

All children in this prospective cohort study of object permanence had been enrolled in the Neuroimaging and Neurodevelopmental Outcome (NEURO) secondary study to the NICHD Neonatal Research Network (NRN) Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) multi-center study^{16,17}. The SUPPORT study was a randomized, multicenter, 2x2 factorial trial of oxygenation (lower vs. higher oxygenation saturation target range) and ventilation (CPAP vs. intubation and surfactant) management strategies beginning in the delivery room among 24 to 27+6/7 week estimated gestational age infants. All surviving infants in the SUPPORT study had a comprehensive neurodevelopmental follow-up visit at 18-22 months of age corrected for prematurity^{16,17}. Object permanence scores were performed and reported only for those children enrolled in this secondary study who were born between June 2005 to February 2009 in one of 15 participating centers of the NRN, across the United States. Ethnicity/race were obtained by maternal self report.

Test Measures

The Bayley Scales of Infant and Toddler Development – 3rd edition¹³ (BSID-III) were administered between 18 and 22 months, age adjusted for prematurity. The cognitive and language scales were used for this study (mean 100, standard deviation 15). Within the cognitive scale, three items (#'s 40, 45 and 50) were used as measures of object permanence. The items sequentially increased in difficulty and were each worth 1 point. First, the child was asked to find a toy hidden under one of two cups (item 40). Second, double visual displacement was used as the toy was hidden under one cup, removed and hidden a second time under the second cup (item 45). Third, the cups were reversed after the toy was hidden (item 50). Object permanence score was defined as the number of items correctly completed (ordinal measure). Object permanence mastery was defined as a score of ≥ 2 (categorical measure).

Statistical Analyses

Because the object permanence score is an ordinal measure (i.e., number of items correctly completed), Poisson regression models with generalized estimating equations were conducted to compare object permanence scores between children in different racial/ethnic groups and maternal education levels after controlling for SUPPORT randomized treatment group, NRN center, and clinically relevant covariates (gender, gestational age, multiple gestations, intraventricular hemorrhage grade III or IV or cystic periventricular leukomalacia based on sonogram (IVH/cPVL), any type of retinopathy of prematurity diagnosed in either eye and bronchopulmonary dysplasia (defined as infants receiving supplemental oxygen by any means at 36 weeks gestational age are considered by default to have BPD). Similar logistic regression models were conducted to compare object permanence mastery by race/ethnicity and maternal education.

controlling for treatment group, center, and medical covariates. It might be helpful if the categories of race/ethnicity and categories of maternal education were presented. Comparable linear regression models were then conducted to examine the relationship between object permanence and BSID-III scores, after accounting for covariates. More detailed definitions of the medical covariates were provided previously in SUPPORT trial studies^{16,17}. All analyses were conducted using SAS version 9.3 statistical software and performed by the Data Coordinating Center (RTI International).

RESULTS

Selected demographic and medical characteristics of the 540 children in this study are shown in Table 1. The percentage of children demonstrating object permanence and the mean object permanence scores by demographic and medical characteristics are shown in Table 2. In the bivariate comparisons, males and children with ROP were less likely to demonstrate object permanence mastery and had lower object permanence scores. In addition those in the lower gestational age strata (24-25 weeks vs. 26-27 weeks) had lower object permanence scores.

There were no significant differences in object permanence mastery and scores among the treatment groups after controlling for medical and social variables (Table 3). There were also no significant differences in object permanence mastery and scores by gestational age, IVH III-IV/cPVL, maternal education or race/ethnicity after controlling for other medical and social factors. Similar to findings in the bivariate model significant differences were found for male gender and ROP, even after accounting for other factors. In addition those children diagnosed with BPD had significantly lower object permanence mastery and scores when controlling for other factors.

The overall mean (SD) BSID-III scores were 91.89 (14.20) for the cognitive composite and 86.38 (16.22) for the language composite. Children who attained object permanence mastery had significantly higher BSID-III cognitive and language scores after controlling for both medical and socio-economic factors (Table 4). Cognitive scores were almost 12 points higher and language scores nearly 9 points higher among those with object permanence mastery, adjusted for multiple confounders including maternal education and race/ethnicity. Children who were male and had IVH III-IV/cPVL or BPD had significantly lower cognitive composite scores (Table 4). Children of mothers with high school education or less had significantly lower BSID-III language scores than those whose mothers had some college education or more. Boys and Hispanic children scored significantly lower on the language scale.

Results found in the models using object permanence score rather than object permanence mastery were comparable (Table 5). Higher object permanence score was associated with higher cognitive and language composite scores ($p < 0.001$). Boys and children with IVH III-IV/cPVL, ROP, or BPD had significantly lower object permanence scores. Boys, children with IVH III-IV/cPVL or BPD, and those who were Hispanic or had mothers with lower educations had significantly lower language composite scores. Model-adjusted mean BSID-III cognitive and language scores for each possible object permanence score are shown in Figure 1.

DISCUSSION

In this prospective, multicenter study we found that object permanence as a measure of early working memory was significantly related to measures of cognition and language, but not associated with race/ethnicity or maternal education. This confirms our previous findings in regards to object permanence and cognition as measured by the BSID-II¹⁸, and provides

additional evidence that object permanence is a culturally neutral measure of early working memory. This is an important finding, as tests of cognition are influenced by race/ethnicity¹⁹, maternal education and parental stress²⁰. The controversy related to biases inherent in measures of intelligence, especially related to race/ethnic factors, is not new²¹ but we continue to use them as the main measure of morbidity and indicator of improvement in medical care.

Interest in studying executive functioning including early working memory, inhibition and reasoning have been increasing over the past decade⁹; however, these skills are difficult to measure in young children²². We used object permanence, a skill described by Piaget²³ as one of the earliest measures of early working memory²⁴, a skill that is related to early white matter injury⁵ and development of dorsolateral prefrontal regions²⁵. Our finding that object permanence was associated with cognition and language scores on the BSID-III indicates that it could potentially augment research by providing an additional measure of development that is potentially free of socio-economic and racial/ethnic biases¹⁸. Better understanding of early executive functioning in extremely preterm children could lead to earlier diagnosis and improved interventions for children born preterm. In conjunction with the BSID-III cognitive score, a measure of object permanence may improve our detection of ongoing problems with executive function at 18–22 months, which is highly related to learning difficulties later in life. Early childhood intervention results in significant improvements in cognitive, academic, and social outcomes²⁶, and tasks that specifically work on early working memory can be developed to potentially enhance executive functioning skills in young children²⁷.

A limitation of this study is that the object permanence items used were selected from the cognitive scale of the BSID-III. Since we also administered the BSID-III Cognitive scale in the study, using these items in both measures could result in a degree of correlation between the

scales. However, our findings for object permanence were significantly different from the BSID-III cognitive scale when race/ethnicity was taken into account. We also found that children with ROP and BPD had significantly lower object permanence scores. This is possibly a marker of illness severity and should be explored in future studies. Another limitation of this study is that this cohort may not be representative sample of ELBW infants and therefore caution should be used in generalizing these findings²⁸. A strength of our study was the utilization of the NICHD NRN, which includes a large number of children from a variety of race, ethnic and socio-economic backgrounds.

In conclusion, our study supports the hypothesis that our measure of object permanence is free of influence from race, ethnic and socio-economic factors. We suggest that this can be used to detect early deficits in working memory in children born extremely low birth weight. Adding this simple task to our current clinical practice would allow us to detect early executive function difficulties in young children. Further investigation of ways to identify specific intervention techniques to enhance early executive skills would be beneficial.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Carla Bann (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chair: Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RN BSN; Bonnie E. Stephens, MD; Barbara Alksninis, PNP; Dawn Andrews, RN; Kristen Angela, RN; Susan Barnett, RRT; Bill Cashore, MD; Melinda Caskey, MD; Kim Francis, RN; Dan Gingras,

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Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Sandra Grimes, RN BSN; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Marie G. Gantz, PhD; Jamie E. Newman, PhD MPH; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University, Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MSED; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Rene Barbieri-Welge; Ayala Ben-Tall; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Elaine Ito; Meghan Lukasik; Wade Rich, RRT; Deborah Pontillo; Donna Posin, OTR/L MPA; Cheryl Runyan; James Wilkes; Paul Zlotnik.

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Rebecca Montman, BSN.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Luc P. Brion, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, BSN RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Esther G. Akpa, RN BSN; Nora I. Alaniz, BS; Susan Dieterich, PhD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Roger G. Faix, MD; Bradley A.

Yoder, MD; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

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Table 1. Sample Characteristics

Characteristic	N (%)
Ventilation	
Early Extubation and CPAP	268 (50)
Early Surfactant and Ventilation	272 (50)
Oxygen level	
High target SpO2 (91-95%)	283 (52)
Low target SpO2 (85-89%)	257 (48)
Gestational age...mean (SD)	26 (1)
Birth weight...mean (SD)	854 (191)
Male	303 (56)

IVH III-IV/cPVL	75 (14)
ROP	62 (12)
BPD	199 (37)
Education	
Less than high school	130 (25)
High school graduate	156 (29)
Some college or more	243 (46)
Race/Ethnicity	
Black, non-Hispanic	170 (31)
White, non-Hispanic	234 (43)
Hispanic—how were white	118 (22)
Hispanic and Black Hispanic classified?	
Other/Unknown	18 (3)

Note: N=540. Were all infants testable? How many missing cases? How were they handled?

Comment [CB1]: Anyone who was Hispanic was classified as Hispanic regardless of how they specified their race

Comment [CB2]: Among the children for whom we have the object permanence form, 10 children were missing 1 of the 3 object permanence items and 1 child was missing 2 of the items. We used the sum of the available items to compute the object permanence score.

Table 2. Mean Object Permanence Scores and Percentages of Study Children with Object Permanence Mastery by Treatment and Demographic Characteristics

Characteristic	Object permanence mastery		Object permanence scores	
	N (%)	p	Mean (SD)	P
Ventilation				
Early Extubation and CPAP	170 (63)	0.755	1.88 (1.14)	0.516
Early Surfactant and Ventilation	169 (62)		1.82 (1.16)	
Oxygen level				
High target SpO2 (91-95%)	180 (64)	0.677	1.86 (1.18)	0.827
Low target SpO2 (85-89%)	159 (62)		1.84 (1.13)	
Gestational age				
24-25 weeks	119 (58)	0.096	1.72 (1.16)	0.032
26-27 weeks	220 (65)		1.93 (1.14)	
Gender				
Male	177 (58)	0.018	1.76 (1.14)	0.041
Female	162 (68)		1.97 (1.16)	
IVH III-IV/cPVL				
Yes	43 (57)	0.300	1.64 (1.23)	0.089
No	295 (64)		1.88 (1.14)	
ROP				
Yes	27 (44)	0.002	1.45 (1.15)	0.005
No	284 (64)		1.89 (1.15)	
BPD				
Yes	116 (58)	0.099	1.73 (1.18)	0.057
No	223 (65)		1.92 (1.13)	
Education				
Less than high school	88 (68)	0.313	1.92 (1.17)	0.671
High school graduate	92 (59)		1.80 (1.21)	
Some college or more	154 (63)		1.86 (1.10)	
Race/Ethnicity				
Black	104 (61)	0.745	1.85 (1.13)	0.368
White	153 (65)		1.70 (1.20)	
Hispanic	71 (60)		1.78 (1.22)	
Other/Unknown	11 (61)		1.93 (1.14)	

Note: N=540

Table 3. Regression Models of Object Permanence Mastery and Scores

Characteristic	Object Permanence Mastery		Object Permanence Score	
	OR (95% CI)	p	Adjusted mean difference (SE)	p
Ventilation				
Early Extubation and CPAP	0.95 (0.62, 1.47)	0.812	0.02 (0.05)	0.669
Early Surfactant and Ventilation	REF		REF	
Oxygen level				
High target SpO2 (91-95%)	1.21 (0.78, 1.87)	0.390	0.06 (0.05)	0.244
Low target SpO2 (85-89%)	REF		REF	
Gestational age	0.95 (0.76, 1.18)	0.622	-0.01 (0.03)	0.783
Male	0.56 (0.36, 0.87)	0.011	-0.15 (0.05)	0.005
IVH III-IV/cPVL	0.76 (0.41, 1.42)	0.384	-0.15 (0.11)	0.154
ROP	0.37 (0.18, 0.76)	0.008	-0.25 (0.13)	0.050
BPD	0.59 (0.36, 0.98)	0.042	-0.15 (0.07)	0.028
Education				
Less than high school	1.21 (0.67, 2.16)	0.522	0.03 (0.07)	0.645
High school	0.87 (0.52, 1.46)	0.592	-0.01 (0.06)	0.928
Some college or more	REF		REF	
Race/Ethnicity				
Black	0.83 (0.47, 1.46)	0.505	-0.03 (0.07)	0.613
White	REF		REF	
Hispanic	1.57 (0.79, 3.12)	0.190	0.04 (0.08)	0.601
Other/Unknown	1.45 (0.41, 5.12)	0.558	0.05 (0.14)	0.690

Note: REF=reference category. N=529 for both models. ~~Can this sentence be deleted, since you do mention center in next line. Models also control for research center.~~ Odds ratios and regression coefficients are adjusted for research-center, ventilation type, oxygen level, gestational age, gender, IVH III-IV/cPVL, ROP, BPD, maternal education, and race/ethnicity.

Comment [CB3]: That makes sense.

Table 4. Regression Models of Bayley III Cognitive and Language Composite Scores by Object Permanence Mastery, Treatment Group and Demographic Characteristics

Characteristic	Cognitive Composite		Language Composite	
	Coefficient (SE)	p	(SE)	P
Object Permanence Mastery	11.70 (1.08)	< 0.001	8.56 (1.43)	< 0.001
Ventilation				
Early Extubation and CPAP	1.56 (1.04)	0.141	0.70 (1.35)	0.608
Early Surfactant and Ventilation	REF			
Oxygen level				
High target SpO2 (91-95%)	-0.15 (1.05)	0.884	0.11 (1.37)	0.939
Low target SpO2 (85-89%)	REF			
Gestational age	0.36 (0.54)	0.505	0.89 (0.70)	0.211
Male	-3.10 (1.00)	0.004	-4.47 (1.33)	0.002
IVH III-IV/cPVL	-5.35 (1.44)	< 0.001	-1.47 (1.89)	0.443
ROP	-3.30 (1.70)	0.059	-3.39 (2.23)	0.136
BPD	-4.42 (1.17)	< 0.001	-3.73 (1.55)	0.020
Education				
Less than high school	-1.77 (1.39)	0.210	-5.43 (1.81)	0.005
High school	-2.09 (1.24)	0.100	-4.00 (1.62)	0.017
Some college or more	REF			
Race/Ethnicity				
Black	-0.69 (1.36)	0.615	-1.96 (1.78)	0.276
White	REF			
Hispanic	-1.12 (1.63)	0.494	-6.19 (2.13)	0.006
Other/Unknown	-1.61 (2.98)	0.592	-1.10 (4.01)	0.784

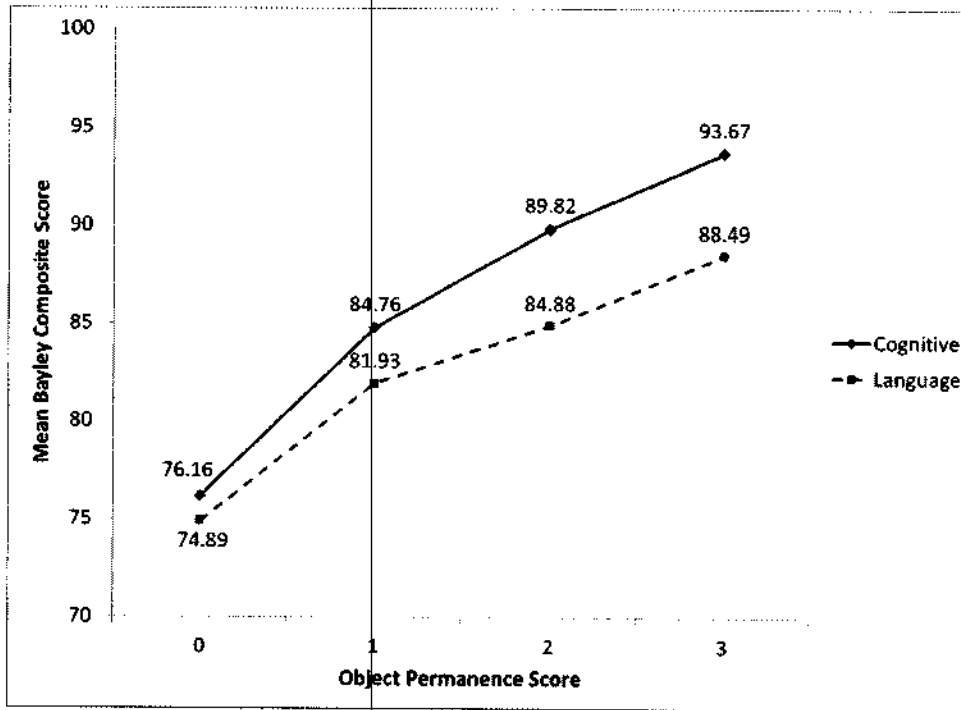
Note: REF=reference category. N=525 for cognitive composite model and N=517 for language composite model. Models also control for research center. Regression coefficients are adjusted for research center, object permanence mastery, ventilation type, oxygen level, gestational age, gender, IVH III-IV/cPVL, ROP, BPD, maternal education, and race/ethnicity.

Table 5. Regression Models of Bayley III Cognitive and Language Composite Scores by Object Permanence Score, Treatment Group and Demographic Characteristics

Characteristic	Cognitive Composite		Language Composite	
	Adjusted mean difference (SE)	p	Adjusted mean difference (SE)	P
Object Permanence Score	5.60 (0.44)	< 0.001	4.28 (0.60)	< 0.001
Ventilation				
Early Extubation and CPAP	1.27 (1.00)	0.212	0.50 (1.32)	0.707
Early Surfactant and Ventilation	REF		REF	
Oxygen level				
High target SpO2 (91-95%)	-0.05 (1.01)	0.960	0.11 (1.34)	0.932
Low target SpO2 (85-89%)	REF		REF	
Gestational age	0.29 (0.52)	0.580	0.85 (0.69)	0.225
Male	-3.14 (0.97)	0.002	-4.43 (1.30)	0.002
IVH III-IV/cPVL	-4.35 (1.39)	0.003	-0.82 (1.88)	0.666
ROP	-3.93 (1.63)	0.020	-3.70 (2.20)	0.099
BPD	-3.98 (1.14)	0.001	-3.44 (1.53)	0.030
Education				
Less than high school	-1.74 (1.34)	0.203	-5.34 (1.78)	0.005
High school	-2.34 (1.20)	0.057	-4.15 (1.59)	0.012
Some college or more	REF		REF	
Race/Ethnicity				
Black	-0.85 (1.31)	0.521	-2.17 (1.75)	0.222
White	REF		REF	
Hispanic	-0.78 (1.57)	0.620	-6.00 (2.09)	0.006
Other/Unknown	-1.40 (2.88)	0.630	-0.84 (3.94)	0.832

Note: REF=reference category. N=525 for cognitive composite model and N=517 for language composite model. Models also control for research center. Regression coefficients are adjusted for research center, object permanence score, ventilation type, oxygen level, gestational age, gender, IVH III-IV/cPVL, ROP, BPD, maternal education, and race/ethnicity.

Figure 1. Model-Adjusted Mean Bayley-III Cognitive and Language Composite Scores by Object Permanence Scores



Note: Means are adjusted for research center, ventilation, oxygen level, gestational age, gender, IVH III-IV/cPVL, ROP, BPD, maternal education, and race/ethnicity.

Definitions of Variables:

- **ROP:**
 - Infant diagnosed with any ROP in either eye

- **IVH Grade:** Severity of IVH is hierarchical. For any grade of IVH indicated, it is not necessary to also have the symptoms associated with any lower grade of IVH.
 - Grade 4: blood/echodensity in the parenchyma
 - Grade 3: ventricular size enlarged *and* blood/echodensity in the ventricle
 - Grade 2: blood/echodensity in the ventricle
 - Grade 1: blood/echodensity in the germinal matrix
 - Grade 0: No IVH

- **PVL:**

Comment [CB4]: I would remove the definitions of the variables here. In an earlier version of the manuscript, I suggested some short descriptions of the variables for the methods section. If you need that, let me know and I will find it.

- Indicator of whether infant had any Periventricular leukomalacia regardless of when the sonogram was taken (i.e., 28 days or 36 weeks).

• **BPD (physiological definition):**

- The physiologic definition of BPD applies to infants who are born at <32 weeks gestational age and who survive to 36 weeks PMA or are transferred or discharged prior to 36 weeks. The physiologic definition of BPD differs from the traditional definition in two main ways. First, infants receiving support via ventilator or CPAP at 36 weeks PMA are considered to have BPD by the physiologic definition regardless of whether they are receiving supplemental oxygen or room air. Second, infants receiving low levels of supplemental oxygen ($\leq 30\%$) at 36 weeks PMA may be eligible for a physiologic challenge in which there is an attempt to wean the infant to room air. Specifically, infants are eligible for the challenge if at 36 weeks PMA they are receiving effective oxygen $< 27\%$ and have majority saturation $\geq 90\%$, or they are receiving effective oxygen 27-30% and have majority saturation $\geq 96\%$, or they are receiving room air by nasal cannula (see form PHYC1). The challenge takes place between 36 and 37 weeks PMA. Infants who are successfully weaned to room air during the challenge do not have BPD by the physiologic definition. Those who are weaned to room air before the challenge can take place also do not have BPD. Those who are not challenged because their level of support increases (support with CPAP or vent or increased oxygen) are considered to have BPD, as are those who fail the challenge.

Infants who are eligible for challenge but who are not challenged because of instability (including surgery or sepsis) or other reasons (such as personnel not available) are classified based on their level of support at 36 weeks. Infants receiving supplemental oxygen by any means at 36 weeks are considered by default to have BPD. Those receiving room air by nasal cannula at 36 weeks will have a missing outcome for BPD. This is because the Network determination of whether receipt of room air via nasal cannula constitutes "respiratory support" depends on the flow of air through the cannula. A flow of $>.5$ liters per minute (lpm) is support, and a flow of $\leq .5$ lpm is not support. Thus, if we knew the flow rate we would classify infants receiving room air by nasal cannula with flow $>.5$ lpm as having BPD by the physiologic definition of BPD and those with flow $\leq .5$ lpm as not having BPD (this determination was made by the SUPPORT subcommittee). The flow rate for infants receiving room air by nasal cannula at 36 weeks PMA who are not challenged is not available on the 2006 or 2008 versions of the NG07.

Infants who are receiving supplemental oxygen at 36 weeks PMA and who are not eligible for the physiologic challenge are considered to have BPD, and those who are breathing room air on their own (with no support) at 36 weeks do not have BPD. Infants who are transferred or discharged before 36 weeks are classified based on the support they are receiving at that time. Those receiving supplemental oxygen or positive

pressure support via CPAP or ventilator have BPD, and those breathing room air on their own do not have BPD. Those receiving room air via nasal cannula at discharge or transfer will have missing outcomes. If BPD would otherwise be missing, an infant who is transferred or discharged on supplemental oxygen, ventilator or CPAP at ≤ 37 weeks PMA will be considered to have BPD (this is used to classify very few cases, if any).

From: Vaucher, Yvonne
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Myriam Peralta, M.D.; Rich, Wade; adas@rti.org
Subject: Re: Vaucher/Finer OA galleys
Date: Monday, November 19, 2012 10:48:06 AM

Ok

Yvonne

Sent from my iPhone

On Nov 19, 2012, at 7:17, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> All:

>

> I propose we change the last sentence on the paper to two sentences as follows:

>

> "It is important to weigh the mortality and neurodevelopmental outcomes at 18 to 22 months of corrected age when deciding on oxygen-saturation targets in extremely preterm infants. As mortality remained lower in the higher oxygen saturation group at the time of follow up and there were no adverse visual or neurodevelopmental problems, lower oxygen saturation targets cannot be recommended in these extremely preterm infants."

>

> The first sentence is modified from Dr. Drazen's sentence. The second is modified from what we had said initially.

>

> Wally

>

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>

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

> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

> Sent: Monday, November 19, 2012 9:04 AM

> To: Wally Carlo, M.D.; 'Finer, Neil'; Vaucher, Yvonne; Myriam Peralta, M.D.

> Cc: Rich, Wade; adas@rti.org

> Subject: RE: Vaucher/Finer OA galleys

>

> These are suggestions - we should say what we want and see what Dr. Drazen says!!

>

> Rosemary D. Higgins, MD

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>

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

> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

> Sent: Monday, November 19, 2012 9:20 AM

> To: Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; Vaucher, Yvonne; Myriam Peralta, M.D.

> Cc: Rich, Wade; adas@rti.org

> Subject: RE: Vaucher/Finer OA galleys

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>

> Wally

>

>

>

> Wally Carlo, M.D.

> Edwin M. Dixon Professor of Pediatrics

> University of Alabama at Birmingham

> Director, Division of Neonatology

> Director, Newborn Nurseries

> 1700 6th Avenue South

> 176F Suite 9380R

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>

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

> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

- > Sent: Monday, November 19, 2012 7:31 AM
- > To: 'Finer, Neil'; Vaucher, Yvonne; Myriam Peralta, M.D.; Wafly Carlo, M.D.
- > Cc: Rich, Wade; Abhik Das (adas@rti.org)
- > Subject: RE: Vaucher/Finer OA galleys
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- > Thanks to everyone and congratulations!!
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- > Rose
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- > Rosemary D. Higgins, MD
- > Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH
- > 6100 Executive Blvd., Room 4B03
- > MSC 7510
- > Bethesda, MD 20892
- > For overnight delivery use Rockville, MD 20852
- > 301-435-7909
- > 301-496-5575
- > 301-496-3790 (FAX)
- > higginsr@mail.nih.gov
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- > From: Finer, Neil [mailto:nfiner@ucsd.edu]
- > Sent: Sunday, November 18, 2012 9:40 PM
- > To: Finer, Neil; Vaucher, Yvonne; mperalta@peds.uab.edu; wcarlo@peds.uab.edu
- > Cc: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
- > Subject: FW: Vaucher/Finer OA galleys
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- > Hi Everyone
- > Yvonne and I have gone through all your suggestions and corrected any other errors
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- > Please review before I send back to editor and send me your OK or changes to the response **MANY THANKS FOR ALL OF YOUR RAPID REPLIES' HAVE A GREAT THANKSGIVING** Be well Neil and Yvonne
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- > From: NEJM Galleys <NejmGalleys@mms.org<mailto:NejmGalleys@mms.org>>
- > Date: Friday, November 16, 2012 6:31 AM
- > To: Neil Finer <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
- > Subject: Vaucher/Finer OA galleys
- >
- > PLEASE DO NOT REPLY TO THIS E-MAIL
- >
- > AUTHOR: Vaucher/Finer
- > MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<mailto:elaurencot@nejm.org>); 800-445-8080 or 617-734-9800
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- > Please check the attached galley proofs of your article. It is important that we receive your changes by noon on Tuesday, November 20.
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- >
- > Thank you.

- >
- >
- >

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.
Cc: Rich, Wade; adas@rti.org
Subject: RE: Vaucher/Finer OA galleys
Date: Monday, November 19, 2012 10:42:00 AM

Yes
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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higginsr@mail.nih.gov

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, November 19, 2012 10:29 AM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Myriam Peralta, M.D.
Cc: Rich, Wade; adas@rti.org
Subject: Re: Vaucher/Finer OA galleys

Is everyone OK with Wally's suggestion?
Neil

On 11/19/12 7:17 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

>All:
>
>I propose we change the last sentence on the paper to two sentences as
>follows:
>
>"It is important to weigh the mortality and neurodevelopmental outcomes
>at 18 to 22 months of corrected age when deciding on oxygen-saturation
>targets in extremely preterm infants. As mortality remained lower in
>the higher oxygen saturation group at the time of follow up and there
>were no adverse visual or neurodevelopmental problems, lower oxygen
>saturation targets cannot be recommended in these extremely preterm infants."
>
>The first sentence is modified from Dr. Drazen's sentence. The second
>is modified from what we had said initially.
>
>Wally
>
>Wally Carlo, M.D.
>Edwin M. Dixon Professor of Pediatrics

>University of Alabama at Birmingham
>Director, Division of Neonatology
>Director, Newborn Nurseries
>1700 6th Avenue South
>176F Suite 9380R
>Birmingham, AL 35233-7335
>Phone: 205 934 4680
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>
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>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
>Sent: Monday, November 19, 2012 9:04 AM
>To: Wally Carlo, M.D.; 'Finer, Neil'; Vaucher, Yvonne; Myriam Peralta,
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>Cc: Rich, Wade; adas@rti.org
>Subject: RE: Vaucher/Finer OA galleys

>

>These are suggestions - we should say what we want and see what Dr.
>Drazen says!!

>

>Rosemary D. Higgins, MD
>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal
>Research Network Pregnancy and Perinatology Branch CDBPM, NIH
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>Date: Friday, November 16, 2012 6:31 AM

>To: Neil Finer <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>Subject: Vaucher/Finer OA galleys

>

>PLEASE DO NOT REPLY TO THIS E-MAIL

>

>AUTHOR: Vaucher/Finer

>MANUSCRIPT EDITOR: Elizabeth Laurencot

>(elaurencot@nejm.org<mailto:elaurencot@nejm.org>); 800-445-8080 or

>617-734-9800

>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: Vaucher/Finer OA galleys
Date: Monday, November 19, 2012 8:31:00 AM
Attachments: [4vauc_oa1208506.pdf](#)
[Response to NEJM for SUPPORT Follow up.docx](#)
Importance: High

Bob

Here are the penultimate galleys for the upcoming NEJM SUPPORT Follow Up paper - can you send me a draft of the press release?? I don't yet have a publication date but likely in the next 3-6 weeks.

Thanks for your help

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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Page 1251 of 2000

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WC: I prefer as they have it (Characteristics of the Patients)>

A 52: if you would like to add the percentages, I will be ok with this The numbers are in the figure (or perhaps we can reference to the figure) A 56: scores we had not use points previously on bayley scores or GMFCS I think to be consistent keep this out.

WC: I think it is best to add %s as they request. It will be easier for the readers also.

A 59: not sure why 977 Marie can probably help with this.

A 61: Perhaps add the ranges

A 65 reference 31 goes at end of line 33 on page 9 I believe.

WC: We Ref 31 could go after the phrase "There are ongoing studies" on line 32.

A 72 is for the groups in this study.

WC: Add "in this study" at the end of line 18.

Table 2 on legends: same change for Bayley standardized mean

WC: Also, on Table 2, there is no need for a comma in the legend after "(Bayley-III)".

Thanks.

Hello All:

A quick look at the galleys led to the following suggestions from me:

A9: Instead of 'initial results', I suggest 'Near term findings'. The former suggests those results were not final, which they are!

WC: Near term can be confusing. I prefer "Previous" as Myriam said or "Previously-reported"

A15: Trailing zeros after a decimal point don't make sense, but may be ok as a stylistic requirement.

WC: Best to put them in as some journals, including NEJM, require them to assure that it is meant to be 0.

A30: I guess Marie and I vouch for the accuracy and completeness of the data and analyses reported, while the subcommittee (or steering committee?) collectively vouches for the fidelity of the study to the protocol?

A31: Say 'standardized' or 'normed' instead of 'standardization'.

A43: Early surfactant/higher target range of oxygen saturation arms.

WC: Agree with Abhik but I would just put "and" instead of "/".

A50. I assume we are talking about 65% of infants in the CPAP group.

A52. Perhaps we can rephrase and say that mortality remained significantly higher, as reported previously?

WC: I would replace "was" with "remained" in line 43.

A63. I would insert "largely" before "reflected".

A72. Add 'in this study' to the end of the sentence.

Thanks

Abhik

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]

Sent: Friday, November 16, 2012 1:40 PM

To: **Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Wally Carlo, M.D.; Gantz, Marie**
Cc: **Rich, Wade**
Subject: **Re: Vaucher/Finer OA galleys**

All,

Please submit all your galley comments by Saturday, Nov 17th. We will make the final revisions on Sunday and submit the revised paper on Monday, Nov 19th since the Thanksgiving holiday is next week.

Yvonne

From: [Finer, Neil](#)
To: [Gantz, Marie](#); [Vaucher, Yvonne](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; mperalta@peds.uab.edu; wcarlo@peds.uab.edu
Cc: [Rich, Wade](#)
Subject: RE: Vaucher/Finer OA galleys
Date: Sunday, November 18, 2012 6:56:37 PM

Many thanks Marie
Neil

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

From: Gantz, Marie [<mailto:mgantz@rti.org>]
Sent: Saturday, November 17, 2012 9:54 AM
To: Vaucher, Yvonne; Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; mperalta@peds.uab.edu; wcarlo@peds.uab.edu
Cc: Rich, Wade
Subject: RE: Vaucher/Finer OA galleys

Hi all,

My comments are below. Two near the bottom are marked as IMPORTANT because they need to be corrected. Will we get to see the supplemental tables before they get published? I would definitely like to check them over.

Marie

- Abstract - In results, it says "Mortality was increased with lower oxygen saturation..." - I think this should either be "in the lower oxygen saturation GROUP" or it should refer to the lower oxygen saturation TARGET, rather than just lower oxygen saturation.
- A39 - should be 18 months CORRECTED age
- A43 - the question of which group we assumed would have an initial outcome rate of 55% is somewhat trivial, but I suppose the answer would be the surfactant group for comparisons of CPAP vs. surfactant and the high sat group for the high vs. low sat comparison.
- A44 - the reason that neonatal outcomes are included in the sentence is that we did adjusted comparisons for the neonatal outcomes that were included in Table 1 (as opposed to unadjusted comparisons of the demographic and birth characteristics).
- A48 - to me the sentence reads as if the percentages should be for moms of 68 kids vs. moms of 990 kids, not the other way around. If that is the case, then the current order of the percentages should be switched. If it's supposed to be moms of 990 kids vs. moms of 68 kids as written in the comment, then the order is fine as-is.
- A50 - it's 65% of infants in the CPAP group.
- A52 - if you are going to add information about the deaths previously reported, I recommend reporting the number rather than the percentage. The reason is that we had the death outcome on all 1316 infants in the previous paper, but in this paper the denominator is slightly smaller because of those who were lost to FU with unknown survival status.
- A53 - might be clearer if it says "...or for EITHER component" meaning death and NDI. Otherwise, it could be interpreted to refer to each of the components of NDI, which was not what was meant.
- A56 - is it correct to say "GMFCS score of ≥ 2 points" (as written) or should it be "GMFCS level ≥ 2 ?" The same comment applies to the Discussion section (line 12) and Tables 2 and 3.
- A59 - there was one infant who was missing the cognitive composite and did not meet NDI criteria on other components (so was missing NDI) but was classified as GMFCS possible level 1 and with an abnormal neuro exam, so met criteria for not having normal status on all exams. If you want to exclude that child for consistency, then the number with normal status on all exams would be 583/976, still 60% (59.7% to be exact).
- Discussion lines 44-46, add back the word "target" as in the original text: "...between infants assigned to a lower oxygen saturation TARGET and those assigned to a higher oxygen saturation TARGET."
- Table 1 - Corrected age at follow up is indented under Neonatal outcomes, but it doesn't seem like a neonatal outcome to me (not a big deal).
- Tables 2 and 3 - IMPORTANT - The first row was INCORRECTLY relabeled as "Follow-up evaluation"

performed" -- the row actually shows the number of children with the primary outcome defined, so it includes those who have NDI status assigned and those who died.

- Table 3 - IMPORTANT - Inequality reversed for GMFCS -- should be ≥ 2 instead of ≤ 2 .

- Figure 1 - label of "Did not have NDI outcome data" and "Had NDI outcome data" is not entirely accurate, because in most cases only one or two of the components were missing. "Had incomplete/complete NDI outcome data" would be more accurate, but it's not a huge issue.

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]

Sent: Friday, November 16, 2012 2:31 PM

To: Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; mperalta@peds.uab.edu;

wcarlo@peds.uab.edu; Gantz, Marie

Cc: Rich, Wade

Subject: Re: Vaucher/Finer OA galleys

All,

We will get this done in time to get the galleys back to the NEJM by Tuesday Nov 20th. I did not mean to imply otherwise in my previous email!

I appreciate everyone's speedy input. I will put the all suggestions together ASAP.

Yvonne

On 11/16/12 9:23 AM, "Finer, Neil" <nfiner@ucsd.edu> wrote:

>Thanks Abhik

>Neil

>

>On 11/16/12 9:05 AM, "Das, Abhik" <adas@rti.org> wrote:

>

>>Hello All:

>>

>>A quick look at the galleys led to the following suggestions from me:

>>

>>A9: Instead of 'initial results', I suggest 'Near term findings'. The

>>former suggests those results were not final, which they are!

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>>A52. Perhaps we can rephrase and say that mortality remained significantly higher, as reported previously?

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>>A63. I would insert 'largely' before 'reflected'.

>>

>>A72. Add '(in this study)' to the end of the sentence.

>>

>>Thanks

>>

>>Abhik

>>

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

>>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

>>Sent: Friday, November 16, 2012 11:30 AM

>>To: 'nfiner@ucsd.edu'; 'yvaucher@ucsd.edu'; 'mperalta@peds.uab.edu';

>>'wcarlo@peds.uab.edu'; Gantz, Marie

>>Cc: 'wrich@ucsd.edu'; Das, Abhik

>>Subject: Re: Vaucher/Finer OA galleys

>>

>>The galleys do not need to go to all of the authors. If there is an author(s) that was instrumental, please send it to those individuals.

>>Thanks

>>Rose

>>

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

>>From: Finer, Neil [mailto:nfiner@ucsd.edu]

>>Sent: Friday, November 16, 2012 10:25 AM

>>To: Vaucher, Yvonne <yvaucher@ucsd.edu>; mperalta@peds.uab.edu

>><mperalta@peds.uab.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>;

>>mgantz@rti.org <mgantz@rti.org>

>>Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>

>>Subject: FW: Vaucher/Finer OA galleys

>>

>>Wow

>>I did not expect these so fast

>>Here are the galleys

>>I would think that perhaps Yvonne and Myriam could look at these first

>>and then send around with their corrections if any to the rest Rose Do

>>you want the galleys seen by every author?

>>Be well

>>Neil

>>

>>From: <Laurencot>, Elizabeth

>><elaurencot@nejm.org<mailto:elaurencot@nejm.org>>

>>Date: Friday, November 16, 2012 6:35 AM

>>To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>>Subject: FW: Vaucher/Finer OA galleys

>>

>>Dear Dr Finer,

>>

>>Attached is a copy of your galley proofs (identical to the copy just

>>sent).

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>>of the galley proofs, that would be most helpful.
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>>Thanks in advance.
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>>Best,
>>Elizabeth
>>
>>Elizabeth Laurençot
>>Manuscript Editor
>>New England Journal of Medicine
>>617-487-6547
>>elaurencot@nejm.org<mailto:elaurencot@nejm.org>
>>
>>
>>From: NEJM Galleys
>>Sent: Friday, November 16, 2012 9:31 AM
>>To: 'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'
>>Subject: Vaucher/Finer OA galleys
>>
>>PLEASE DO NOT REPLY TO THIS E-MAIL
>>
>>AUTHOR: Vaucher/Finer
>>MANUSCRIPT EDITOR: Elizabeth Laurençot
>>(elaurencot@nejm.org<mailto:elaurencot@nejm.org>); 800-445-8080 or
>>617-734-9800
>>
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>>please call one of the numbers listed above; if you cannot reach your
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>>

>>Thank you.

>>

>>

>>

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>

From: Vaucher, Yvonne
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Vaucher/Finer OA galleys
Date: Friday, November 16, 2012 8:39:47 PM

Thanks Wally!

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

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, November 16, 2012 5:18 PM
To: Myriam Peralta, M.D.; Vaucher, Yvonne; Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Vaucher/Finer OA galleys

Hi Everyone!!!

I have added Abhik's and Myriam's below to try to make it easier. I have only commented if I had something different to say.

Have a good weekend!

Wally

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

From: Myriam Peralta, M.D.
Sent: Friday, November 16, 2012 5:47 PM
To: 'Vaucher, Yvonne'; Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Gantz, Marie
Cc: Rich, Wade
Subject: RE: Vaucher/Finer OA galleys

Yvonne: I am just getting to see my emails. Here are my initial comments
A7: Just use members as you are including everyone.

A9: can you change Initial to "Previous"?

A 20 and A 21: I think it may go better : "The risk of neurodevelopmental impairment increases with decreasing gestational age, greater severity of illness and neonatal complications". I think they way it was rearranged reads as if neurodevelopmental impairment is only consequence of neonatal complication.

WC: I think it is ok the way it was. It has two separate statements. But Myriam's suggestion is also ok.

A 24 looks ok to me.

A31 agree with Abik use standardized mean .

A 32. is oK for the text, only in the appendix we used CP in general.

A 44 I think we can take out neonatal from the sentence.

A 47: alternative could be Characteristics of the sample.
WC: I prefer as they have it (Characteristics of the Patients)>

A 52: if you would like to add the percentages, I will be ok with this The numbers are in the figure (or perhaps we can reference to the figure) A 56: scores we had not use points previously on bayley scores or GMFCS I think to be consistent keep this out.

WC: I think it is best to add %s as they request. It will be easier for the readers also.

A 59: not sure why 977 Marie can probably help with this.

A 61: Perhaps add the ranges

A 65 reference 31 goes at end of line 33 on page 9 I believe.

WC: We Ref 31 could go after the phrase "There are ongoing studies" on line 32.

A 72 is for the groups in this study.

WC: Add "in this study" at the end of line 18.

Table 2 on legends: same change for Bayley standardized mean

WC: Also, on Table 2, there is no need for a comma in the legend after "(Bayley-III)".

Thanks.

Hello All:

A quick look at the galleys led to the following suggestions from me:

A9: Instead of 'initial results', I suggest 'Near term findings'. The former suggests those results were not final, which they are!

WC: Near term can be confusing. I prefer "Previous" as Myriam said or "Previously-reported"

A15: Trailing zeros after a decimal point don't make sense, but may be ok as a stylistic requirement.

WC: Best to put them in as some journals, including NEJM, require them to assure that it is meant to be 0.

A30: I guess Marie and I vouch for the accuracy and completeness of the data and analyses reported, while the subcommittee (or steering committee?) collectively vouches for the fidelity of the study to the protocol?

A31: Say 'standardized' or 'normed' instead of 'standardization'.

A43: Early surfactant/higher target range of oxygen saturation arms.

WC: Agree with Abhik but I would just put "and" instead of "/".

A50. I assume we are talking about 65% of infants in the CPAP group.

A52. Perhaps we can rephrase and say that mortality remained significantly higher, as reported previously?

WC: I would replace "was" with "remained" in line 43.

A63. I would insert "largely" before "reflected".

A72. Add 'in this study' to the end of the sentence.

Thanks

Abhik

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]

Sent: Friday, November 16, 2012 1:40 PM

To: Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Wally Carlo, M.D.;

Gantz, Marie
Cc: Rich, Wade
Subject: Re: Vaucher/Finer OA galleys

All,

Please submit all your galley comments by Saturday, Nov 17th. We will make the final revisions on Sunday and submit the revised paper on Monday, Nov 19th since the Thanksgiving holiday is next week.

Yvonne

From: [Vaucher, Yvonne](#)
To: [Finer, Neil](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); mperalta@peds.uab.edu; wcarlo@peds.uab.edu; [Gantz, Marie](#)
Cc: [Rich, Wade](#)
Subject: Re: Vaucher/Finer OA galleys
Date: Friday, November 16, 2012 2:31:47 PM

All,

We will get this done in time to get the galleys back to the NEJM by Tuesday Nov 20th. I did not mean to imply otherwise in my previous email! I appreciate everyone's speedy input. I will put the all suggestions together ASAP.

Yvonne

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>Neil

>

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>>Sent: Friday, November 16, 2012 11:30 AM
>>To: 'nfiner@ucsd.edu'; 'yvaucher@ucsd.edu'; 'mperalta@peds.uab.edu';
>>'wcarlo@peds.uab.edu'; Gantz, Marie
>>Cc: 'wrich@ucsd.edu'; Das, Abhik
>>Subject: Re: Vaucher/Finer OA galleys

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>>author(s) that was instrumental, please send it to those individuals.
>>Thanks
>>Rose

>>

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

>>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
>>Sent: Friday, November 16, 2012 10:25 AM
>>To: Vaucher, Yvonne <yvaucher@ucsd.edu>; mperalta@peds.uab.edu
>><mperalta@peds.uab.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>;
>>mgantz@rti.org <mgantz@rti.org>
>>Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
>>Subject: FW: Vaucher/Finer OA galleys

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>>Wow

>>I did not expect these so fast
>>Here are the galleys
>>I would think that perhaps Yvonne and Myriam could look at these first
>>and then send around with their corrections if any to the rest Rose Do
>>you want the galleys seen by every author?

>>Be well

>>Neil

>>

>>From: <Laurencot>, Elizabeth
>><elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>>
>>Date: Friday, November 16, 2012 6:35 AM
>>To: UCSD Pediatrics <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>
>>Subject: FW: Vaucher/Finer OA galleys

>>

>>Dear Dr Finer,

>>

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>>

>>Thanks in advance.

>>

>>Best,

>>Elizabeth

>>

>>Elizabeth Laurençot

>>Manuscript Editor

>>New England Journal of Medicine

>>617-487-6547

>>elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>

>>

>>

>>From: NEJM Galleys

>>Sent: Friday, November 16, 2012 9:31 AM

>>To: 'nfiner@ucsd.edu'<<mailto:nfiner@ucsd.edu>>

>>Subject: Vaucher/Finer OA galleys

>>

>>PLEASE DO NOT REPLY TO THIS E-MAIL

>>

>>AUTHOR: Vaucher/Finer

>>MANUSCRIPT EDITOR: Elizabeth Laurençot

>>(elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>); 800-445-8080 or

>>617-734-9800

>>

>>Please check the attached galley proofs of your article. It is important

>>that we receive your changes by noon on Tuesday, November 20.

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>>(<http://www.adobe.com/products/acrobat/readermain.html>).

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>>

>>Thank you.

>>

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>>this message in error, please contact the sender immediately by return
>>email and delete the original message from all computer systems. Thank
>>you.
>

From: [Finer, Neil](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: Vaucher/Finer OA galleys
Date: Friday, November 16, 2012 12:24:16 PM

I forwarded all that I received
Neil

On 11/16/12 8:54 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

>Hi,
>I will likely get to these tomorrow as I am at a meeting. Did they send
>the supplementary appendix with all of the acknowledgments?
>Thanks
>Rose
>
>----- Original Message -----
>From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
>Sent: Friday, November 16, 2012 10:25 AM
>To: Vaucher, Yvonne <yvaucher@ucsd.edu>; mperalta@peds.uab.edu
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>email and delete the original message from all computer systems. Thank
>you.

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Vaucher/Finer OA galleys
Date: Friday, November 16, 2012 11:56:17 AM

Thx

On 11/16/12 8:41 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

>Wally in front of Marie who is in front of Michele

>

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

>From: Finer, Neil [mailto:nfiner@ucsd.edu]

>Sent: Friday, November 16, 2012 11:38 AM

>To: Vaucher, Yvonne <yvaucher@ucsd.edu>; Wally Carlo <wcarlo@peds.uab.edu>

>Cc: Higgins, Rosemary (NIH/NICHD) [E]

>Subject: Re: Vaucher/Finer OA galleys

>

>Hi Yvonne

>Wally needs to be before Michelle

>Please note that change on the galleys

>I would also assume that Marie should precede Michelle?

>Rose can you and Wally comment on this and decide the order of the

>authors? With Respect to Marie and Michelle?

>Thanks

>Neil

>From: <Vaucher>, Yvonne Vaucher

><yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>

>Date: Friday, November 16, 2012 8:19 AM

>To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>Subject: Re: Vaucher/Finer OA galleys

>

>Neil,

>

>Why is Michelle Walsh listed after Wally and before Marie Gantz in the

>author list? Shouldn't she be in the same order as everyone else outside

>the main authors? Maybe his is the way we sent it in-I will check.

>

>From: <Finer>, Neil Finer <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>Date: Friday, November 16, 2012 7:25 AM

>To: Yvonne Vaucher <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>,

>"mperalta@peds.uab.edu<mailto:mperalta@peds.uab.edu>"

><mperalta@peds.uab.edu<mailto:mperalta@peds.uab.edu>>, Wally Carlo

><wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>>,

>"mgantz@rti.org<mailto:mgantz@rti.org>"

><mgantz@rti.org<mailto:mgantz@rti.org>>

>Cc: Rose Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>,

>"Rich, Wade" <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>

>Subject: FW: Vaucher/Finer OA galleys

>

>Wow

>I did not expect these so fast

>Here are the galleys

>I would think that perhaps Yvonne and Myriam could look at these first

>and then send around with their corrections if any to the rest

>Rose

>Do you want the galleys seen by every author?

>Be well

>Neil

>

>From: <Laurencot>, Elizabeth

><elaurencot@nejm.org<mailto:elaurencot@nejm.org>>

>Date: Friday, November 16, 2012 6:35 AM

>To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>

>Subject: FW: Vaucher/Finer OA galleys

>

>Dear Dr Finer,

>

>Attached is a copy of your galley proofs (identical to the copy just
>sent).

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>e-mail with answers to the numbered queries as well as any changes you
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>Tuesday and Wednesday; please do let me know if you will not be available.

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>In the meantime, if you could please drop me a note confirming receipt of
>the galley proofs, that would be most helpful.

>

>Thanks in advance.

>

>Best,

>Elizabeth

>

>Elizabeth Laurencot

>Manuscript Editor

>New England Journal of Medicine

>617-487-6547

>elaurencot@nejm.org<mailto:elaurencot@nejm.org>

>

>

>From: NEJM Galleys

>Sent: Friday, November 16, 2012 9:31 AM

>To: 'nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>'

>Subject: Vaucher/Finer OA galleys

>

>PLEASE DO NOT REPLY TO THIS E-MAIL

>

>AUTHOR: Vaucher/Finer

>MANUSCRIPT EDITOR: Elizabeth Laurencot

>(elaurencot@nejm.org<mailto:elaurencot@nejm.org>); 800-445-8080 or

>617-734-9800

>

>Please check the attached galley proofs of your article. It is important
>that we receive your changes by noon on Tuesday, November 20.

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>

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>Please note that this material is confidential and embargoed until
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>contact NEJM Media Relations at 781-434-7847 or at
>Mediasupport@nejm.org<mailto:Mediasupport@nejm.org>.

>

>Thank you.

>

>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "adas@rti.org"
Subject: Re: Vaucher/Finer OA galleys
Date: Friday, November 16, 2012 11:55:11 AM

Very nice - great food! Susan Hintz, alan Jobe and Danny benjamin are also here.

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

From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, November 16, 2012 11:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Vaucher/Finer OA galleys

Thanks; Neil sent it to me after I asked him. How is Brazil?!

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 16, 2012 11:46 AM
To: Das, Abhik
Subject: Fw: Vaucher/Finer OA galleys
Importance: High

For you

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, November 16, 2012 10:25 AM
To: Vaucher, Yvonne <yvaucher@ucsd.edu>; mperalta@peds.uab.edu <mperalta@peds.uab.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; mgantz@rti.org <mgantz@rti.org>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
Subject: FW: Vaucher/Finer OA galleys

Wow

I did not expect these so fast

Here are the galleys

I would think that perhaps Yvonne and Myriam could look at these first and then send around with their corrections if any to the rest Rose Do you want the galleys seen by every author?

Be well

Neil

From: <Laurencot>, Elizabeth <elaurencot@nejm.org<mailto:elaurencot@nejm.org>>
Date: Friday, November 16, 2012 6:35 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Subject: FW: Vaucher/Finer OA galleys

Dear Dr Finer,

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In the meantime, if you could please drop me a note confirming receipt of the galley proofs, that would be most helpful.

Thanks in advance.

Best,
Elizabeth

Elizabeth Laurençot
Manuscript Editor
New England Journal of Medicine
617-487-6547
elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>

From: NEJM Galleys
Sent: Friday, November 16, 2012 9:31 AM
To: 'nfiner@ucsd.edu'<<mailto:nfiner@ucsd.edu>>
Subject: Vaucher/Finer OA galleys

PLEASE DO NOT REPLY TO THIS E-MAIL

AUTHOR: Vaucher/Finer
MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>); 800-445-8080 or 617-734-9800

Please check the attached galley proofs of your article. It is important that we receive your changes by noon on Tuesday, November 20.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "adas@rti.org"
Subject: Fw: Vaucher/Finer OA galleys
Date: Friday, November 16, 2012 11:45:41 AM
Attachments: 4Vauc_aa1208506.pdf
Importance: High

For you

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, November 16, 2012 10:25 AM
To: Vaucher, Yvonne <yvaucher@ucsd.edu>; mperalta@peds.uab.edu <mperalta@peds.uab.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; mgantz@rti.org <mgantz@rti.org>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>
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Rose

Do you want the galleys seen by every author?

Be well

Neil

From: <Laurencot>, Elizabeth <elaurencot@nejm.org<mailto:elaurencot@nejm.org>>
Date: Friday, November 16, 2012 6:35 AM
To: UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Subject: FW: Vaucher/Finer OA galleys

Dear Dr Finer,

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Subject: Vaucher/Finer OA galleys

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AUTHOR: Vaucher/Finer
MANUSCRIPT EDITOR: Elizabeth Laurençot (elaurencot@nejm.org<<mailto:elaurencot@nejm.org>>); 800-445-8080 or 617-734-9800

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From: Vaucher, Yvonne
To: Gantz, Marie; Finer, Neil; mperalta@peds.uab.edu; wcarlo@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade
Subject: Re: Vaucher/Finer OA galleys
Date: Friday, November 16, 2012 11:16:31 AM

All,
I am on call all weekend and OOT all next week. I will do the best I can to review the galleys ASAP and keep up with everyone's emails.

Yvonne

On 11/16/12 7:58 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

>I also should have mentioned that I will be traveling all day on
>Wednesday the 21st so I will not be able to look at any follow up emails
>from that day until late in the evening.

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org

>828-254-6255

>

>

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

>From: Finer, Neil [mailto:nfiner@ucsd.edu]

>Sent: Friday, November 16, 2012 10:48 AM

>To: Gantz, Marie; Vaucher, Yvonne; mperalta@peds.uab.edu;

>wcarlo@peds.uab.edu

>Cc: Rosemary Higgins; Rich, Wade

>Subject: Re: Vaucher/Finer OA galleys

>

>Thanks Marie

>Neil

>

>On 11/16/12 7:45 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

>

>>That plan sounds good. I will check all of the numbers -- in one of our

>>previous NEJM papers there was a numeric typo in the galleys.

>>

>>Marie

>>

>>Marie Gantz, Ph.D.

>>Senior Research Statistician

>>RTI International

>>mgantz@rti.org

>>828-254-6255

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

>>From: Finer, Neil [mailto:nfiner@ucsd.edu]

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>>To: Vaucher, Yvonne; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; Gantz,

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>>Cc: Rosemary Higgins; Rich, Wade
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>>Subject: Vaucher/Finer OA galleys
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>>AUTHOR: Vaucher/Finer
>>MANUSCRIPT EDITOR: Elizabeth Laurençot
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>>you.
>

From: [Wally Carlo, M.D.](#)
To: [Gantz, Marie](#); [Finer, Neil](#); [Vaucher, Yvonne](#); [Myriam Peralta, M.D.](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: NEJM ms 12-08506
Date: Friday, November 16, 2012 9:53:57 AM

Great!

Happy Thanksgiving to everyone also.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: [Gantz, Marie \[mailto:mgantz@rti.org\]](mailto:mgantz@rti.org)
Sent: Friday, November 16, 2012 8:47 AM
To: [Finer, Neil](#); [Vaucher, Yvonne](#); [Myriam Peralta, M.D.](#); [Wally Carlo, M.D.](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: NEJM ms 12-08506

Thanks for the information, Neil. Looking forward to seeing the proofs. Hope everyone has a happy Thanksgiving.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-8255

From: [Finer, Neil \[mailto:nfiner@ucsd.edu\]](mailto:nfiner@ucsd.edu)
Sent: Friday, November 16, 2012 9:25 AM
To: [Vaucher, Yvonne](#); mperalta@peds.uab.edu; wcarlo@peds.uab.edu; [Gantz, Marie](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: FW: NEJM ms 12-08506

Good Morning

A Note about the galleys from the NEJM

Be well and enjoy your Thanksgiving

And thanks for all that you have done to make this possible
Be well
Neil

From: Quilty, Elizabeth J. [mailto:EQilty@nejm.org]
Sent: Friday, November 16, 2012 5:32 AM
To: Finer, Neil
Subject: NEJM ms 12-08506

Dear Dr. Finer,

Production of your manuscript has begun. Your page proofs will be sent to you in PDF format by e-mail, by Friday, Nov. 30.

When you receive your proofs, please read them carefully to make sure that the edited version conveys your intended meaning. Note that we reformat figures and tables according to our house style; please review any tables and figures for accuracy. At this stage of production, we try to keep changes to a minimum, but we will correct errors and make other changes that are necessary for accuracy or clarity.

Your e-mail notification will include detailed instructions for responding to our queries and conveying other changes by phone or e-mail; it will also include a deadline for your response. Please adhere to the deadline.

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If you will not be able to read your e-mail during the week of Nov. 25, please let me know.

Sincerely yours,
Liz Quilty
Manager of Editorial Scheduling and Tracking
NEJM

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From: Das, Abhik
To: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT paper appendix
Date: Tuesday, November 13, 2012 1:28:43 PM

Were you looking for this?

http://www.nejm.org/doi/suppl/10.1056/NEJMoa0911781/suppl_file/nejm_support_1959sa1.pdf

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20852-3903
e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: Das, Abhik
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); Dale_Phelps@URMC.Rochester.edu
Cc: [Wallace, Dennis](#); [Nolen, Tracy](#)
Subject: FW: SUPPORT ROP adjudication
Date: Friday, November 09, 2012 2:24:59 PM

FYI

From: Gantz, Marie
Sent: Friday, November 09, 2012 2:20 PM
To: Das, Abhik
Subject: RE: SUPPORT ROP adjudication

There were 95 infants who survived but did not have a final ROP status. Of those, there were 77 cases where at least 2 of the 3 reviewers agreed and we used that as the "majority rule" adjudicated outcome. In the other 18 cases, either only one of the reviewers thought the outcome could be adjudicated (13) or all three agreed that it could not be (5).

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-251-6255

From: Das, Abhik
Sent: Friday, November 09, 2012 1:17 PM
To: Gantz, Marie
Subject: SUPPORT ROP adjudication

Marie:

How many babies needed adjudication, and how many of them could be adjudicated (i.e., could be definitely assigned based on available data) and how many remained missing/unable to classify even after adjudication?

Thanks

Abhik

From: Bradley Yoder
To: Archer, Stephanie (NIH/NICHD) [E]; Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Kristin Zaterka-Baxter (kzaterka@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@rti.org); Michele Walsh (mcw3@cwru.edu); Nancy Newman (nxs5@cwru.edu); Neil Finer (nfiner@ucsd.edu); Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich (wrich@ucsd.edu); Wally Carlo (wacarlo@uab.edu)
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu); Jamie Newman (newman@rti.org)
Subject: RE: Breathing Outcomes Study - PAS Abstract 2013
Date: Friday, November 09, 2012 12:44:10 PM

Agree with Marie; otherwise looks good. There is one double period after 1st sentence of Results.

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Friday, November 09, 2012 7:15 AM
To: Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Bradley Yoder; Kristin Zaterka-Baxter (kzaterka@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@rti.org); Michele Walsh (mcw3@cwru.edu); Nancy Newman (nxs5@cwru.edu); Neil Finer (nfiner@ucsd.edu); Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Wade Rich (wrich@ucsd.edu); Wally Carlo (wacarlo@uab.edu)
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu); Jamie Newman (newman@rti.org)
Subject: FW: Breathing Outcomes Study - PAS Abstract 2013

Attached is an abstract of Tim's paper for PAS. We need any changes back ASAP.

Thank you,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
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From: Newman, Jamie [mailto:newman@rti.org]
Sent: Friday, November 09, 2012 8:44 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Breathing Outcomes Study - PAS Abstract 2013

Stephanie,
Are you distributing PAS abstracts to subcommittees or is Rose?
Thanks, Jamie

Jamie E. Newman, PhD, MPH
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, November 08, 2012 8:35 PM
To: 'higginsr@mail.nih.gov'; Newman, Jamie; 'nfiner@ucsd.edu'
Subject: Breathing Outcomes Study - PAS Abstract 2013

Hi Rose, Neil and Jamie,

Attached is an abstract of the Breathing Outcomes Study that I'd like to submit to PAS. The abstract is essentially the same as the abstract of the manuscript.

Thanks

Tim

From: [Finer, Neil](#)
To: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Abbot Luptook \(aluptook@wihri.org\)](#); [Abhik Das \(adas@rti.org\)](#); [Brad Yoder \(Bradley.yoder@hsc.utah.edu\)](#); [Kristin Zaterka-Baxter \(kzaterka@rti.org\)](#); [Kurt Schibler \(kurt.schibler@cchmc.org\)](#); [Marie Gantz \(mgantz@rti.org\)](#); [Michele Walsh \(mcw3@cwru.edu\)](#); [Nancy Newman \(nxs5@cwru.edu\)](#); [Roger Faix \(roger.faix@hsc.utah.edu\)](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Rich, Wade](#); [Wally Carlo \(wacarolo@uab.edu\)](#)
Cc: [Tim Stevens \(Timothy_Stevens@URMC.Rochester.edu\)](#); [Jamie Newman \(newman@rti.org\)](#)
Subject: RE: Breathing Outcomes Study - PAS Abstract 2013
Date: Friday, November 09, 2012 12:12:03 PM

Nice work Tim
This looks fine to me
Neil

From: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#) [<mailto:archerst@mail.nih.gov>]
Sent: Friday, November 09, 2012 6:15 AM
To: [Abbot Luptook \(aluptook@wihri.org\)](#); [Abhik Das \(adas@rti.org\)](#); [Brad Yoder \(Bradley.yoder@hsc.utah.edu\)](#); [Kristin Zaterka-Baxter \(kzaterka@rti.org\)](#); [Kurt Schibler \(kurt.schibler@cchmc.org\)](#); [Marie Gantz \(mgantz@rti.org\)](#); [Michele Walsh \(mcw3@cwru.edu\)](#); [Nancy Newman \(nxs5@cwru.edu\)](#); [Finer, Neil](#); [Roger Faix \(roger.faix@hsc.utah.edu\)](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Rich, Wade](#); [Wally Carlo \(wacarolo@uab.edu\)](#)
Cc: [Tim Stevens \(Timothy_Stevens@URMC.Rochester.edu\)](#); [Jamie Newman \(newman@rti.org\)](#)
Subject: FW: Breathing Outcomes Study - PAS Abstract 2013

Attached is an abstract of Tim's paper for PAS. We need any changes back ASAP.

Thank you,

Stephanie

Stephanie Wilson Archer
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Tel. 301-496-0430
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From: [Newman, Jamie \[mailto:newman@rti.org\]](#)
Sent: Friday, November 09, 2012 8:44 AM
To: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Subject: FW: Breathing Outcomes Study - PAS Abstract 2013

Stephanie,
Are you distributing PAS abstracts to subcommittees or is Rose?
Thanks, Jamie

Jamie E. Newman, PhD, MPH
RTI International

Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, November 08, 2012 8:35 PM
To: 'higginsr@mail.nih.gov'; Newman, Jamie; 'nfiner@ucsd.edu'
Subject: Breathing Outcomes Study - PAS Abstract 2013

Hi Rose, Neil and Jamie,

Attached is an abstract of the Breathing Outcomes Study that I'd like to submit to PAS. The abstract is essentially the same as the abstract of the manuscript.

Thanks

Tim

From: Gantz, Marie
To: Archer, Stephanie (NIH/NICHD) [E]; nfiner@ucsd.edu; wacarlo@uab.edu; Michele.walsh@cwru.edu; alaptook@wihri.org; bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; Newman, Jamie; Das, Abhik; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; richard.ehrenkranz@yale.edu; MPeralta@peds.uab.edu; bvohr@wihri.org; (b)(6)@aol.com; kimberly.yolton@cchmc.org; Roy.Heyne@utsouthwestern.edu; Patricia.W.Evans@uth.tmc.edu; yvaucher@ucsd.edu; iadamsc@emory.edu; emcgowan@tuftsmedicalcenter.org; (b)(6)@gmail.com; apappas@med.wayne.edu; srhintz@stanford.edu; Michael.Acarregui@providence.org; JaFuller@salud.unm.edu; golds005@mc.duke.edu; cbauer@peds.med.miami.edu; moshea@wfubmc.edu; gary_myers@URMC.Rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Timothy_Stevens@URMC.Rochester.edu
Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper
Date: Wednesday, November 07, 2012 2:32:15 PM
Attachments: Manuscript - Tables and Figures - 10-23-12_MG.docx
Manuscript -Stevens BreathingOutcomes Edits NF Oct 29 2012_MG.docx

My comments and edits are in the attached.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
328-254-6255

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Wednesday, October 24, 2012 1:00 PM
To: Neil Finer (nfiner@ucsd.edu); Wally Carlo (wacarlo@uab.edu); Michele Walsh (Michele.walsh@cwru.edu); Gantz, Marie; Abbot Laptook (alaptook@wihri.org); Brad Yoder (bradley.yoder@hsc.utah.edu); Roger Faix (roger.faix@hsc.utah.edu); Newman, Jamie; Das, Abhik; Kurt Schibler (kurt.schibler@cchmc.org); Wade Rich (wrich@ucsd.edu); Nancy Newman (nxs5@cwru.edu); Richard Ehrenkranz (richard.ehrenkranz@yale.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Betty Vohr (bvohr@wihri.org); Dee Wilson (b)(6)@aol.com); Kim Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); Patricia Evans (Patricia.W.Evans@uth.tmc.edu); Yvonne Vaucher (yvaucher@ucsd.edu); Ira Adams-Chapman (iadamsc@emory.edu); Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org); Anna Bodnar (b)(6)@gmail.com); Athina Pappas (apappas@med.wayne.edu); Susan Hintz (srhintz@stanford.edu); Mike Acarregui (Michael.Acarregui@providence.org); Janell Fuller (JaFuller@salud.unm.edu); Ricki Goldstein (golds005@mc.duke.edu); Charles Bauer (cbauer@peds.med.miami.edu); Mike O`Shea (moshea@wfubmc.edu); Gary Myers (gary_myers@URMC.Rochester.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu)
Subject: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Attached is a draft of Tim's SUPPORT Breathing Outcomes paper for the coauthors to review.

Please send any comments back to Tim by **Wednesday, November 7th**.

Thank you,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver National Institute of Child Health and Human Development

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Tuesday, October 23, 2012 9:35 PM
To: Newman, Jamie <newman@rti.org> (newman@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: Breathing Outcomes

Hi Jamie and Rose,

Here is the next version of the manuscript. Barbara double checked the tobacco exposure and provided updated values.

Can you forward the manuscript to the reviewers?

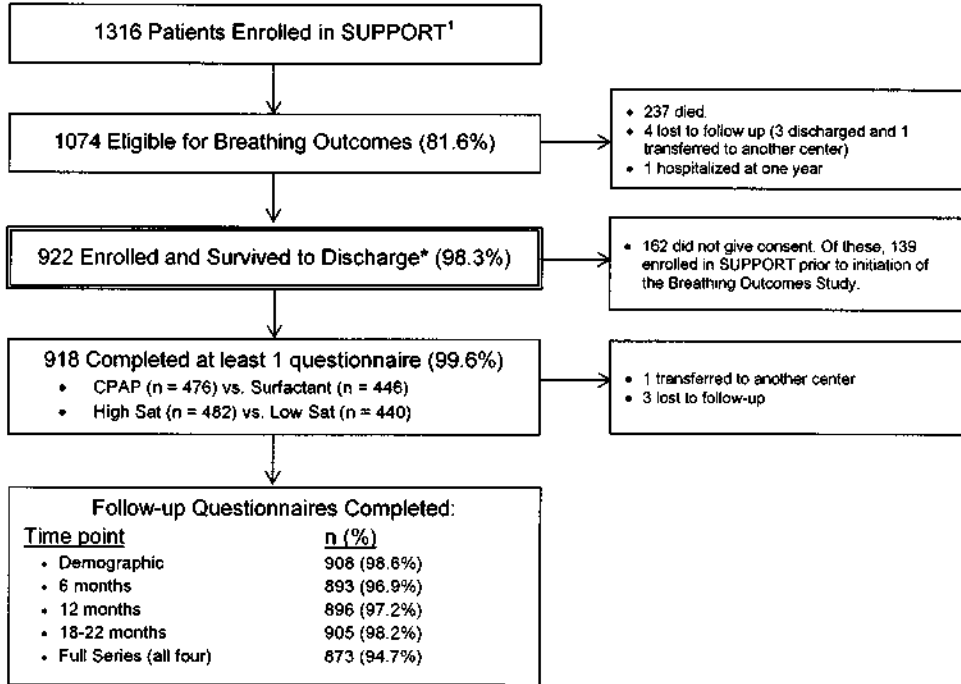
Thanks

Tim

Figure 1.

Patient flow diagram including follow up rates.

Comment [MS1]: In the figure, the numbers do not add up going from box to box, and the off-shoot boxes look like they are in the wrong place at times. For example shouldn't the deaths be an off-shoot of the first box (with n=1316) rather than the second one?



* Follow-up Cohort

Table 1.

Demographic and neonatal characteristics of follow-up cohorts.

	Low Sat N=440	High Sat N=482	CPAP N=476	Surfactant N=446
Birth Weight (g, mean ± s.d.)	858 ± 186	844 ± 190	850 ± 184	851 ± 193
Gestational Age (w, mean ± s.d.)	25.99 ± 1.0	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0
24 wks 0 days - 25 wks 6 dys - no. (%)	158 (35.5)	184 (37.5)	183 (37.7)	159 (35.3)
25 wks 0 days - 27 wks 6 dys - no. (%)	287 (64.5)	307 (62.5)	303 (62.4)	291 (64.7)
Male - no. (%)	222 (49.7)	264 (53.8)	238 (49.0)	248 (54.9)
Non-Hispanic Black - no. (%)	168 (37.6)	157 (32.0)	173 (36.0)	152 (33.6)
Non-Hispanic White - no. (%)	176 (39.4) *	226 (46.0) *	196 (40.3)	206 (45.6)
Hispanic - no. (%)	88 (19.7)	91 (18.5)	98 (20.2)	81 (17.9)
Other/unknown - no. (%)	15 (3.4)	17 (3.5)	19 (3.9)	13 (2.9)
Length of NICU Hospitalization (median, (min-max))	90, (39 - 365)	93, (46 - 366)	91, (44 - 366)	93, (39 - 365)
BPD (supplemental O2) - no. (%)	160 (36.3) **	221 (45.8) **	187 (39.1)	194 (43.5)
BPD (physiologic definition) - no. (%)	165 (37.4)	193 (40.0)	183 (38.3)	175 (39.2)
Discharged home on oxygen - no. (%)	105 (24.0)	111 (23.2)	108 (22.8)	108 (24.4)
Discharged home on respiratory medications - no. (%)	101 (27.3)	106 (27.1)	110 (27.8)	97 (26.6)
Discharged home October - March - no. (%)	232 (52.9)	227 (47.5)	232 (48.8)	227 (51.4)

* p < 0.05, ** p < 0.01

Table 2.

Family and environmental exposure history of follow up cohorts.

	Low Sat N=440	High Sat N=482	CPAP N=476	Surfactant N=446
First degree relative with asthma - no. (%)	142 (31.8)	159 (32.4)	152 (31.3)	149 (33.0)
Family history of COPD, emphysema, etc - no. (%)	48 (10.7)	43 (8.8)	53 (10.9)	38 (8.4)
Family history of food allergies - no. (%)	164 (40.6)	166 (37.6)	168 (38.5)	162 (39.6)
Family history of Chronic Respiratory Disease - no. (%)	7 (1.7)	4 (0.9)	1 (0.2)	10 (2.5)
Breast fed - no. (%)	167 (37.4)	148 (30.1)	166 (34.2)	149 (33.0)
Smoking in house - no. (%)	189 (44.1)	186 (39.3)	189 (40.6)	186 (42.7)
Spent time at daycare - no. (%)	163 (41.5)	142 (33.2)	163 (38.4)	142 (35.8)
Living with children under 12 - no. (%)	241 (61.3)	264 (61.7)	255 (60.1)	250 (63.0)
Pets in home- no. (%)	124 (31.6)	132 (30.8)	137 (32.3)	119 (30.0)
Flu Shot - no. (%)	307 (78.1)	342 (80.1)	335 (79.0)	314 (79.3)
RSV Shot - no. (%)	281 (71.5)	313 (73.1)	308 (72.6)	286 (72.0)

Table 3.

Respiratory outcomes for lower and higher oxygen saturation cohorts at the 6 month interview and the combined 6, 12 and 18-22 month interviews (listed as 6-22 months below).

	<u>Low Sat</u>	<u>High Sat</u>	<u>ARR (95% CI)</u>	<u>p-value</u>
Primary Outcomes				
<i>Has your child's chest sounded wheezy or whistling more than twice in one week?</i>				
6 months	94 (22.0)	129 (27.7)	0.73 (0.53, 1.01)	0.06
6-22 months	203 (46.7)	233 (49.1)	0.92 (0.70, 1.22)	0.57
<i>Has your child had a cough for more than 3 days without a cold?</i>				
6 months	63 (16.9)	76 (19.3)	0.84 (0.57, 1.22)	0.35
6-22 months	127 (30.8)	141 (31.1)	1.01 (0.75, 1.37)	0.93
Secondary Outcomes				
Symptoms				
<i>Wheezing/whistling more than twice in one week or cough more than 3 days</i>				
6 months†	162 (43.5)	195 (49.5)	0.78 (0.58, 1.05)	0.1
6-22 months	276 (66.8)	316 (69.5)	0.87 (0.65, 1.18)	0.37
<i>Has your child's chest sounded wheezy or whistling?</i>				
6 months	135 (36.3)	171 (43.4)	0.73 (0.54, 1.00)	<0.05
6-22 months	245 (59.3)	286 (62.9)	0.85 (0.64, 1.13)	0.27
<i>Has your baby's chest sounded wheezy or whistling apart from colds?</i>				
6 months	61 (16.4)	84 (21.3)	0.73 (0.50, 1.06)	0.1
6-22 months	117 (28.4)	165 (36.3)	0.67 (0.49, 0.91)	0.01
Illnesses				
<i>Has your child had asthma, reactive airway disease or BPD flare-up diagnosed by a doctor?</i>				
6 months†	51 (13.7)	62 (15.7)	0.84 (0.56, 1.27)	0.41
6-22 months†	140 (33.9)	158 (35.0)	1.01 (0.75, 1.37)	0.93
<i>Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?</i>				
6 months	72 (19.4)	78 (19.8)	0.98 (0.67, 1.41)	0.9
6-22 months	161 (39.0)	183 (40.4)	0.96 (0.72, 1.28)	0.79
<i>Any of asthma, reactive airway disease, BPD flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor</i>				
6 months	95 (25.5)	109 (27.7)	0.91 (0.65, 1.27)	0.58
6-22 months	204 (49.4)	241 (53.1)	0.91 (0.69, 1.21)	0.52
<i>Has your child had croup diagnosed by a doctor?</i>				
6 months††	9 (2.4)	11 (2.8)	0.87 (0.36, 2.12)	0.9
6-22 months†	46 (11.2)	39 (8.6)	1.35 (0.84, 2.17)	0.21
Health Services				
<i>Has your child ever had to visit the doctor or Emergency Room for breathing or wheezing problems?</i>				
6 months	167 (44.9)	188 (47.8)	0.82 (0.60, 1.11)	0.20
6-22 months	292 (70.1)	319 (70.1)	0.98 (0.72, 1.34)	0.89
<i>Has your child had to stay in a hospital overnight?</i>				
6 months	105 (28.2)	118 (30.0)	0.89 (0.64, 1.23)	0.47
6-22 months	169 (41.0)	199 (43.7)	0.90 (0.68, 1.20)	0.48
<i>Has your child had to stay in a hospital overnight for wheezing/breathing problems?</i>				
6 months	69 (18.6)	73 (18.6)	0.98 (0.67, 1.44)	0.93
6-22 months	129 (31.3)	141 (30.8)	0.90 (0.65, 1.25)	0.53

Comment [MG2]: Why not report actual p values since they are reported for p>0.05?

Medications

<i>Treated with a diuretic medication?</i>				
6 months†	27 (6.3)	24 (5.2)	1.29 (0.72, 2.32)	0.39
6-22 months†	31 (7.1)	24 (5.0)	1.50 (0.85, 2.64)	0.16
<i>Treated with an inhaled steroid medication?</i>				
6 months	51 (11.9)	53 (11.4)	1.12 (0.73, 1.71)	0.61
6-22 months	112 (25.6)	129 (26.9)	0.97 (0.71, 1.32)	0.82
<i>Treated with a nebulized medication?</i>				
6 months††	5 (1.2)	18 (3.9)	0.30 (0.11, 0.81)	0.02
6-22 months†	29 (6.6)	42 (8.8)	0.73 (0.44, 1.22)	0.23
<i>Treated with a systemic steroid medication?</i>				
6 months††	11 (2.6)	8 (1.7)	1.54 (0.61, 3.86)	0.36
6-22 months	44 (10.1)	42 (8.8)	1.13 (0.71, 1.80)	0.62
<i>Treated with oxygen at home?</i>				
6 months†	90 (24.3)	80 (20.3)	1.22 (0.83, 1.79)	0.31
6-22 months	86 (25.1)	73 (20.0)	1.13 (0.71, 1.80)	0.14

Comment [MG3]: Why do the numbers go down from those at 6 months if this is combined over 6 to 22 months?

Family

Have you had to change your plans because of your child's breathing problems?

6 months	58 (15.5)	69 (17.5)	0.85 (0.57, 1.27)	0.43
6-22 months	139 (33.7)	170 (37.4)	0.87 (0.65, 1.17)	0.36

Results presented as number/total number (%); ARR – adjusted relative risk with adjustments for stratification factors (study center and gestational age group) and familial clustering. Where models did not converge, adjustments are limited to center and gestational age (†) or gestational age and familial clustering (††).

Table 4.

Respiratory outcomes for CPAP and surfactant cohorts at the 6 month interview and the combined 6, 12 and 18-22 month interviews (listed as 6-22 months below).

	<u>CPAP</u>	<u>Surfactant</u>	<u>ARR (95% CI)</u>	<u>p-value</u>
<u>Primary Outcomes</u>				
<i>Has your child's chest sounded wheezy or whistling more than twice in one week?</i>				
6 months	107 (23.2)	116 (26.9)	0.79 (0.58, 1.09)	0.16
6-22 months	224 (47.7)	212 (48.2)	0.90 (0.68, 1.19)	0.47
<i>Has your child had a cough for more than 3 days without a cold?</i>				
6 months†	63 (16.2)	76 (20.2)	0.77 (0.53, 1.12)	0.17
18-22 months	127 (28.4)	141 (33.7)	0.81 (0.60, 1.10)	0.18
<u>Secondary Outcomes</u>				
<u>Symptoms</u>				
<i>Wheezing/whistling more than twice in one week or cough more than 3 days</i>				
6 months	178 (45.8)	179 (47.5)	0.95 (0.70, 1.28)	0.72
6-22 months	303 (67.8)	289 (68.7)	0.95 (0.70, 1.29)	0.74
<i>Has your child's chest sounded wheezy or whistling?</i>				
6 months	151 (38.8)	155 (41.1)	0.89 (0.66, 1.21)	0.47
6-22 months	269 (60.2)	262 (62.2)	0.86 (0.64, 1.15)	0.31
<i>Has your baby's chest sounded wheezy or whistling apart from colds?</i>				
6 months	66 (17.0)	79 (21.0)	0.77 (0.53, 1.11)	0.16
6-22 months	129 (28.9)	153 (36.5)	0.68 (0.50, 0.92)	0.01
<u>Illnesses</u>				
<i>Has your child had asthma, reactive airway disease or BPD flare-up diagnosed by a doctor?</i>				
6 months†	48 (12.3)	65 (17.2)	0.66 (0.44, 1.00)	<0.05
6-22 months†	144 (32.2)	154 (36.8)	0.81 (0.60, 1.09)	0.16
<i>Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?</i>				
6 months	70 (18.0)	80 (21.2)	0.82 (0.57, 1.19)	0.3
6-22 months	167 (37.4)	177 (42.2)	0.81 (0.61, 1.09)	0.17
<i>Any of asthma, reactive airway disease, BPD flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor</i>				
6 months	96 (24.7)	108 (28.7)	0.81 (0.58, 1.13)	0.22
6-22 months	213 (47.7)	232 (55.2)	0.71 (0.53, 0.95)	0.02
<i>Has your child had croup diagnosed by a doctor?</i>				
6 months††	7 (1.8)	13 (3.5)	0.48 (0.19, 1.26)	0.14
6-22 months†	40 (9.0)	45 (10.8)	0.77 (0.49, 1.23)	0.28
<u>Health Services</u>				
<i>Has your child ever had to visit the doctor and Emergency Room for breathing or wheezing problems</i>				
6 months	173 (44.6)	182 (48.3)	0.81 (0.60, 1.10)	0.18
6-22 months	304 (68.0)	307 (72.9)	0.73 (0.53, 1.00)	<0.05
<i>Has your child had to stay in a hospital overnight?</i>				
6 months	106 (27.3)	117 (31.0)	0.79 (0.57, 1.10)	0.17
6-22 months	181 (40.7)	186 (44.3)	0.87 (0.66, 1.16)	0.35
<i>Has your child had to stay in a hospital overnight for wheezing/breathing problems?</i>				
6 months	64 (16.5)	76 (27.0)	0.72 (0.49, 1.05)	0.09
6-22 months	130 (29.1)	139 (33.1)	0.82 (0.61, 1.11)	0.21

Medications

<i>Treated with a diuretic medication?</i>				
6 months†	23 (5)	28 (6.5)	0.72 (0.40, 1.29)	0.27
6-22 months†	24 (5.1)	31 (7.0)	0.68 (0.39, 1.20)	0.18
<i>Treated with an inhaled steroid medication?</i>				
6 months	54 (11.7)	50 (11.6)	1.00 (0.66, 1.53)	0.99
6-22 months	128 (27.1)	113 (25.5)	1.10 (0.80, 1.50)	0.56
<i>Treated with a nebulized medication?</i>				
6 months††	13 (2.8)	10 (2.3)	1.18 (0.49, 2.86)	0.71
6-22 months†	39 (8.3)	32 (7.2)	1.11 (0.67, 1.84)	0.69
<i>Treated with a systemic steroid medication?</i>				
6 months††	12 (2.6)	7 (1.6)	1.45 (0.53, 3.91)	0.47
6-22 months	48 (10.2)	38 (8.6)	1.22 (0.77, 1.95)	0.4
<i>Treated with oxygen at home?</i>				
6 months†	80 (20.6)	90 (23.9)	0.82 (0.56, 1.21)	0.32
6-22 months	94 (21.0)	106 (25.3)	0.80 (0.56, 1.15)	0.23

Family

<i>Have you had to change your plans because of your child's breathing problems?</i>				
6 months	50 (12.8)	77 (20.4)	0.58 (0.39, 0.87)	<0.01
6-22 months	145 (32.4)	164 (39.0)	0.74 (0.55, 1.00)	<0.05

Results presented as number/total number (%); ARR – adjusted relative risk with adjustments for stratification factors (study center and gestational age group) and familial clustering. Where models did not converge, adjustments are limited to center and gestational age (+) or gestational age and familial clustering (††).

Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

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Word Count:

Text: MeSH terms:

Bronchopulmonary Dysplasia

Infant, Newborn

Infant, Low Birth Weight

Infant, Extremely Low Birth Weight

Infant, Premature

Infant, Extremely Low Gestational Age

Infant mortality

Respiratory morbidity

Intensive care, neonatal

Hospital Readmission

Oximetry

Randomized controlled trial

Retinopathy of prematurity (ROP)

Continuous Positive Airway Pressure

Intubation, intratracheal

Pulmonary surfactants/therapeutic use

Oxygen inhalation therapy/methods

Oxygen administration & dosage

Follow-up studies

ABSTRACT

BACKGROUND:

The NICHD SUPPORT Trial found no significant differences in the composite outcomes of death or BPD, death or ROP and death or neurodevelopmental impairment between infants randomized to treated with lower (85-89%) versus higher (91-95%) oxygen saturation targets or with to CPAP versus early surfactant (Surfactant). Though the composite incidence of death or ROP was similar, infants randomized to treated with lower rather than higher saturation targets had less ROP but greater mortality.

METHODS:

The Breathing Outcomes Sub-Study assessed reported here followed infants 24-27 6/7 weeks' gestation who were enrolled in SUPPORT, at 6 month intervals from hospital discharge to 18-22 months CA with using a series of 4 standardized parental interviews to assess respiratory-related symptoms, illnesses, medication use and health care utilization. Findings in the The study arms of low and high saturation targets and CPAP and Surfactant were compared.

Comment [R1]: Commas added for clarity

RESULTS:

From a cohort of 922 eligible infants, All four interviews were completed on 873 (94.7%) of 922 eligible infants. completed the four part interview series. The two prespecified primary outcomes, incidences of recurrent wheezing and chronic cough, were 47.9% and 32.0%, respectively, and did not differ between study arms of either randomized intervention. Among secondary outcomes, infants in the lower saturation group had a lower incidence of wheezing (36.3% vs. 43.4%, $p < 0.05$) and nebulizer use at 6 months CA and of wheezing without a cold (28.4% vs. 36.3%, $p < 0.01$) at 18-22 months CA. CPAP compared with surfactant treated group infants at 18-22 months CA had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p < 0.05$), fewer respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p = 0.02$) and fewer physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p < 0.05$).

CONCLUSION:

Treatment with lower rather than higher oxygen saturation targets may be associated with less wheezing by 18-22 months CA, a benefit which is insufficient to offset the higher mortality seen in this group as part of SUPPORT. We also conclude that CPAP and limited ventilation rather than intubation and surfactant for in infants 24 – 27 6/7th weeks' is safe and results in less respiratory morbidity by 18-22 months CA.

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BACKGROUND

Extremely preterm infants are at greater risk of respiratory symptoms and need for pulmonary care in early childhood than later preterm or term infants [1-7] and contribute substantially to the public health burden of childhood respiratory disease in the United States. [8] Mechanical ventilation and supplemental oxygen use in the early neonatal period has each been identified as a major risk factor for development of BPD and pulmonary morbidity in infancy, childhood and beyond. [1, 2, 9, 10] Though infants with Bronchopulmonary Dysplasia (BPD) are at highest risk for poor pulmonary outcome, neonates without BPD are also at risk for airway dysfunction and pulmonary morbidity during infancy. [4, 11]

The multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) studied infants 24 0/7th -27 6/7th weeks' gestation treated with each of two respiratory strategies designed to minimize mechanical ventilation and supplemental oxygen exposure: 1) ~~treatment-management~~ with lower (85-89%) compared with higher (91-95%) oxygen saturation targets and 2) early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (Surfactant). Our Network previously reported results of SUPPORT demonstrating no significant difference in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants randomized to ~~treated with~~ either of the two respiratory interventions. [12, 13] (Vaucher when available) It is important to note that although the composite incidence of death or BPD was similar, infants randomized to ~~treated with~~ lower rather than higher saturation targets had a significantly lower incidence of retinopathy of prematurity (ROP) but a significantly higher risk of mortality. [13]

We ~~now~~ report on The Breathing Outcomes Study, a secondary outcome to the SUPPORT Trial, which ~~sought to~~ compared respiratory morbidities among extremely preterm infants treated with the SUPPORT study interventions as neonates. ~~It was~~ We hypothesized that infants treated with lower rather than higher oxygen saturation targets and CPAP rather than early surfactant will each have less frequent episodes of recurrent wheezing and cough and less need for outpatient pulmonary care at 18-22 months' corrected age (CA).

METHODS

Infants eligible for The Breathing Outcomes Study were ~~these~~ infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. One thousand three hundred sixteen (1316) infants from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009. Infants were eligible for SUPPORT if their gestational age was between 24 weeks 0 days to 27 completed weeks' (up to 27 6/7ths) by best obstetrical estimate and were born at a participating center, planned to receive full resuscitation if necessary, and without major congenital malformations. Because a goal of the Breathing Outcomes Study was to obtain health outcomes on as many of the SUPPORT subjects as possible, and because enrollment into the Breathing Outcomes Study

began after SUPPORT had begun enrollment, written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT Trial or separately for those patients already enrolled in SUPPORT. As a result, the Breathing Outcomes Study cohort was a subset of the SUPPORT cohort. The study was approved by the institutional review boards at all participating Network centers and by RTI International, the data center for the NICHD Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for both SUPPORT and Breathing Outcomes. [12, 13]

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned in the delivery room to receive CPAP after birth, followed by a limited ventilation strategy if intubation were needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age. Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with either a saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Randomization for both study interventions was accomplished using block randomization with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported. [13, 14]

Assessments of the Breathing Outcomes Study

For subjects enrolled in Breathing Outcomes, a parent or primary caregiver was interviewed by research staff either in person or by phone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at 6, 12 and 18-22 months corrected age. The study questionnaires were drafted based upon questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study. [15, 16] ~~Questions were added to the Tucson questionnaires~~ ~~were added~~ questions to more fully elicit the respiratory health and health service use specific to preterm infants (e.g. palivizumab injections). To standardize administration of the interview, a lead interviewer at each participating center underwent training consisting of a teleconference with 1 of 2 project trainers (Rochester site) to discuss each study question and the written interview script associated with it. Interview trainees then interviewed a standardized patient simulated by the project trainers. Lead interviewers at each center were then able to train additional interviewers at their sites as needed. To minimize misinterpretation of other respiratory sounds as wheezing, a verbal description of wheezing and a brief audio clip of wheezing were played for the interviewee at the beginning of the interview. Questionnaires originally written in English were translated into Spanish using a certified translation service (Cornell Translation Service, Ithaca, NY). Interviews were conducted in either English or Spanish as appropriate.

To minimize loss of recall over time, interviews were conducted at 6 month intervals beginning at the time of hospital discharge. Study personnel conducted the first parent interview using a questionnaire designed to collect information on family history of respiratory diseases and atopy, home environment including tobacco and pet exposures, and diet at discharge from the hospital. Based upon the preference of each participating center, the 6, 12 and 18-22 month interviews were conducted either by

Comment [R2]: Since the windows for these interviews spanned up to two months, may be better to say "at or near"

Comment [R3]: Though you reference the Tucson study, I think it would still be important to note that the two primary outcome questions (9-10) elicit history of cough or wheezing since the "last contact," i.e. over the last 6 months give or take.

Comment [R4]: Actually, since these children were not all discharged at 0 months corrected age, and since some were seen closer to 22 months adjusted age at the final interview, this is only approximately true. May suffice to qualify this with "approximately".

trained staff at the local center (15 centers) or by long distance telephone interview from the Rochester center (5 centers). At each of the 6, 12 and 18-22 month interviews, the parent or caregiver was asked to base their responses on the 6 month interval since the last interview. If an interview at one time point was not completed, interviewees were asked to base their responses during the next interview upon the interval history since the last completed interview. Taken together, the four questionnaire series administered by interviewing the parent or primary caregiver was designed to provide a complete respiratory history over the first 18-22 months' corrected age. In addition to reporting interview responses during the first 18-22 months corrected age, we report responses from the 6 month interview because preterm infants are at especially high risk of respiratory morbidity during the first 6 months of age. REF

The 6 and 12 month interviews were based on questionnaires designed to elicit the frequency and characteristics of respiratory symptoms, including wheezing and cough; incidence of physician-diagnosed asthma, reactive airway disease or "BPD flare-up"; incidence of bronchiolitis, bronchitis or pneumonia, croup; use of medications to treat respiratory illnesses including diuretics, nebulized bronchodilators, inhaled steroids, systemic steroids or oxygen; use of health services including respiratory related physician visits, emergency room visits and hospitalizations; use of preventive therapies including palivizumab and influenza immunization; and impact on the family including whether the parent or caregiver needed to change plans due their child's breathing. In addition to the questions above, the 18-22 month interview included additional questions to elicit whether the child had atopic symptoms or conditions, including eczema and food or medication allergy.

Outcomes

Primary Outcomes: Two primary outcomes were assessed by parental report: the incidence of recurrent wheezing and incidence of chronic cough. From these in addition, the incidence of the combined outcome, recurrent wheezing or chronic cough, was also considered assessed. The incidence of wheezing was ascertained using the primary question used and validated in the Tucson Study (a large prospective birth cohort study of term infants), "Has his/her chest sounded wheezy or whistling?". [15] Recurrent wheezing was defined as wheezing occurring more than twice in any week. The incidence of chronic cough ascertained using the Tucson question, "Has [your] child had a cough for 3 days or more when he/she did not have a cold?"[15].

Secondary outcomes and covariates: Secondary outcomes were interview responses to the 6, 12 and 18-22 month questionnaires for respiratory symptoms, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, the following covariates were evaluated: family history, environmental exposures including tobacco smoke, diet and use of preventive therapies as outlined above. In addition, each patient's outcomes from SUPPORT were available to the Breathing Outcomes Study analysis.

Statistical Analyses

The available subject pool for the Breathing Outcomes Study was limited to subjects enrolled in SUPPORT who survived to hospital discharge and consented to participation. For Breathing Outcomes, a

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Comment [T5]: Where is the data for 18-22 months shown for the 4 groups. In Table 1 the title is Neonatal and Demographic characteristics. Is it a combination of findings from all assessments?

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Comment [T6]: Already stated in Methods

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sample size of 817 subjects was calculated as necessary to detect an absolute risk difference of 0.1 in the incidence of recurrent wheezing between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of recurrent wheezing of 29%. Sample size calculations for SUPPORT have been reported. [12, 13] Based upon SUPPORT's target enrollment of 1310 patients and assuming a 22% mortality (NICHD historical data for calendar year 2000), we anticipated 1021 patients potentially eligible for the Breathing Outcomes Study.

Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. For categorical variables with low frequency ($n < 5$), Fisher exact tests were used. The two primary analyses used the number of patients with either recurrent wheezing or chronic cough as the numerator and the number of infants for whom that outcome was known as the denominator. Using Poisson regression models to adjust for gestational age, stratum, study center and familial clustering, adjusted relative risk (ARR) values and 95% confidence intervals were calculated and are reported. When Poisson models did not converge, relative risk adjusted for gestational age and center is reported (indicated in tables by †). When the two adjustment models failed to converge due to low prevalence ($< 5\%$), unadjusted relative risks are reported (indicated by †† in table). Results were considered statistically significant if the two-sided p value was less than 0.05; a trend towards significance was considered if the two sided p value was between 0.05 and 0.10 inclusive. No adjustments have been made for multiple comparisons. All calculations were performed using SAS software (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study (Figure 1). Follow up rates at each time point are listed in Figure 1; Parents of a total of 873 patients infants completed the four questionnaire series (94.7%).

Characteristics of the follow-up cohort:

Among the follow up cohort, ~~the group managed with~~ randomized to lower compared with higher saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with bronchopulmonary dysplasia (BPD) defined using the traditional criteria of supplemental oxygen uses at 36 weeks' post menstrual age (PMA). The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to surfactant (Table 1). There was not a significant difference between groups in the proportion of infants with BPD defined using the physiologic definition. Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and surfactant groups (Table 2).

Primary Outcomes:

The overall incidences of the two primary outcomes for the 873 infants with complete data, episodes of wheezing more than twice per week and cough lasting more than 3 days, in the follow up cohort during the first 18-22 months corrected age were 47.3% and 33.0%, respectively. There was not a significant difference in incidence of these outcomes between either the subcohort of infants treated with randomized to lower compared with higher oxygen saturation targets nor between the subcohort

Comment [T7]: Should be clear that all of your data is for 837 infants.

infants treated with randomized to treatment with CPAP rather than surfactant (Tables 3 and 4, respectively). The combined outcome of episodes of wheezing more than twice per week or cough lasting more than 3 days for the total cohort was 64.6% and did not differ significantly between subcohorts treated with randomized to lower rather than higher saturation target or CPAP rather than surfactant (Tables 3 and 4, respectively).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months corrected age, infants randomized to lower compared with higher saturation targets had a lower incidence of wheezing and in use of nebulized medications since NICU discharge (36.3% vs. 43.4%, $p < 0.05$ and 1.2% vs. 3.9%, $p = 0.02$, respectively) (Table 3). Supporting these differences in wheezing was a trend toward a lower incidence of recurrent wheezing defined as wheezing episodes occurring more than twice per week (22.0% vs. 27.7%, $p = 0.06$) (Table 3). Over the first 18-22 months of corrected age (listed as 6- 22 months in Tables 3 and 4), infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (28.4% vs. 36.3%, $p = 0.01$) (Table 3);

Early CPAP Intervention

At 6 months corrected age, infants treated randomized to treatment with CPAP rather than surfactant were reported to have fewer asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor since NICU discharge (12.3% vs. 17.2%, $p < 0.05$) and a trend toward fewer hospitalizations for wheezing or breathing problems (16.5% vs. 27.0%, $p = 0.09$). Perhaps related to these differences, parents or primary caregivers of infants treated with randomized to CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (12.8% vs. 20.4%, $p < 0.01$) (Table 4).

During the first 6-22 months corrected age, infants receiving randomized to early CPAP versus surfactant were significantly less likely to have wheezing episodes occurring without a cold (28.9% vs. 36.5%, $p = 0.01$), respiratory illnesses diagnosed by a doctor (one or more episodes of asthma, reactive airway disease or BPD flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, $p = 0.02$), wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, $p < 0.05$). Compared with those of surfactant-treated infants in the surfactant group, parents or guardians of infants in the CPAP group CPAP-treated infants were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, $p < 0.05$).

DISCUSSION

We report respiratory outcomes during the first 18-22 months' corrected age for a cohort of extremely premature infants (24-27 6/7 weeks' gestation) treated in the NICHD SUPPORT Trial. We found no significant differences in reported respiratory outcomes at 18-22 months corrected age between patients treated with randomized to lower rather than higher saturation targets or with to CPAP rather

Comment [R8]: For children with a positive hx of wheezing is this based on the secondary question which asks about wheezing "on average" rather than the one re the "worst two weeks"?

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Comment [T9]: Confusing. Tables say 6,12 and 22 m

Comment [R10]: Agree this is confusing. The headings of the table notes 6,12, 18-22; but the rows in the table specify 6 and 6-22. Think you need to specify under methods how the "6-22 month" data points were calculated to show how they reflect "the first 18-22 months of corrected age". Moreover, since each of these interviews reflect events "since the last contact" the 6 month interview presumably reflects the time period since NICU discharge. So does the "6-22 month" data point reflect the 12 and 18-22 month interviews or 6, 12, and 18-22 month. If the latter then it would come close reflecting the "first 18-22 months of corrected age," though I think the suggested rewording by Betty below ("between discharge and 18-22 months corrected age") is more accurate. However, if it does not include the 6 month interview, then would reflect the first 6 to 18-22 months of corrected age, which is what you describe two paragraphs below for Early CPAP.

Comment [R11]: See preceding comment.

than surfactant in either of the two primary outcomes, incidence of recurrent wheezing and incidence of cough lasting more than 3 days without a cold.

In secondary analyses, extremely preterm infants ~~managed with~~ randomized to low compared with high saturation targets were less likely to have wheezing or use a home nebulizer at 6 months corrected age and to have wheezing apart from a cold between discharge and during the first 18-22 months corrected age. In the main SUPPORT trial, patients ~~managed with~~ randomized to lower compared with higher saturation targets were exposed to lower concentration of inspired oxygen. Several pulmonary outcome studies have found an association between neonatal oxygen exposure and expiratory flow dysfunction and airway hyperreactivity among infants with or without BPD. [2, 7, 17-19] Our results, taken together with current literature, suggest that lower oxygen exposure in the neonatal period may be associated with reduced wheezing in infancy. However, based upon the findings of greater mortality among patients in SUPPORT ~~treated with~~ randomized to lower rather than higher saturation targets, the benefit of reduced wheezing and nebulizer use does not justify management of patients 24-27 6/7 weeks' gestation with lower oxygen saturation targets. If oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant injury other than targeting lower oxygen saturations will be needed. [20, 21]

Comment [MG12]: This statement makes it sound like this was an outcome reported in the primary SUPPORT paper, but I don't recall that being the case.

Patients ~~treated with~~ randomized to CPAP and limited ventilation rather than intubation and surfactant administration within 1 hour had fewer asthma, reactive airway disease or BPD flare-up episodes at 6 months corrected age and a trend toward fewer hospitalizations for respiratory problems. Perhaps related to these findings was a significant reduction in the proportion of parents reporting that they needed to change plans due to their child's breathing difficulties. During the first 18-22 months corrected age, patients randomized to ~~receiving~~ early CPAP rather than surfactant were significantly less likely to have had wheezing episodes occurring without a cold, respiratory illnesses diagnosed by a physician or physician or emergency room visits for breathing or wheezing problems. Parents of CPAP compared with surfactant ~~treated-group~~ infants were less likely to report changing their plans due to the child's breathing problems. These respiratory benefits were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria, was similar between CPAP and surfactant arms in the SUPPORT study and in the Breathing Outcomes' follow-up cohort. Our data are consistent with follow up data from The COIN Trial, which despite finding no difference in the incidence of death or BPD among 610 infants randomized to either CPAP or conventional management, found better pulmonary function at 8 weeks corrected among a 39 patient subcohort of study infants randomized to ~~treated with~~ CPAP. [22, 23] These observations suggest that treatment of infants 24-27 6/7 weeks gestation at risk for RDS with CPAP is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone and that longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions in randomized clinical trials.

We found that regardless of treatment arm, respiratory symptoms and health care usage are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months corrected age. Overall in the Breathing Outcomes cohort, recurrent wheezing occurred in 47.9% of patients and asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor in 34.5%. Treatment of these conditions

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prompted not only frequent physician visits (63.8% of children), emergency room visits (46.6%) and hospitalizations (42.5%), which have the potential to add to health care costs [8] but also to frequent use of both inhaled (26.3%) and systemic (9.4%) steroids which have potential long term effects on growth and development. [24, 25]

The strengths of this study include the large number of extremely preterm infants enrolled. This is the largest respiratory follow up study of a randomized clinical trial. Other strengths include the high follow up rates for enrolled patients and use of comprehensive respiratory questionnaires administered in a scripted interview by trained personnel. Though not as objective as pulmonary function testing, respiratory history was used as outcome measures due to clinical and financial concerns associated with use of invasive pulmonary testing and potential complications of sedation in former preterm infants. In addition, parental report of wheezing has been shown to correlate with pulmonary function testing and data extracted from office records and provides an estimate of the burden of respiratory morbidity to the patient and family as well as the health care system. [26, 27] Among potential weaknesses, respiratory history data were taken by parental report, which has the potential for classification and recall bias. To minimize classification bias, all primary and follow up study data of this randomized trial were collected in a blinded manner. Hence, though it may affect the precision of point estimates, classification bias is unlikely to have introduced systematic bias into our study that favors one study arm over another. To reduce recall bias, parent interviews were conducted at 6 month intervals. [27] Because the Breathing Outcomes Study was approved and began enrollment after SUPPORT had begun and because we wished to follow all available SUPPORT subjects, study results are not reported as competing outcomes (e.g. death or recurrent wheezing) but rather as respiratory outcomes of the cohort of SUPPORT subjects that survived to hospital discharge. As has been previously reported, the results of SUPPORT and thereby potentially the follow up studies associated with it may not be fully generalizable to all extremely preterm infants because the need for antenatal consent resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort. [28]

In summary, we found no significant differences in the incidence of recurrent wheezing or chronic cough at 18-22 months corrected age between extremely preterm survivors who were randomized at delivery to either lower or higher saturation targets and early CPAP or surfactant. In secondary analyses, we found reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months corrected age in the lower saturation group. However, because randomization to management with lower saturation targets was associated with greater mortality in SUPPORT [13], we conclude that the benefit of reduced wheezing and nebulizer use seen in the Breathing Outcomes Study does not justify treatment with lower saturation targets in patients 24-27 6/7 weeks' gestation. Also in secondary analyses, we report fewer respiratory symptoms, physician diagnosed respiratory problems and reduced health care use among infants randomized to treated with CPAP rather than early surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over surfactant. [12, 13]{add Vaucher reference when available}. Those findings coupled with the respiratory outcomes identified in this report reported here suggest that treatment of extremely premature infants with CPAP and limited ventilation rather than intubation and

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Comment [T13]: This data is not shown or discussed in the results section. Do you need a column on your tables for total cohort. You could combine tables 3 and 4 in landscape and add a total cohort column ??
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early surfactant administration is safe and may result in less respiratory morbidity during the first 18-22 months corrected age. The findings also clearly demonstrate the increased risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation and the need for close medical monitoring post-discharge.

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Acknowledgements

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We wish to acknowledge the Tucson Children's Respiratory Study (Marifyn Lindell, RN), Tucson, Az for support of this project by sharing respiratory symptom questionnaires which were adapted for use in this study.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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From: Kennedy, Kathleen A
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Another revision (exams in zone III)
Date: Wednesday, October 31, 2012 4:18:17 PM

I removed the "mature" description from the manuscript awhile back. I think it was used in the SUPPORT documents but it doesn't add anything but confusion to "vessels fully to the ora serrata".

Since we don't collect information about whether the vessels were just barely in zone III or almost to the ora serrata, I don't really think we can answer the questions that are relevant to ophthalmologists about when it's ok to stop doing exams. So I no longer think that trying to put more detail in this paper about the outcome of babies with one study exam recorded in zone III will be very helpful. And it opens up a can of worms about the atypical or implausible outcomes among these babies that Lisa and Marie have uncovered. I think it would be best to leave that part of the paper as is (just say that 2/251 with one exam in zone III later developed severe ROP).

Lisa is working on a few more minor tweaks for Figures 2 and 3 (shouldn't take long).

Once Dale looks at the most recent revision of the manuscript, I think we'll be ready to send it on for internal review.

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, October 29, 2012 4:04 PM
To: Kennedy, Kathleen A
Subject: RE: Another revision (exams in zone III)

Part 1: I agree that "favorable ROP" is one exam with vessels fully to the ora serrata, [I would not insert the word 'mature' unless it is part of the protocol definition-- if it is in the protocol, use it.] or two consecutive exams with vessels in zone III.

We did not require the absence of "severe ROP" and I would not add that.

Part 2:

There are some ophthalmologists who say that one examination with vessels in zone III means the baby is safe.

We need our data to the contrary to show that this is not correct.

We want to include all infants who had zone III reported on the data forms.

So: if we take all eyes that were recorded to have zone III vessels, they would fall out in a flow sheet as follows:

- A. there was no next examination recorded (died, lost to follow up, did not return, ophthalmologist refused to schedule)
- B. there was a next examination recorded
 - B1. zone III again and considered 'favorable final'
 - B2. zone II but no severe ROP ever developed
 - B2. zone II and went on to develop severe ROP in subsequent exams

Group A does not provide any information for the question: missing (unless you get information from the lawyer that detachments occurred).

Group B1. is the majority and they are favorable as we expect most to be

Group B2. is a 'near miss', a warning that zone III is sometimes misidentified --

Group B3. is the red flag Do we have any such cases?

Dale

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Monday, October 29, 2012 1:09 PM
To: Wrage, Lisa Ann; Phelps, Dale
Cc: higginsr@mail.nih.gov
Subject: RE: Another revision (exams in zone III)

Based on this, it sounds like we should change our description of "favorable" ROP to one exam with mature vessels to the ora serrata or two consecutive exams with vessels in zone III and no severe ROP. As Dale said before, it's implied that you can't have severe ROP and a favorable outcome on the same exam, but we can be more explicit. We can't say anything else about how much ROP was present when the two consecutive exams were deemed to meet the "favorable" criteria.

The more we debate this, the less inclined I've become to think that we can do something useful with the information on babies who had 1 exam in zone III. I was hoping that we could use this data to help with adjudicated outcomes in future trials, but I'm very skeptical that we can do that. I know that we had a few adjudicated outcomes in our site because they only had 1 exam in zone III and our ophthalmologist didn't think they were of sufficient clinical risk to warrant another exam. I'm guessing that decision was based not on whether they had ROP or not (we could get that info from study forms) but whether the vessels were just barely in zone III or almost to the ora serrata. The former are probably the ones who are still at risk (the reason for the two exam requirement). The latter may be at minimal risk but they look the same on the study forms. So maybe we should just drop this for now unless the reviewers ask about it. Do you agree, Dale?

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, October 29, 2012 12:33 PM
To: Phelps, Dale; Kennedy, Kathleen A
Cc: higginsr@mail.nih.gov
Subject: RE: Another revision

Kathleen and Dale,

I asked Marie to verify / clear up how favorable outcome was determined and this was her reply:

A favorable outcome was (a) one exam with mature vessels (zone=4) or (b) two consecutive exams with vessels in zone III (zone=3).

To address Dale's comment that no "plus disease" was assumed, looking back at the data, there was one case (center 11 network 77161) where the infant reached final status by having two exams with vessels in zone III (in both eyes) and then in a later exam the left eye was coded as lowest zone of any vessels=3, highest stage in lowest zone=1, plus disease=Y (which seems likely to be a typo but I don't think it would have qualified as threshold ROP because ROP was only stage 1). There was another infant (center 21 network 70331) who reached a positive outcome because of having mature vessels, but a previous exam was coded as vessels in zone III with no ROP but with plus disease=Y (which also would not qualify as threshold ROP, and I don't even know if it is possible to have plus disease with no ROP). I don't think there is reason to be concerned about either of those cases.

To answer Kathleen's question about "Was it two eye exams with vessels in Zone 3 or two eye exams with no ROP and vessels in Zone 3?" we did not consider ROP in that part of the definition (which was consistent with the protocol and manual, as Kathleen notes). Of infants who had a favorable outcome because of having mature vessels, none were classified as having ROP at the time. However, of those who had a favorable outcome because of having 2 consecutive exams with vessels in zone III, most were coded as having ROP at the time.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 24, 2012 2:14 PM
To: Kathleen.A.Kennedy@uth.tmc.edu; Wrage, Lisa Ann
Cc: higginsr@mail.nih.gov
Subject: RE: Another revision

This is a quick answer about the favorable outcome.

Two consecutive examinations with vessels or ROP in zone III, (without plus disease was assumed).

I'll try to get back to you on the rest before my flight leaves in 1 hr.

Dale

Dale Phelps

From my Droid

-----Original message-----

From: "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>

To: "Wrage, Lisa Ann" <wrage@rti.org>

Cc: "Phelps, Dale" <Dale_Phelps@URMC.Rochester.edu>, "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>

Sent: Wed, Oct 24, 2012 16:40:05 GMT+00:00

Subject: RE: Another revision

Lisa, thanks again for your work on this.

Remaining questions for Lisa:

I'm still not clear on how a favorable study endpoint was defined. Was it two eye exams with vessels in Zone 3 or two eye exams with no ROP and vessels in Zone 3? The manual just says "Vessels in zone III for two sequential eye examinations". I don't know if that's because it was considered "favorable" if they had exams with mild ROP in zone 3 or if it was assumed that the ophthalmologist would keep following them if that occurred. Or maybe it just never happens. I think we should be very clear about this in the manuscript.

I like the new Figure 2. I think it would look better if you could make the fonts bolder (as they were on the previous version) and the titles on the x-axis need to be centered below the appropriate group of bars. I think it would look a little better if the bars for each week were slightly closer together but that's a minor point and it probably won't look better if you have to move them too close to each other.

I've relabeled the title for Table 3 to say that these are "95% confidence intervals". The tracking changes made it a little hard to see some of the numbers in the revised table. Please verify.

I don't think the new Figure 3 really solves the problem of the figure appearing to be different from the data in the table. You just can't see where the line starts departing from zero. I also like the original colors better. The light yellow is hard to see.

Dale,

I never got a response to the email I sent on 9/12. Here's a copy of the part that was directed to you: "The attached revision is my attempt to do what everyone asked whenever feasible. The changes that I made in response to other people's suggestions are highlighted in yellow. I'd appreciate it if you'd look at those parts to see if you agree with the changes. I wasn't able to make all the changes that you suggested to the What's new? and the Abstract because of the word limits. The biggest changes have to do with incorporating 2 new similar papers (we really need to get this done and published before there are more) and trying to clarify the Discussion about postmenstrual vs chronologic age. It didn't even make sense to me after I'd taken a break from it for a while. We may need to tweak the wording some more when Lisa finishes the analyses but I don't think there will be major changes. As always, I look forward to your comments on this."

The most recent changes to the manuscript (based on Lisa's responses to the 9/12 email) are highlighted in gray in the attachment.

All,

When these questions are resolved, I think we will have done everything that's reasonable to respond to the subcommittee's comments. (I asked Wally and Neil for clarification of some of their comments and never got a response so I think we can go with what we have). I'd really like to send this to Bill Truog for internal review soon. I think we're very close.

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From: Ehrenkranz, Richard
To: Stevens, Timothy
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper
Date: Wednesday, October 31, 2012 11:46:51 AM
Attachments: Manuscript -Stevens BreathingOutcomes Edits NF 31Oct12-rae.docx

Sorry,
Richard

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

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Wednesday, October 31, 2012 11:39 AM
To: Ehrenkranz, Richard
Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Hi Rich

Thanks for your review. The document with you edits did not come with your note. Can you resend?

Thanks

Tim

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

From: Ehrenkranz, Richard [<mailto:richard.ehrenkranz@yale.edu>]
Sent: Wednesday, October 31, 2012 11:26 AM
To: Stevens, Timothy
Cc: 'higginsr@mail.nih.gov'
Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Tim:

Excellent draft. I added several minor edits/suggestions to Neil's Richard

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Hi Tim

I have added my edits

This reads well

Nice work

Neil

Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

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Word Count:

Text: MeSH terms:

Bronchopulmonary Dysplasia
Infant, Newborn
Infant, Low Birth Weight
Infant, Extremely Low Birth Weight
Infant, Premature
Infant, Extremely Low Gestational Age
Infant mortality
Respiratory morbidity
Intensive care, neonatal
Hospital Readmission
Oximetry
Randomized controlled trial
Retinopathy of prematurity (ROP)
Continuous Positive Airway Pressure
Intubation, intratracheal
Pulmonary surfactants/therapeutic use
Oxygen inhalation therapy/methods
Oxygen administration & dosage
Follow-up studies

ABSTRACT

BACKGROUND:

The NICHD SUPPORT Trial found no difference in the composite outcomes of death or BPD, death or ROP and death or neurodevelopmental impairment between infants treated with lower (85-89%) versus higher (91-95%) oxygen saturation targets or with CPAP versus early surfactant (Surfactant). Though the composite incidence of death or ROP was similar, infants treated with lower rather than higher saturation targets had less ROP but greater mortality.

METHODS:

The Breathing Outcomes Sub-Study ~~assessed reported here~~ followed infants 24-27 6/7 weeks' gestation, who were enrolled in SUPPORT, at 6 month intervals from hospital discharge to 18-22 months CA ~~with~~ using a series of 4 standardized parental interviews to assess respiratory-related symptoms, illnesses, medication use and health care utilization. ~~Findings in the~~ The study arms of low and high saturation and CPAP and Surfactant were compared.

Comment [R1]: Commas added for clarity

Comment [rae2]: CA has not been defined yet. Need to state "...corrected age (CA)..."

RESULTS:

~~From a cohort of 922 eligible infants, All four interviews were completed on 873 (94.7%) of 922 eligible infants, completed the four part interview series.~~ The two prespecified primary outcomes, incidences of recurrent wheezing and chronic cough, were 47.9% and 32.0%, respectively, and did not differ between study arms of either randomized intervention. Among secondary outcomes, infants in the lower saturation group had a lower incidence of wheezing (36.3% vs. 43.4%, $p < 0.05$) and nebulizer use at 6 months CA and of wheezing without a cold (28.4% vs. 36.3%, $p < 0.01$) at 18-22 months CA. CPAP compared with surfactant treated infants at 18-22 months CA had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p < 0.05$), fewer respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p = 0.02$) and fewer physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p < 0.05$).

CONCLUSION:

Treatment with lower rather than higher oxygen saturation targets may be associated with less wheezing by 18-22 months CA, a benefit which is insufficient to offset the higher mortality seen in this group as part of SUPPORT. ~~We also conclude that~~ CPAP and limited ventilation rather than intubation and surfactant ~~for~~ infants 24 – 27 6/7th weeks' is safe and results in less respiratory morbidity by 18-22 months CA.

Word count: 315

BACKGROUND

Extremely preterm infants are at greater risk of respiratory symptoms and need for pulmonary care in early childhood than later preterm or term infants [1-7] and contribute substantially to the public health burden of childhood respiratory disease in the United States. [8] Mechanical ventilation and supplemental oxygen use in the early neonatal period has each been identified as a major risk factor for development of BPD and pulmonary morbidity in infancy, childhood and beyond. [1, 2, 9, 10] Though infants with Bronchopulmonary Dysplasia (BPD) are at highest risk for poor pulmonary outcome, neonates without BPD are also at risk for airway dysfunction and pulmonary morbidity during infancy. [4, 11]

Comment [rae3]: Need to define BPD, so this should be "bronchopulmonary dysplasia (BPD)..." in this line and just "...BPD..." on the next line. Mike O'Shea already pointed this out.

The multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) studied infants 24 0/7th -27 6/7th weeks' gestation treated with each of two respiratory strategies designed to minimize mechanical ventilation and supplemental oxygen exposure: 1) treatment with lower (85-89%) compared with higher (91-95%) oxygen saturation targets and 2) early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (Surfactant). Our Network previously reported results of SUPPORT demonstrating no difference in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants treated with either of the two respiratory interventions. [12, 13] (Vaucher when available) It is important to note that although the composite incidence of death or BPD was similar, infants treated with lower rather than higher saturation targets had a significantly lower incidence of retinopathy of prematurity (ROP) but a significantly higher risk of mortality. [13]

We now report on The Breathing Outcomes Study, a secondary outcome to the SUPPORT Trial, which ~~seught to~~ compared respiratory morbidity among extremely preterm infants treated with the SUPPORT study interventions as neonates. ~~It was~~ We hypothesized that infants treated with lower rather than higher oxygen saturation targets and CPAP rather than early surfactant will each have less frequent episodes of recurrent wheezing and cough and less need for outpatient pulmonary care at 18-22 months' corrected age (CA).

METHODS

Infants eligible for The Breathing Outcomes Study were ~~these~~ infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. One thousand three hundred sixteen (1316) infants from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009. Infants were eligible for SUPPORT if their gestational age was between 24 weeks 0 days to 27 completed weeks' (up to 27 6/7ths) by best obstetrical estimate and were born at a participating center, planned to receive full resuscitation if necessary, and without major congenital malformations. Because a goal of the Breathing Outcomes Study was to obtain health outcomes on as many of the SUPPORT subjects as possible, and because enrollment into the Breathing Outcomes Study

began after SUPPORT had begun enrollment, written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT Trial or separately for those patients already enrolled in SUPPORT. As a result, the Breathing Outcomes Study cohort was a subset of the SUPPORT cohort. The study was approved by the institutional review boards at all participating Network centers and by RTI International, the data center for the NICHD Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for both SUPPORT and Breathing Outcomes.[12, 13]

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned in the delivery room to receive CPAP after birth, followed by a limited ventilation strategy if intubation were needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age. Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with either a saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Randomization for both study interventions was accomplished using block randomization with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported.[13, 14]

Assessments of the Breathing Outcomes Study

For subjects enrolled in Breathing Outcomes, a parent or primary caregiver was interviewed by research staff either in person or by phone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at 6, 12 and 18-22 months corrected age. The study questionnaires were drafted based upon questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study.[15, 16] Questions were added to the Tucson questionnaires were added questions to more fully elicit the respiratory health and health service use specific to preterm infants (e.g. palivizumab injections). To standardize administration of the interview, a lead interviewer at each participating center underwent training consisting of a teleconference with 1 of 2 project trainers (Rochester site) to discuss each study question and the written interview script associated with it. Interview trainees then interviewed a standardized patient simulated by the project trainers. Lead interviewers at each center were then able to train additional interviewers at their sites as needed. To minimize misinterpretation of other respiratory sounds as wheezing, a verbal description of wheezing and a brief audio clip of wheezing were played for the interviewee at the beginning of the interview. Questionnaires originally written in English were translated into Spanish using a certified translation service (Cornell Translation Service, Ithaca, NY). Interviews were conducted in either English or Spanish as appropriate.

To minimize loss of recall over time, interviews were conducted at 6 month intervals beginning at the time of hospital discharge. Study personnel conducted the first parent interview using a questionnaire designed to collect information on family history of respiratory diseases and atopy, home environment including tobacco and pet exposures, and diet at discharge from the hospital. Based upon the preference of each participating center, the 6, 12 and 18-22 month interviews were conducted either by

Comment [R4]: Since the windows for these interviews spanned up to two months, may be better to say "at or near"

Comment [rae5]: Insert "(CA)" after corrected age and then use the abbreviation throughout the paper.

Comment [R6]: Though you reference the Tucson study, I think it would still be important to note that the two primary outcome questions (9-10) elicit history of cough or wheezing since the "last contact," i.e. over the last 6 months give or take.

Comment [R7]: Actually, since these children were not all discharged at 0 months corrected age, and since some were seen closer to 22 months adjusted age at the final interview, this is only approximately true. May suffice to qualify this with "approximately".

trained staff at the local center (15 centers) or by long distance telephone interview from the Rochester center (5 centers). At each of the 6, 12 and 18-22 month interviews, the parent or caregiver was asked to base their responses on the 6 month interval since the last interview. If an interview at one time point was not completed, interviewees were asked to base their responses during the next interview upon the interval history since the last completed interview. Taken together, the four questionnaire series administered by interviewing the parent or primary caregiver was designed to provide a complete respiratory history over the first 18-22 months' corrected age. In addition to reporting interview responses during the first 18-22 months corrected age, we report responses from the 6 month interview because preterm infants are at especially high risk of respiratory morbidity during the first 6 months of age. REF

The 6 and 12 month interviews were based on questionnaires designed to elicit the frequency and characteristics of respiratory symptoms, including wheezing and cough; incidence of physician-diagnosed asthma, reactive airway disease or "BPD flare-up"; incidence of bronchiolitis, bronchitis or pneumonia, croup; use of medications to treat respiratory illnesses including diuretics, nebulized bronchodilators, inhaled steroids, systemic steroids or oxygen; use of health services including respiratory related physician visits, emergency room visits and hospitalizations; use of preventive therapies including palivizumab and influenza immunization; and impact on the family including whether the parent or caregiver needed to change plans due their child's breathing. In addition to the questions above, the 18-22 month interview included additional questions to elicit whether the child had atopic symptoms or conditions, including eczema and food or medication allergy.

Outcomes

Primary Outcomes: Two primary outcomes were assessed by parental report: the incidence of recurrent wheezing and incidence of chronic cough. ~~From these~~ In addition, the incidence of the combined outcome, recurrent wheezing or chronic cough, was also considered assessed. The incidence of wheezing was ascertained using the primary question used and validated in the Tucson Study (a large prospective birth cohort study of term infants), "Has his/her chest sounded wheezy or whistling?" [15] Recurrent wheezing was defined as wheezing occurring more than twice in any week. The incidence of chronic cough ascertained using the Tucson question, "Has [your] child had a cough for 3 days or more when he/she did not have a cold?" [15].

Secondary outcomes and covariates: Secondary outcomes were interview responses to the 6, 12 and 18-22 month questionnaires for respiratory symptoms, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, the following covariates were evaluated: family history, environmental exposures including tobacco smoke, diet and use of preventive therapies as outlined above. In addition, each patient's outcomes from SUPPORT were available to the Breathing Outcomes Study analysis.

Statistical Analyses

The available subject pool for the Breathing Outcomes Study was limited to subjects enrolled in SUPPORT who survived to hospital discharge and consented to participation. For Breathing Outcomes, a

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Comment [T8]: Where is the data for 18-22 months shown for the 4 groups. In Table 1 the title is Neonatal and Demographic characteristics. Is it a combination of findings from all assessments?

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Comment [T9]: Already stated in Methods

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sample size of 817 subjects was calculated as necessary to detect an absolute risk difference of 0.1 in the incidence of recurrent wheezing between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of recurrent wheezing of 29%. Sample size calculations for SUPPORT have been reported. [12, 13] Based upon SUPPORT's target enrollment of 1310 patients and assuming a 22% mortality (NICHD historical data for calendar year 2000), we anticipated 1021 patients potentially eligible for the Breathing Outcomes Study.

Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. For categorical variables with low frequency ($n < 5$), Fisher exact tests were used. The two primary analyses used the number of patients with either recurrent wheezing or chronic cough as the numerator and the number of infants for whom that outcome was known as the denominator. Using Poisson regression models to adjust for gestational age strata, study center and familial clustering, adjusted relative risk (ARR) values and 95% confidence intervals were calculated and are reported. When Poisson models did not converge, relative risk adjusted for gestational age and center is reported (indicated in tables by †). When the two adjustment models failed to converge due to low prevalence ($< 5\%$), unadjusted relative risks are reported (indicated by †† in table). Results were considered statistically significant if the two-sided p value was less than 0.05; a trend towards significance was considered if the two sided p value was between 0.05 and 0.10 inclusive. No adjustments have been made for multiple comparisons. All calculations were performed using SAS software (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study (Figure 1). Follow up rates at each time point are listed in Figure 1; Parents of a total of 873 patients infants completed the four questionnaire series (94.7%).

Comment [T10]: Should be clear that all of your data is for 837 infants.

Characteristics of the follow-up cohort:

Among the follow up cohort, the group managed with lower compared with higher saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with bronchopulmonary dysplasia (BPD) defined using the traditional criteria of supplemental oxygen uses at 36 weeks' post menstrual age (PMA). The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to surfactant (Table 1). There was no difference between groups in the proportion of infants with BPD defined using the physiologic definition. Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and surfactant groups (Table 2).

Comment [rae11]: BPD has already been defined as the abbreviation for bronchopulmonary dysplasia [see first paragraph of the introduction].

Primary Outcomes:

The overall incidences of the two primary outcomes for the 873 infants with complete data, episodes of wheezing more than twice per week and cough lasting more than 3 days, in the follow up cohort during the first 18-22 months corrected age were 47.3% and 33.0%, respectively. There was no difference in incidence of these outcomes between either the subcohort of infants treated with lower compared with higher oxygen saturation targets nor between the subcohort infants treated with CPAP rather than

surfactant (Tables 3 and 4, respectively). The combined outcome of episodes of wheezing more than twice per week or cough lasting more than 3 days for the total cohort was 64.6% and did not differ significantly between subcohorts treated with lower rather than higher saturation target or CPAP rather than surfactant (Tables 3 and 4, respectively).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months corrected age, infants randomized to lower compared with higher saturation targets had a lower incidence of wheezing and in use of nebulized medications since NICU discharge (36.3% vs. 43.4%, $p < 0.05$ and 1.2% vs. 3.9%, $p = 0.02$, respectively) (Table 3). Supporting these differences in wheezing was a trend toward a lower incidence of recurrent wheezing defined as wheezing episodes occurring more than twice per week (22.0% vs. 27.7%, $p = 0.06$) (Table 3). Over the first 18-22 months of corrected age (listed as 6- 22 months in Tables 3 and 4), infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (28.4% vs. 36.3%, $p = 0.01$) (Table 3).

Early CPAP Intervention

At 6 months corrected age, infants treated with CPAP rather than surfactant were reported to have fewer asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor since NICU discharge (12.3% vs. 17.2%, $p < 0.05$) and a trend toward fewer hospitalizations for wheezing or breathing problems (16.5% vs. 27.0%, $p = 0.09$). Perhaps related to these differences, parents or primary caregivers of infants treated with CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (12.8% vs. 20.4%, $p < 0.01$) (Table 4).

During the first 6-22 months corrected age, infants receiving early CPAP versus surfactant were significantly less likely to have wheezing episodes occurring without a cold (28.9% vs. 36.5%, $p = 0.01$), respiratory illnesses diagnosed by a doctor (one or more episodes of asthma, reactive airway disease or BPD flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, $p = 0.02$), wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, $p < 0.05$). Compared with those of surfactant treated infants, parents or guardians of CPAP treated infants were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, $p < 0.05$).

Comment [R12]: For children with a positive hx of wheezing is this based on the secondary question which asks about wheezing "on average" rather than the one re the "worst two weeks"?

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Comment [T13]: Confusing. Tables say 6,12 and 22 m

Comment [R14]: Agree this is confusing. The headings of the table notes 6,12, 18-22; but the rows in the table specify 6 and 6-22. Think you need to specify under methods how the "6-22 month" data points were calculated to show how they reflect "the first 18-22 months of corrected age." Moreover, since each of these interviews reflect events "since the last correct" the 6 month interview presumably reflects the time period since NICU discharge. So does the "6-22 month" data point reflect the 12 and 18-22 month interviews or 6, 12, and 18-22 month. If the latter then it would come close reflecting the "first 18-22 months of corrected age," though I think the suggested rewording by Betty below ("between discharge and 18-22 months corrected age") is more accurate. However, if it does not include the 6 month interview, then would reflect the first 6 to 18-22 months of corrected age, which is what you describe two paragraphs below for Early CPAP.

Comment [R15]: See preceding comment.

DISCUSSION

We report respiratory outcomes during the first 18-22 months' corrected age for a cohort of extremely premature infants (24-27 6/7 weeks' gestation) treated in the NICHD SUPPORT Trial. We found no significant differences in reported respiratory outcomes at 18-22 months corrected age between patients treated with lower rather than higher saturation targets or with CPAP rather than surfactant in either of the two primary outcomes, incidence of recurrent wheezing and incidence of cough lasting more than 3 days without a cold.

In secondary analyses, extremely preterm infants managed with low compared with high saturation targets were less likely to have wheezing or use a home nebulizer at 6 months corrected age and to have wheezing apart from a cold ~~between discharge and during the first~~ 18-22 months corrected age. In the main SUPPORT trial, patients managed with lower compared with higher saturation targets were exposed to lower concentration of inspired oxygen. Several pulmonary outcome studies have found an association between neonatal oxygen exposure and expiratory flow dysfunction and airway hyperreactivity among infants with or without BPD. [2, 7, 17-19] Our results, taken together with current literature, suggest that lower oxygen exposure in the neonatal period may be associated with reduced wheezing in infancy. However, based upon the findings of greater mortality among patients in SUPPORT treated with lower rather than higher saturation targets, the benefit of reduced wheezing and nebulizer use does not justify management of patients 24-27 6/7 weeks' gestation with lower oxygen saturation targets. If oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant injury other than targeting lower oxygen saturations will be needed. [20, 21]

Patients treated with CPAP and limited ventilation rather than intubation and surfactant administration within 1 hour had fewer asthma, reactive airway disease or BPD flare-up episodes at 6 months corrected age and a trend toward fewer hospitalizations for respiratory problems. Perhaps related to these findings was a significant reduction in the proportion of parents reporting that they needed to change plans due to their child's breathing difficulties. During the first 18-22 months corrected age, patients receiving early CPAP rather than surfactant were significantly less likely to have had wheezing episodes occurring without a cold, respiratory illnesses diagnosed by a physician or physician or emergency room visits for breathing or wheezing problems. Parents of CPAP compared with surfactant treated infants were less likely to report changing their plans due to the child's breathing problems. These respiratory benefits were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria, was similar between CPAP and surfactant arms in the SUPPORT study and in the Breathing Outcomes' follow-up cohort. Our data are consistent with follow up data from The COIN Trial, which despite finding no difference in the incidence of death or BPD among 610 infants randomized to either CPAP or conventional management, found better pulmonary function at 8 weeks corrected among a 39 patient subcohort of study infants treated with CPAP. [22, 23] These observations suggest that treatment of infants 24-27 6/7 weeks gestation at risk for RDS with CPAP is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone and that longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions in randomized clinical trials.

We found that regardless of treatment arm, respiratory symptoms and health care usage are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months corrected age. Overall in the Breathing Outcomes cohort, recurrent wheezing occurred in 47.9% of patients and asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor in 34.5%. Treatment of these conditions prompted not only frequent physician visits (63.8% of children), emergency room visits (46.6%) and hospitalizations (42.5%), which have the potential to add to health care costs [8] but also to frequent use of both inhaled (26.3%) and systemic (9.4%) steroids which have potential long term effects on growth and development. [24, 25]

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Comment [T16]: This data is not shown or discussed in the results section. Do you need a column on your tables for total cohort. You could combine tables 3 and 4 in landscape and add a total cohort column ??

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The strengths of this study include the large number of extremely preterm infants enrolled. This is the largest respiratory follow up study of a randomized clinical trial. Other strengths include the high follow up rates for enrolled patients and use of comprehensive respiratory questionnaires administered in a scripted interview by trained personnel. Though not as objective as pulmonary function testing, respiratory history was used as outcome measures due to clinical and financial concerns associated with use of invasive pulmonary testing and potential complications of sedation in former preterm infants. In addition, parental report of wheezing has been shown to correlate with pulmonary function testing and data extracted from office records and provides an estimate of the burden of respiratory morbidity to the patient and family as well as the health care system. [26, 27] Among potential weaknesses, respiratory history data were taken by parental report, which has the potential for classification and recall bias. To minimize classification bias, all primary and follow up study data of this randomized trial were collected in a blinded manner. Hence, though it may affect the precision of point estimates, classification bias is unlikely to have introduced systematic bias into our study that favors one study arm over another. To reduce recall bias, parent interviews were conducted at 6 month intervals.[27] Because the Breathing Outcomes Study was approved and began enrollment after SUPPORT had begun and because we wished to follow all available SUPPORT subjects, study results are not reported as competing outcomes (e.g. death or recurrent wheezing) but rather as respiratory outcomes of the cohort of SUPPORT subjects that survived to hospital discharge. As has been previously reported, the results of SUPPORT and thereby potentially the follow up studies associated with it may not be fully generalizable to all extremely preterm infants because the need for antenatal consent resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort. [28]

In summary, we found no significant differences in the incidence of recurrent wheezing or chronic cough at 18-22 months corrected age between extremely preterm survivors who were randomized at delivery to either lower or higher saturation targets and early CPAP or surfactant. In secondary analyses, we found reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months corrected age in the lower saturation group. However, because management with lower saturation targets was associated with greater mortality in SUPPORT [13], we conclude that the benefit of reduced wheezing and nebulizer use seen in the Breathing Outcomes Study does not justify treatment with lower saturation targets in patients 24-27 6/7 weeks' gestation. Also in secondary analyses, we report fewer respiratory symptoms, physician diagnosed respiratory problems and reduced health care use among infants treated with CPAP rather than early surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over surfactant. [12, 13]{add Vaucher reference when available). Those findings coupled with the respiratory outcomes identified in this report reported here suggest that treatment of extremely premature infants with CPAP and limited ventilation rather than intubation and early surfactant administration is safe and may result in less respiratory morbidity during the first 18-22 months corrected age. The findings also clearly demonstrate the increased risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation and the need for close medical monitoring post-discharge.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We wish to acknowledge the Tucson Children's Respiratory Study (Marilyn Lindell, RN), Tucson, Az for support of this project by sharing respiratory symptom questionnaires which were adapted for use in this study.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhole, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

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Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nysten, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Rene Barbieri-Welge; Ayala Ben-Tall; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Elaine Ito; Meghan Lukasik; Deborah Pontillo; Donna Posin, OTR/L MPA; Cheryl Runyan; James Wilkes; Paul Zlotnik.

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Belf, MD; John A. Widness, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Rosemary L. Jensen; Caryn Graff Havens, MPH, MBA; Linda J. Reubens, RN CCRC; Joan Merzbach, LMSW.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

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From: Ehrenkranz, Richard
To: Poindexter, Brenda B; Susan Hintz; jlanger@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; "Das, Abhik"
Subject: RE: updated growth abstract for call tomorrow
Date: Wednesday, October 31, 2012 11:11:21 AM
Attachments: PAS growth abst 30Oct12-rae.docx

The Abstract is looking good. I made some space savings suggestions in the attached version. Also, is the BSID III motor going to replace language in the table or added as another row?

Richard

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Tuesday, October 30, 2012 1:56 PM
To: Ehrenkranz, Richard; Susan Hintz; jlanger@rti.org
Cc: 'higginsr@mail.nih.gov'; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); 'Das, Abhik'
Subject: RE: updated growth abstract for call tomorrow

All,

I am attaching an updated draft of the abstract. I made the change to the conclusion, added definition of profound/severe NDI, and deleted the rows in the table for the BSID III <70 and <85 values. We are currently at 94% of allowed space. I am waiting on the revised tables from John that we discussed on Friday and also on the modeling for length and HC. We should have enough space to add these if significant. Hope those of you on east coast are staying dry! John – let us know when you think you'll have the updated analyses complete (I understand the storm may be interfering with your plans).

Thanks, Brenda

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Friday, October 26, 2012 2:49 PM
To: Poindexter, Brenda B; Susan Hintz; jlanger@rti.org
Cc: 'higginsr@mail.nih.gov'; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); 'Das, Abhik'
Subject: RE: updated growth abstract for call tomorrow

Hi:

I have attached a version with the Conclusion that I suggested. I highlighted suggested last sentence. I added the abbreviation EPT for extremely preterm. Can middle initials be added to our names? Have a good weekend.

Richard

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The information contained in this email may be privileged and confidential. If you are the intended

recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Poindexter, Brenda B [<mailto:bpoindex@iupui.edu>]
Sent: Thursday, October 25, 2012 12:22 PM
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Cc: 'higginsr@mail.nih.gov'; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); 'Das, Abhik'
Subject: updated growth abstract for call tomorrow

All,

Attached is the latest version of the abstract. We are already at the character limit, so we will need to be creative in editing. John and I talked today – he is running the logistic regression models for length and HC growth – if significant, I would love to include something about length because I think it would be both novel and timely. NDI is not in the current draft – John can walk us through the data tomorrow, but we need to talk on the call about the hearing impairment portion of NDI. We definitely do not have room in the abstract for multiple NDI definitions. I would like everyone to think about whether we need to put both Bayley cutoffs (<70 and <85) in the abstract.

Talk to everyone tomorrow –

Brenda

Title: HAVE WE CAUGHT UP? GROWTH AND NEURODEVELOPMENTAL OUTCOMES IN EP INFANTS

B Poindexter, MD MS¹, S Hintz, MD MS², J Langer, MS³ and R Ehrenkranz, MD⁴. ¹Indiana University, Indianapolis, IN, United States; ²Stanford University, Palo Alto, CA, United States; ³RTI, Rockville, MD, United States and ⁴Yale University, New Haven, CT, United States.

Background: The association between poor growth in the NICU and adverse neurodevelopmental outcomes of extremely preterm (EP) infants has been previously described. As provision of early nutrition and tests of neurodevelopmental outcomes have changed, a more contemporary reassessment of the relationship is needed.

Objective: To describe current growth outcomes in EP infants and to evaluate the association between in-hospital growth and neurodevelopmental and growth outcomes at 18-22 ~~mos~~ months corrected age (CA).

Design/Methods: A multicenter cohort of infants in the NICHD Neonatal Research Network born 2008-2010 who survived to hospital discharge and eligible for follow-up (GA <27 weeks) were divided into quartiles of in-hospital growth velocity rates. Anthropometric measures were obtained at birth, 36 weeks PMA, and at 18-22 ~~mos~~ CA months corrected age. Neurodevelopmental follow-up (FU) included exam and Bayley Scales of Infant Development (BSID) III. Severe/profound Neurodevelopmental impairment (NDI), defined as one or more of following: BSID III cognitive or motor score <70, severe/profound CP, bilateral blindness, or no functional hearing.

Comment [rae1]: Should "Neurodevelopmental" begin with a lower case "N" or should "impairment" begin with an uppercase "I"?

Results: Of the 1616 infants who survived to discharge, 1396 (86%) were evaluated at 18-22 months CA. Growth failure (weight <10th %tile) was present in 74% at 36 weeks PMA and in 39% at FU. As the rate of weight gain increased between quartile 1 and 4 (12 to 18 g/kg/d), the incidence of adverse outcomes decreased significantly.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
BSID III Cognitive - mean (SD)	85.9 (17.4)	87.4 (15.4)	90.3 (15.5)	92.7 (13.3)
BSID III Language - mean (SD)	80.2 (19)	83 (16.9)	85.8 (17.5)	88.9 (15.8)
CP moderate/severe (%)	14.1	7.7	4.9	1.2
GMFCS ≥2 (%)	16.9	9.6	7.3	1.8
Severe/profound NDI (%)	27.6	18.2	12.6	5.5

Comment [rae2]: Is BSID III Motor-mean (SD) going to be added to this table?

Weight gain quartile (1 vs 4) was associated with increased likelihood of NDI (OR 7.6; 95% CI 4-14.4).

Conclusions: Growth failure remains a common outcome of EP infants. Since in-hospital growth is independently associated with neurodevelopmental outcomes, effort to improve growth remain essential.

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Subject: Re: Author Review | Stevens, SUPPORT Breathing Outcomes paper
Date: Monday, October 29, 2012 2:58:55 PM
Attachments: Manuscript -Stevens BreathingOutcomes Edits NF Oct 29 2012.docx

Hi Tim

I have added my edits

This reads well

Nice work

Neil

From: Roy Heyne <Roy.Heyne@UTSouthwestern.edu<mailto:Roy.Heyne@UTSouthwestern.edu>>
Date: Monday, October 29, 2012 11:35 AM
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Cc: Timothy Stevens

<Timothy_Stevens@URMC.Rochester.edu<mailto:Timothy_Stevens@URMC.Rochester.edu>>

Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Tim, I agree with Betty's comments/edits and have added some of my own. Good work.

From: Vohr, Betty [mailto:BVohr@WIHL.org]

Sent: Saturday, October 27, 2012 11:31 AM

To: Archer, Stephanie (NIH/NICHD) [E]; Neil Finer (nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>); Wally Carlo (wacarlo@uab.edu<mailto:wacarlo@uab.edu>); Michele Walsh (Michele.walsh@cwru.edu<mailto:Michele.walsh@cwru.edu>); Marie Gantz (mgantz@rti.org<mailto:mgantz@rti.org>); Laptook, Abbot; Brad Yoder (bradley.yoder@hsc.utah.edu<mailto:bradley.yoder@hsc.utah.edu>); Roger Faix (roger.faix@hsc.utah.edu<mailto:roger.faix@hsc.utah.edu>); Jamie Newman (newman@rti.org<mailto:newman@rti.org>); Abhik Das (adas@rti.org<mailto:adas@rti.org>); Kurt Schibler (kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>); Wade Rich (wrich@ucsd.edu<mailto:wrich@ucsd.edu>); Nancy Newman (nxs5@cwru.edu<mailto:nxs5@cwru.edu>); Richard Ehrenkranz (richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu<mailto:MPeralta@peds.uab.edu>); Dee Wilson (b)(6)@aol.com<mailto:(b)(6)@aol.com>); Kim Yolton

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Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu<mailto:Timothy_Stevens@URMC.Rochester.edu>)

Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Steve, Very nice. I have some edits and suggestions and queries in tracking. Best wishes. Betty

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>]

Sent: Wednesday, October 24, 2012 1:00 PM

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Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu<mailto:Timothy_Stevens@URMC.Rochester.edu>)

Subject: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Attached is a draft of Tim's SUPPORT Breathing Outcomes paper for the coauthors to review.

Please send any comments back to Tim by Wednesday, November 7th.

Thank you,

Stephanie

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]<mailto:[mailto:Timothy_Stevens@URMC.Rochester.edu]>

Sent: Tuesday, October 23, 2012 9:35 PM

To: Newman, Jamie <newman@rti.org<mailto:newman@rti.org>> (newman@rti.org<mailto:newman@rti.org>);

Higgins, Rosemary (NIH/NICHD) [E]

Subject: Breathing Outcomes

Hi Jamie and Rose,

Here is the next version of the manuscript. Barbara double checked the tobacco exposure and provided updated values.

Can you forward the manuscript to the reviewers?

Thanks

Tim

<hr>
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Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

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Word Count:

Text: MeSH terms:

Bronchopulmonary Dysplasia
Infant, Newborn
Infant, Low Birth Weight
Infant, Extremely Low Birth Weight
Infant, Premature
Infant, Extremely Low Gestational Age
Infant mortality
Respiratory morbidity
Intensive care, neonatal
Hospital Readmission
Oximetry
Randomized controlled trial
Retinopathy of prematurity (ROP)
Continuous Positive Airway Pressure
Intubation, intratracheal
Pulmonary surfactants/therapeutic use
Oxygen inhalation therapy/methods
Oxygen administration & dosage
Follow-up studies

ABSTRACT

BACKGROUND:

The NICHD SUPPORT Trial found no difference in the composite outcomes of death or BPD, death or ROP and death or neurodevelopmental impairment between infants treated with lower (85-89%) versus higher (91-95%) oxygen saturation targets or with CPAP versus early surfactant (Surfactant). Though the composite incidence of death or ROP was similar, infants treated with lower rather than higher saturation targets had less ROP but greater mortality.

METHODS:

The Breathing Outcomes ~~Sub-Study assessed reported here~~ followed infants 24-27 6/7 weeks' gestation, who were enrolled in SUPPORT, at 6 month intervals from hospital discharge to 18-22 months CA ~~with using~~ a series of 4 standardized parental interviews to assess respiratory-related symptoms, illnesses, medication use and health care utilization. ~~Findings in the~~ The study arms of low and high saturation and CPAP and Surfactant were compared.

Comment [R1]: Comma added for clarity

RESULTS:

~~From a cohort of 922 eligible infants,~~ All four interviews were completed on 873 (94.7%) of 922 eligible infants, completed the four part interview series. The two prespecified primary outcomes, incidences of recurrent wheezing and chronic cough, were 47.9% and 32.0%, respectively, and did not differ between study arms of either randomized intervention. Among secondary outcomes, infants in the lower saturation group had a lower incidence of wheezing (36.3% vs. 43.4%, $p < 0.05$) and nebulizer use at 6 months CA and of wheezing without a cold (28.4% vs. 36.3%, $p < 0.01$) at 18-22 months CA. CPAP compared with surfactant treated infants at 18-22 months CA had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p < 0.05$), fewer respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p = 0.02$) and fewer physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p < 0.05$).

CONCLUSION:

Treatment with lower rather than higher oxygen saturation targets may be associated with less wheezing by 18-22 months CA, a benefit which is insufficient to offset the higher mortality seen in this group as part of SUPPORT. ~~We also conclude that~~ CPAP and limited ventilation rather than intubation and surfactant ~~for~~ in infants 24 – 27 6/7th weeks' is safe and results in less respiratory morbidity by 18-22 months CA.

Word count: 315

BACKGROUND

Extremely preterm infants are at greater risk of respiratory symptoms and need for pulmonary care in early childhood than later preterm or term infants [1-7] and contribute substantially to the public health burden of childhood respiratory disease in the United States. [8] Mechanical ventilation and supplemental oxygen use in the early neonatal period has each been identified as a major risk factor for development of BPD and pulmonary morbidity in infancy, childhood and beyond. [1, 2, 9, 10] Though infants with Bronchopulmonary Dysplasia (BPD) are at highest risk for poor pulmonary outcome, neonates without BPD are also at risk for airway dysfunction and pulmonary morbidity during infancy. [4, 11]

The multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) studied infants 24 0/7th -27 6/7th weeks' gestation treated with each of two respiratory strategies designed to minimize mechanical ventilation and supplemental oxygen exposure: 1) treatment with lower (85-89%) compared with higher (91-95%) oxygen saturation targets and 2) early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (Surfactant). Our Network previously reported results of SUPPORT demonstrating no difference in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants treated with either of the two respiratory interventions. [12, 13] (Vaucher when available) It is important to note that although the composite incidence of death or BPD was similar, infants treated with lower rather than higher saturation targets had a significantly lower incidence of retinopathy of prematurity (ROP) but a significantly higher risk of mortality. [13]

We now report on The Breathing Outcomes Study, a secondary outcome to the SUPPORT Trial, which sought to compare respiratory morbidities among extremely preterm infants treated with the SUPPORT study interventions as neonates. ~~It was~~ We hypothesized that infants treated with lower rather than higher oxygen saturation targets and CPAP rather than early surfactant will each have less frequent episodes of recurrent wheezing and cough and less need for outpatient pulmonary care at 18-22 months' corrected age (CA).

METHODS

Infants eligible for The Breathing Outcomes Study were ~~these~~ infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. One thousand three hundred sixteen (1316) infants from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009. Infants were eligible for SUPPORT if their gestational age was between 24 weeks 0 days to 27 completed weeks' (up to 27 6/7ths) by best obstetrical estimate and were born at a participating center, planned to receive full resuscitation if necessary, and without major congenital malformations. Because a goal of the Breathing Outcomes Study was to obtain health outcomes on as many of the SUPPORT subjects as possible, and because enrollment into the Breathing Outcomes Study

began after SUPPORT had begun enrollment, written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT Trial or separately for those patients already enrolled in SUPPORT. As a result, the Breathing Outcomes Study cohort was a subset of the SUPPORT cohort. The study was approved by the institutional review boards at all participating Network centers and by RTI International, the data center for the NICHD Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for both SUPPORT and Breathing Outcomes. [12, 13]

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned in the delivery room to receive CPAP after birth, followed by a limited ventilation strategy if intubation were needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age. Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with either a saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Randomization for both study interventions was accomplished using block randomization with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported. [13, 14]

Assessments of the Breathing Outcomes Study

For subjects enrolled in Breathing Outcomes, a parent or primary caregiver was interviewed by research staff either in person or by phone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at 6, 12 and 18-22 months corrected age. The study questionnaires were drafted based upon questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study. [15, 16] Questions were added to the Tucson questionnaires to more fully elicit the respiratory health and health service use specific to preterm infants (e.g. palivizumab injections). To standardize administration of the interview, a lead interviewer at each participating center underwent training consisting of a teleconference with 1 of 2 project trainers (Rochester site) to discuss each study question and the written interview script associated with it. Interview trainees then interviewed a standardized patient simulated by the project trainers. Lead interviewers at each center were then able to train additional interviewers at their sites as needed. To minimize misinterpretation of other respiratory sounds as wheezing, a verbal description of wheezing and a brief audio clip of wheezing were played for the interviewee at the beginning of the interview. Questionnaires originally written in English were translated into Spanish using a certified translation service (Cornell Translation Service, Ithaca, NY). Interviews were conducted in either English or Spanish as appropriate.

To minimize loss of recall over time, interviews were conducted at 6 month intervals beginning at the time of hospital discharge. Study personnel conducted the first parent interview using a questionnaire designed to collect information on family history of respiratory diseases and atopy, home environment including tobacco and pet exposures, and diet at discharge from the hospital. Based upon the preference of each participating center, the 6, 12 and 18-22 month interviews were conducted either by

Comment [R2]: Since the windows for these interviews spanned up to two months, may be better to say "at or near"

Comment [R3]: Though you reference the Tucson study, I think it would still be important to note that the two primary outcome questions (9-10) elicit history of cough or wheezing since the "last contact," i.e. over the last 6 months give or take.

Comment [R4]: Actually, since these children were not all discharged at 0 months corrected age, and since some were seen closer to 22 months adjusted age at the final interview, this is only approximately true. May suffice to qualify this with "approximately".

trained staff at the local center (15 centers) or by long distance telephone interview from the Rochester center (5 centers). At each of the 6, 12 and 18-22 month interviews, the parent or caregiver was asked to base their responses on the 6 month interval since the last interview. If an interview at one time point was not completed, interviewees were asked to base their responses during the next interview upon the interval history since the last completed interview. Taken together, the four questionnaire series administered by interviewing the parent or primary caregiver was designed to provide a complete respiratory history over the first 18-22 months' corrected age. In addition to reporting interview responses during the first 18-22 months corrected age, we report responses from the 6 month interview because preterm infants are at especially high risk of respiratory morbidity during the first 6 months of age. REF

The 6 and 12 month interviews were based on questionnaires designed to elicit the frequency and characteristics of respiratory symptoms, including wheezing and cough; incidence of physician-diagnosed asthma, reactive airway disease or "BPD flare-up"; incidence of bronchiolitis, bronchitis or pneumonia, croup; use of medications to treat respiratory illnesses including diuretics, nebulized bronchodilators, inhaled steroids, systemic steroids or oxygen; use of health services including respiratory related physician visits, emergency room visits and hospitalizations; use of preventive therapies including palivizumab and influenza immunization; and impact on the family including whether the parent or caregiver needed to change plans due their child's breathing. In addition to the questions above, the 18-22 month interview included additional questions to elicit whether the child had atopic symptoms or conditions, including eczema and food or medication allergy.

Outcomes

Primary Outcomes: Two primary outcomes were assessed by parental report: the incidence of recurrent wheezing and incidence of chronic cough. From these in addition, the incidence of the combined outcome, recurrent wheezing or chronic cough, was also considered assessed. The incidence of wheezing was ascertained using the primary question used and validated in the Tucson Study (a large prospective birth cohort study of term infants), "Has his/her chest sounded wheezy or whistling?". [15] Recurrent wheezing was defined as wheezing occurring more than twice in any week. The incidence of chronic cough ascertained using the Tucson question, "Has [your] child had a cough for 3 days or more when he/she did not have a cold?" [15].

Secondary outcomes and covariates: Secondary outcomes were interview responses to the 6, 12 and 18-22 month questionnaires for respiratory symptoms, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, the following covariates were evaluated: family history, environmental exposures including tobacco smoke, diet and use of preventive therapies as outlined above. In addition, each patient's outcomes from SUPPORT were available to the Breathing Outcomes Study analysis.

Statistical Analyses

The available subject pool for the Breathing Outcomes Study was limited to subjects enrolled in SUPPORT who survived to hospital discharge and consented to participation. For Breathing Outcomes, a

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Comment [T5]: Where is the data for 18-22 months shown for the 4 groups. In Table 1 the title is Neonatal and Demographic characteristics. Is it a combination of findings from all assessments?

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Comment [T6]: Already stated in Methods

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sample size of 817 subjects was calculated as necessary to detect an absolute risk difference of 0.1 in the incidence of recurrent wheezing between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of recurrent wheezing of 29%. Sample size calculations for SUPPORT have been reported. [12, 13] Based upon SUPPORT's target enrollment of 1310 patients and assuming a 22% mortality (NICHD historical data for calendar year 2000), we anticipated 1021 patients potentially eligible for the Breathing Outcomes Study.

Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. For categorical variables with low frequency ($n < 5$), Fisher exact tests were used. The two primary analyses used the number of patients with either recurrent wheezing or chronic cough as the numerator and the number of infants for whom that outcome was known as the denominator. Using Poisson regression models to adjust for gestational age strata, study center and familial clustering, adjusted relative risk (ARR) values and 95% confidence intervals were calculated and are reported. When Poisson models did not converge, relative risk adjusted for gestational age and center is reported (indicated in tables by †). When the two adjustment models failed to converge due to low prevalence ($< 5\%$), unadjusted relative risks are reported (indicated by †† in table). Results were considered statistically significant if the two-sided p value was less than 0.05; a trend towards significance was considered if the two sided p value was between 0.05 and 0.10 inclusive. No adjustments have been made for multiple comparisons. All calculations were performed using SAS software (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study (Figure 1). Follow up rates at each time point are listed in Figure 1; Parents of a total of 873 patients infants completed the four questionnaire series (94.7%).

Comment [T7]: Should be clear that all of your data is for 837 infants.

Characteristics of the follow-up cohort:

Among the follow up cohort, the group managed with lower compared with higher saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with bronchopulmonary dysplasia (BPD) defined using the traditional criteria of supplemental oxygen uses at 36 weeks' post menstrual age (PMA). The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to surfactant (Table 1). There was no difference between groups in the proportion of infants with BPD defined using the physiologic definition. Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and surfactant groups (Table 2).

Primary Outcomes:

The overall incidences of the two primary outcomes for the 873 infants with complete data, episodes of wheezing more than twice per week and cough lasting more than 3 days, in the follow up cohort during the first 18-22 months corrected age were 47.3% and 33.0%, respectively. There was no difference in incidence of these outcomes between either the subcohort of infants treated with lower compared with higher oxygen saturation targets nor between the subcohort infants treated with CPAP rather than

surfactant (Tables 3 and 4, respectively). The combined outcome of episodes of wheezing more than twice per week or cough lasting more than 3 days for the total cohort was 64.6% and did not differ significantly between subcohorts treated with lower rather than higher saturation target or CPAP rather than surfactant (Tables 3 and 4, respectively).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months corrected age, infants randomized to lower compared with higher saturation targets had a lower incidence of wheezing and in use of nebulized medications since NICU discharge (36.3% vs. 43.4%, $p < 0.05$ and 1.2% vs. 3.9%, $p = 0.02$, respectively) (Table 3). Supporting these differences in wheezing was a trend toward a lower incidence of recurrent wheezing defined as wheezing episodes occurring more than twice per week (22.0% vs. 27.7%, $p = 0.06$) (Table 3). Over the first 18-22 months of corrected age (listed as 6-22 months in Tables 3 and 4), infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (28.4% vs. 36.3%, $p = 0.01$) (Table 3).

Early CPAP Intervention

At 6 months corrected age, infants treated with CPAP rather than surfactant were reported to have fewer asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor since NICU discharge (12.3% vs. 17.2%, $p < 0.05$) and a trend toward fewer hospitalizations for wheezing or breathing problems (16.5% vs. 27.0%, $p = 0.09$). Perhaps related to these differences, parents or primary caregivers of infants treated with CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (12.8% vs. 20.4%, $p < 0.01$) (Table 4).

During the first 6-22 months corrected age, infants receiving early CPAP versus surfactant were significantly less likely to have wheezing episodes occurring without a cold (28.9% vs. 36.5%, $p = 0.01$), respiratory illnesses diagnosed by a doctor (one or more episodes of asthma, reactive airway disease or BPD flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, $p = 0.02$), wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, $p < 0.05$). Compared with those of surfactant treated infants, parents or guardians of CPAP treated infants were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, $p < 0.05$).

Comment [R8]: For children with a positive hx of wheezing is this based on the secondary question which asks about wheezing "on average" rather than the one is the "worst two weeks"?

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Comment [T9]: Confusing. Tables say 6,12 and 22 m

Comment [R10]: Agree this is confusing. The headings of the table notes 6,12, 18-22; but the rows in the table specify 6 and 6-22. Think you need to specify under methods how the "6-22 month" data points were calculated to show how they reflect "the first 18-22 months of corrected age." Moreover, since each of these interviews reflect events "since the last contact" the 6 month interview presumably reflects the time period since NICU discharge. So does the "6-22 month" data point reflect the 12 and 18-22 month interviews or 6, 12, and 18-22 month. If the latter then it would come close reflecting the "first 18-22 months of corrected age," though I think the suggested rewording by Betty below ("between discharge and 18-22 months corrected age") is more accurate. However, if it does not include the 6 month interview, then would reflect the first 6 to 18-22 months of corrected age, which is what you describe two paragraphs below for Early CPAP.

Comment [R11]: See preceding comment.

DISCUSSION

We report respiratory outcomes during the first 18-22 months' corrected age for a cohort of extremely premature infants (24-27 6/7 weeks' gestation) treated in the NICHD SUPPORT Trial. We found no significant differences in reported respiratory outcomes at 18-22 months corrected age between patients treated with lower rather than higher saturation targets or with CPAP rather than surfactant in either of the two primary outcomes, incidence of recurrent wheezing and incidence of cough lasting more than 3 days without a cold.

In secondary analyses, extremely preterm infants managed with low compared with high saturation targets were less likely to have wheezing or use a home nebulizer at 6 months corrected age and to have wheezing apart from a cold ~~between discharge and during the first~~ 18-22 months corrected age. In the main SUPPORT trial, patients managed with lower compared with higher saturation targets were exposed to lower concentration of inspired oxygen. Several pulmonary outcome studies have found an association between neonatal oxygen exposure and expiratory flow dysfunction and airway hyperreactivity among infants with or without BPD. [2, 7, 17-19] Our results, taken together with current literature, suggest that lower oxygen exposure in the neonatal period may be associated with reduced wheezing in infancy. However, based upon the findings of greater mortality among patients in SUPPORT treated with lower rather than higher saturation targets, the benefit of reduced wheezing and nebulizer use does not justify management of patients 24-27 6/7 weeks' gestation with lower oxygen saturation targets. If oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant injury other than targeting lower oxygen saturations will be needed. [20, 21]

Patients treated with CPAP and limited ventilation rather than intubation and surfactant administration within 1 hour had fewer asthma, reactive airway disease or BPD flare-up episodes at 6 months corrected age and a trend toward fewer hospitalizations for respiratory problems. Perhaps related to these findings was a significant reduction in the proportion of parents reporting that they needed to change plans due to their child's breathing difficulties. During the first 18-22 months corrected age, patients receiving early CPAP rather than surfactant were significantly less likely to have had wheezing episodes occurring without a cold, respiratory illnesses diagnosed by a physician or physician or emergency room visits for breathing or wheezing problems. Parents of CPAP compared with surfactant treated infants were less likely to report changing their plans due to the child's breathing problems. These respiratory benefits were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria, was similar between CPAP and surfactant arms in the SUPPORT study and in the Breathing Outcomes' follow-up cohort. Our data are consistent with follow up data from The COIN Trial, which despite finding no difference in the incidence of death or BPD among 610 infants randomized to either CPAP or conventional management, found better pulmonary function at 8 weeks corrected among a 39 patient subcohort of study infants treated with CPAP. [22, 23] These observations suggest that treatment of infants 24-27 6/7 weeks gestation at risk for RDS with CPAP is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone and that longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions in randomized clinical trials.

We found that regardless of treatment arm, respiratory symptoms and health care usage are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months corrected age. Overall in the Breathing Outcomes cohort, recurrent wheezing occurred in 47.9% of patients and asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor in 34.5%. Treatment of these conditions prompted not only frequent physician visits (63.8% of children), emergency room visits (46.6%) and hospitalizations (42.5%), which have the potential to add to health care costs [8] but also to frequent use of both inhaled (26.3%) and systemic (9.4%) steroids which have potential long term effects on growth and development. [24, 25]

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Comment [T12]: This data is not shown or discussed in the results section. Do you need a column on your tables for total cohort. You could combine tables 3 and 4 in landscape and add a total cohort column ??

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The strengths of this study include the large number of extremely preterm infants enrolled. This is the largest respiratory follow up study of a randomized clinical trial. Other strengths include the high follow up rates for enrolled patients and use of comprehensive respiratory questionnaires administered in a scripted interview by trained personnel. Though not as objective as pulmonary function testing, respiratory history was used as outcome measures due to clinical and financial concerns associated with use of invasive pulmonary testing and potential complications of sedation in former preterm infants. In addition, parental report of wheezing has been shown to correlate with pulmonary function testing and data extracted from office records and provides an estimate of the burden of respiratory morbidity to the patient and family as well as the health care system. [26, 27] Among potential weaknesses, respiratory history data were taken by parental report, which has the potential for classification and recall bias. To minimize classification bias, all primary and follow up study data of this randomized trial were collected in a blinded manner. Hence, though it may affect the precision of point estimates, classification bias is unlikely to have introduced systematic bias into our study that favors one study arm over another. To reduce recall bias, parent interviews were conducted at 6 month intervals. [27] Because the Breathing Outcomes Study was approved and began enrollment after SUPPORT had begun and because we wished to follow all available SUPPORT subjects, study results are not reported as competing outcomes (e.g. death or recurrent wheezing) but rather as respiratory outcomes of the cohort of SUPPORT subjects that survived to hospital discharge. As has been previously reported, the results of SUPPORT and thereby potentially the follow up studies associated with it may not be fully generalizable to all extremely preterm infants because the need for antenatal consent resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort. [28]

In summary, we found no significant differences in the incidence of recurrent wheezing or chronic cough at 18-22 months corrected age between extremely preterm survivors who were randomized at delivery to either lower or higher saturation targets and early CPAP or surfactant. In secondary analyses, we found reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months corrected age in the lower saturation group. However, because management with lower saturation targets was associated with greater mortality in SUPPORT [13], we conclude that the benefit of reduced wheezing and nebulizer use seen in the Breathing Outcomes Study does not justify treatment with lower saturation targets in patients 24-27 6/7 weeks' gestation. Also in secondary analyses, we report fewer respiratory symptoms, physician diagnosed respiratory problems and reduced health care use among infants treated with CPAP rather than early surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over surfactant. [12, 13](add Vaucher reference when available). Those findings coupled with the respiratory outcomes identified in this report reported here suggest that treatment of extremely premature infants with CPAP and limited ventilation rather than intubation and early surfactant administration is safe and may result in less respiratory morbidity during the first 18-22 months corrected age. The findings also clearly demonstrate the increased risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation and the need for close medical monitoring post-discharge.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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From: [Wrage, Lisa Ann](#)
To: [Kennedy, Kathleen A](#)
Cc: dale_phelps@urmc.rochester.edu; [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: Another revision
Date: Monday, October 29, 2012 4:42:45 PM
Attachments: [ROP Natural History Study Manuscript \(revised for internal review\)_edlw29Oct12.doc](#)

Hi Kathleen,

Please see below & attached update (basically just includes updated figures. I can still tweak the figures more – just wanted you to take a look.

Thanks.

Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Wednesday, October 24, 2012 12:40 PM
To: Wrage, Lisa Ann
Cc: dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD)
Subject: RE: Another revision

Lisa, thanks again for your work on this.

Remaining questions for Lisa:

- 1) I'm still not clear on how a favorable study endpoint was defined. Was it **two eye exams with vessels in Zone 3** or **two eye exams with no ROP and vessels in Zone 3**? The manual just says "Vessels in zone III for two sequential eye examinations". I don't know if that's because it was considered "favorable" if they had exams with mild ROP in zone 3 or if it was assumed that the ophthalmologist would keep following them if that occurred. Or maybe it just never happens. I think we should be very clear about this in the manuscript.

Lisa: You've seen Marie's comments

- 2) I like the new Figure 2. I think it would look better if you could make the fonts bolder (as they were on the previous version) and the titles on the x-axis need to be centered below the appropriate group of bars. I think it would look a little better if the bars for each week were slightly closer together but that's a minor point and it probably won't look better if you have to move them too close to each other.

Lisa: take a look at the tweaked version & see if I am getting there. If you need more bolding let me know.

- 3) I've relabeled the title for Table 3 to say that these are "95% confidence intervals". The tracking changes made it a little hard to see some of the numbers in the revised table. Please verify.

Lisa: verified

- 4) I don't think the new Figure 3 really solves the problem of the figure appearing to be different from the data in the table. You just can't see where the line starts departing from zero. I also like the original colors better. The light yellow is hard to see.

Lisa: take a look at the tweaked version – I also tried putting a longer line in (for each) at zero but it also looked a little weird. Anyway – can always tweak some more.

Dale,

I never got a response to the email I sent on 9/12. Here's a copy of the part that was directed to you: "The attached revision is my attempt to do what everyone asked whenever feasible. The changes that I made in response to other people's suggestions are highlighted in yellow. I'd appreciate it if you'd look at those parts to see if you agree with the changes. I wasn't able to make all the changes that you suggested to the What's new? and the Abstract because of the word limits. The biggest changes have to do with incorporating 2 new similar papers (we really need to get this done and published before there are more) and trying to clarify the Discussion about postmenstrual vs chronologic age. It didn't even make sense to me after I'd taken a break from it for a while. We may need to tweak the wording some more when Lisa finishes the analyses but I don't think there will be major changes. As always, I look forward to your comments on this."

The most recent changes to the manuscript (based on Lisa's responses to the 9/12 email) are highlighted in gray in the attachment.

All,

When these questions are resolved, I think we will have done everything that's reasonable to respond to the subcommittee's comments. (I asked Wally and Neil for clarification of some of their comments and never got a response so I think we can go with what we have). I'd really like to send this to Bill Truog for internal review soon. I think we're very close.

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 19, 2012 2:18 PM
To: Kennedy, Kathleen A
Cc: Das, Abhik
Subject: RE: Another revision

Hi Kathleen,

Here's an updated version of the paper. I've addressed most of the issues you brought up. Some of the graphs may need more tweaking, I've added in a couple of new ones along with some comments to see how you like them. I have not found an obvious way to put confidence intervals around the cumulative distribution of age of onset graphs, I'll be double checking that, but I wanted to get you the rest of these updates to look at. Please see below for additional comments (in red) (as well is in the update).

Thanks and have a nice weekend.

Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Tuesday, October 16, 2012 3:36 PM

To: Wrage, Lisa Ann
Subject: RE: Another revision

I like the configuration/arrangement of the bars. To my eye at least, it would look better if all the components of the ROP bar were shades of blue and the gray or black colors were used for death and death or ROP.

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 16, 2012 10:11 AM
To: Kennedy, Kathleen A
Subject: FW: Another revision

Hi Kathleen,

Could you take a look at this (unfinished draft) of the bar figure now with stacked bars for the ROP groups and please let me know if you think you are going to like an updated version with the stacked bar vs. the old version.

I am finishing up the rest of the other updates as well.

Thanks.

Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 02, 2012 10:43 AM
To: 'Kennedy, Kathleen A'; dale_phelps@umc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Another revision

Hi, I have not forgotten about this, I just have been busy with PAS, I'm getting started with this now.
Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Wednesday, September 12, 2012 8:26 PM
To: Wrage, Lisa Ann; dale_phelps@umc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Another revision

Lisa, here's a summary of what we "discussed" yesterday and the additional comments/requests from the other reviews.

I think it might look better (less busy and cluttered) if we could stack the bars (same colors) for ROP. We would still have separate bars for Died before exam and Severe ROP or death. If we do this, I think we need to separate out "ROP less than severe" from "Any ROP". (We don't want to stack Severe ROP on top of Any ROP that includes Severe ROP.) So we'd have stacked bars of No ROP,

ROP less than severe, and Severe ROP. The legend might need to be somewhere else (off to the side or at the bottom of the graph) though.

From Lisa: draft #2 of this graph is in the paper, let me know if you like this version.

Don't worry about changing Figure 3. Several people have suggested that it's redundant with Table 3 and should be removed.

From Lisa OK, makes sense.

Brad Yoder asked for clarification on the statement "Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP." I've added "Among infants who had one exam without stage 3 ROP or plus disease and vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP." I based that on a prior email from you. Marie has said in her comments that this wasn't stated in the study protocol but it was "implied". I'm not sure how best to get a clear resolution on this. My guess is that it never came up because the ophthalmologists would, on clinical grounds, schedule a follow-up exam if the baby had stage 3 ROP or plus disease even if they thought the vessels were in Zone III (if that ever happened). I've asked Dale how we can best convey to the reader what was really done.

From Lisa : I have explained in a comment in the paper where this came from.

Could you please check the denominators again in Table 2? I have a comment from you in a prior version that mentions changes to the denominator for the sepsis variables but the ones that have missing data listed in the table are fungal sepsis and intraventricular hemorrhage (not late onset sepsis). Is that right?

From Lisa: I checked these and they looked right.

Neil and others have asked about statistical comparisons of the data in Table 2. I don't think it's necessary but I wouldn't be surprised if the reviewers ask for it. I ran the numbers and added this: "Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP)." Let me know if that's ok with you. Dale suggested, and I agree, that it would be better to express "Days of supplemental oxygen" as medians and IQRs.

From Lisa, this is fine. I've added the median/IQR for the supplemental oxygen variable.

Marie asked about comparing (statistically) the curves in Figure 5 (Figure 4 in the revision) to support the statement (based on eyeball) that the vessels matured later in infant with Mild/Moderate ROP as compared to no ROP. I think we'd have to combine the GA groups together to do that but, if it's feasible, it would be worth trying to do that. Marie also asked about doing a statistical comparison of the curves in each of the graphs in Figure 4. Is that possible? It would be fantastic to have confidence intervals for all of this [Table 3 and Figure 4 (Figure 3 in the revision)], but I don't see how that would be feasible. Can you explain to me why the curves in Figure 4 (Figure 3 in the revision) appear to separate from the baseline of 0 before the min age of severe ROP in Table 3? That doesn't seem right to me, unless smoothing the curve makes it look like that. I've added a few sentences on analysis to the Methods. Could you please revise those when we decide how we're going to modify this?

From Lisa I've addressed each of these things in the draft update. I've added some info and comments and tweaked some wording in the text. I'm going to double check around about CIs on

those cumulative distributions, I've found no obvious way to get those.

Dale, the attached revision is my attempt to do what everyone asked whenever feasible. The changes that I made in response to other people's suggestions are highlighted in yellow. I'd appreciate it if you'd look at those parts to see if you agree with the changes. I wasn't able to make all the changes that you suggested to the What's new? and the Abstract because of the word limits. The biggest changes have to do with incorporating 2 new similar papers (we really need to get this done and published before there are more) and trying to clarify the Discussion about postmenstrual vs chronologic age. It didn't even make sense to me after I'd taken a break from it for a while. We may need to tweak the wording some more when Lisa finishes the analyses but I don't think there will be major changes. As always, I look forward to your comments on this.

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From: Wrage, Lisa Ann [<mailto:wrage@rni.org>]
Sent: Tuesday, September 11, 2012 11:13 AM
To: Kennedy, Kathleen A
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)

Hi Kathleen,
See below:

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Tuesday, September 11, 2012 11:41 AM
To: Wrage, Lisa Ann
Subject: FW: Onset of ROP Observational Study (SUPPORT Secondary)

Could you please take a look at Abhik's comments #5 and #7?

For number 5, if it's doable, I think it might look better (less busy and cluttered) if we could stack the bars (same colors) for ROP. We would still have separate bars for Died before exam and Severe ROP or death. If we do this, I think we need to separate out "ROP less than severe" from "Any ROP". (We don't want to stack Severe ROP on top of Any ROP that includes Severe ROP.) So we'd have stacked bars of No ROP, ROP less than severe, and Severe ROP.

Lisa: I like the graph as it is, but he may have been thinking that stacking would eliminate possible confusion around that issue of including severe ROP in both bars. Since the ROP bar might get kind of long I may have to switch % to the X axis and GA to the Y axis, not sure, and it might look weird, but it also might be fine, I will just try it and see what you think.

For number 7, I don't know if the other line can be dotted such that it's distinguishable from the solid line. If that can be accomplished, it might be worth doing.

Lisa: It should be able to be dotted. I am assuming that you mean to include all infants with any ROP in that line??

Thanks.

Lisa

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From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Friday, July 27, 2012 12:28 PM
To: Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)

Kathleen:

This looks very good. I only have a few minor comments/suggestions in the attached.

Thanks

Abhik

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Friday, July 27, 2012 9:53 AM
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WTHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@JHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Archer, Stephanie
Subject: Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

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Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy, MD MPH¹; Lisa A. Wrage, MPH²; Rosemary D. Higgins, MD³; Neil N. Finer, MD⁴; Waldemar A. Carlo, MD⁵; Michele C. Walsh, MD MS⁶; Abbot R. Lupton, MD⁷; Roger G. Faix, MD⁸; Bradley A. Yoder, MD⁹; Kurt Schibler, MD⁹; Marie G. Gantz, PhD²; Abhik Das, PhD¹⁰; Nancy S. Newman, RN⁶; Wade Rich, RRT⁴; Dale L. Phelps, MD¹¹; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Comment [KKA1]: 2854 words excluding title page, abstract, tables, subtitles, figures, figure legends, and references; needs to be <= 3000

Abbreviations:

ELBW – extremely low birth weight (<1000g birth weight)
GA – gestational age
PMA – postmenstrual age
ROP – retinopathy of prematurity
SUPPORT – Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

Keywords

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retinopathy of prematurity, screening, extremely preterm infants

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What's Known on this Subject

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Because earlier treatment is now recommended, updated information regarding the timing of onset of ROP is needed.

Comment [KKA2]: 40/40 words

What This Study Adds

Our data support the timing of examinations in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. We did not replicate the observation that the onset of ROP is more closely correlated with postmenstrual than chronological age.

Comment [KKA3]: 40/40 words

Abstract

Comment [KKA4]: 214 words, needs to be <=250

Objective: To determine if current ROP examination criteria are appropriate for severely treated ROP in our population of extremely low gestation infants.

Patients and Methods: Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Inborn infants of 24^{0/7} to 27^{6/7} wks gestational age (GA) with consent prior to delivery were enrolled in 2005-2009. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was a primary outcome for the trial. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

Results: 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had a final ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

Conclusions: Our contemporary data support continued use of the 2006 guidelines. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines^{1, 2} are based on natural history data from the CRYO-ROP³ and LIGHT-ROP⁴ studies. The CRYO-ROP study⁵ remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.⁶ Over the past two decades, survival of lower birth weight infants has increased.^{7, 8} For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.⁷ The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age. The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for (threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.⁴ Based on the results of the ET-ROP study, earlier treatment is now recommended.⁹ With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP, defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP Study¹⁰ and a population-based cohort study of infants born 2004-2007 in Sweden¹¹ reported the age of onset of stages 1, 2, and 3 ROP; the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from the Canadian Neonatal Network reported the age of onset of Type 1 ROP in a cohort of 214 infants \leq 27 weeks gestation;¹² this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort¹³ reported that "No preterm infants required treatment before the 33th postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be

Comment [KKA5]: Dale, I've searched before for newer references for this statement. If we want a reference to support a statement that survival has improved, we need a report of survival for the same cohort (by either BW or GA) in two different time periods. This is the most recent report of that kind that I could find. I added the newer reference even though it doesn't support this statement because it reports survival of ELGA infants during the time of the SUPPORT trial.

curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 ⁶/₇ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)¹⁴ to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O₂ saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24 ⁰/₇ – 27 ⁶/₇ weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Repeat examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III on 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up was curtailed at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in the either eye.

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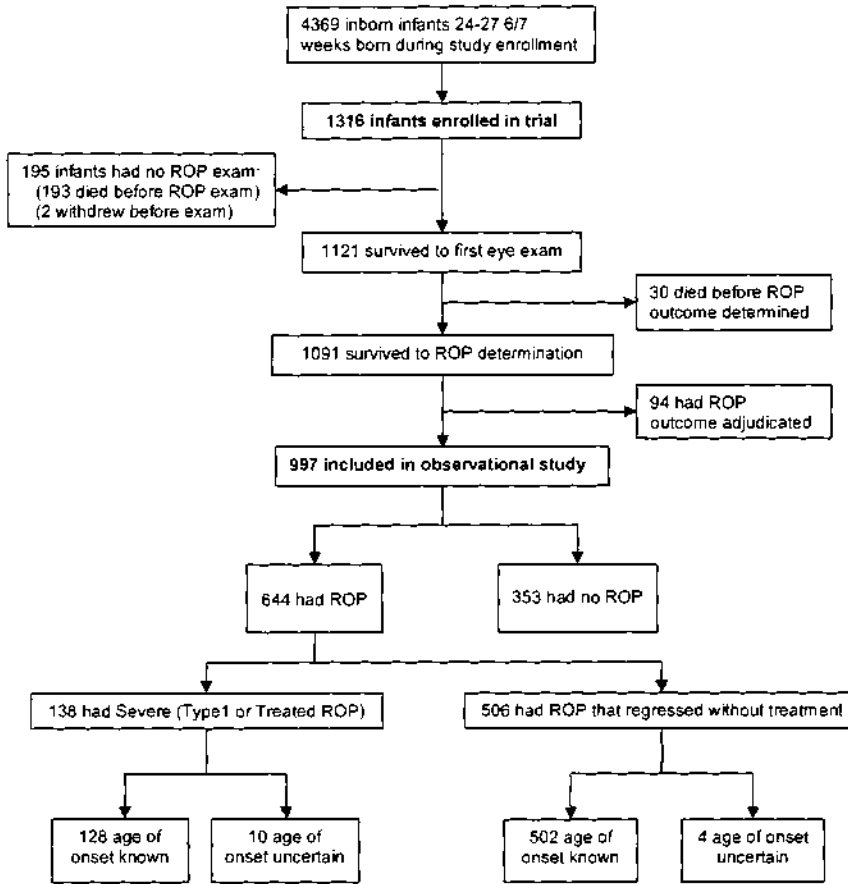
Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-five percent (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of subjects in the original trial and current analysis

Comment [KKA6]: This wasn't clearly stated this way in the MOP. Dale and I are still trying to get the data to sort this out

Comment [KKA7]: In an email exchange on 5/29, Lisa said that none of the adjudicated cases were adjudicated as "probably met criteria for severe ROP". Based on Table 2 in the Supplement for SUPPORT, it looks like there were a few "unknown's" though. I don't think we've ever seen any data regarding how many of these adjudications were done when there was only one exam with vessels in zone III. I'm sure we could get that with some additional effort but I'm inclined to see what the reviewers say before doing more work on this.



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP ¹	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138

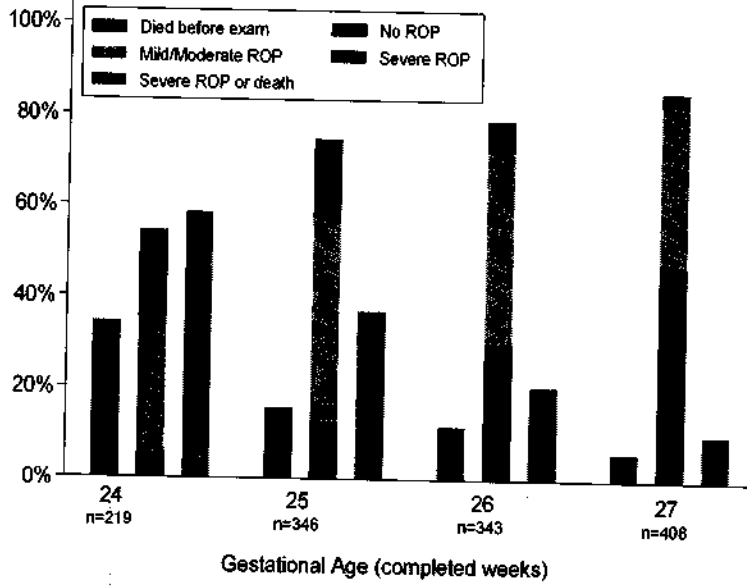
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA ² [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

¹ Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

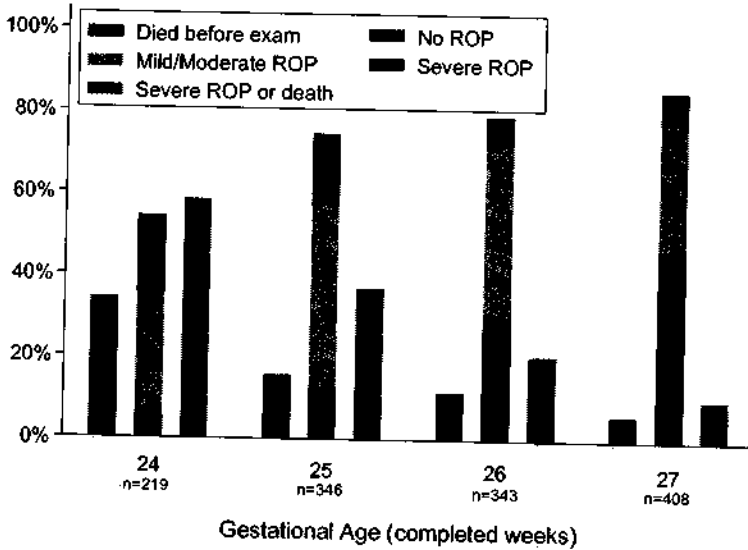
² based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all 1316 infants in SUPPORT Trial



Comment [KKA8]: This came from Lisa on 10/19. I've asked if she can make the fonts bold and align the labels on the x-axis.



As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP).

Table 2. Risk factors for ROP

Risk Factor	No ROP	Any ROP ¹	Severe (Treated or Type 1) ROP
n	353	644	138
Late-onset sepsis (+ culture) [n (%)]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23 ² (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98 ² (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

¹ Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

² missing data for 1 infant

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

Table 3. Postmenstrual and chronological age of onset¹ of any stage ROP (among infants with ROP age of onset determined)

ROP type	n	min ²	Postmenstrual Age (weeks)							Max ²
			1%	5%	25%	50%	75%	95%	99%	
Any ROP (95%CI)	635	29.3								46.7
Type 2 ROP ³ (95%CI)	158	29.3								46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1								53.1

ROP type	n	min	Chronological Age (weeks)							max
			1%	5%	25%	50%	75%	95%	99%	
Any ROP (95%CI)	635	4.0								19.7

Type 2 ROP ³ (95% CI)	158	4.4								22.7
Severe (Type 1 /treated) ROP (95% CI)	128	6.4								28.4

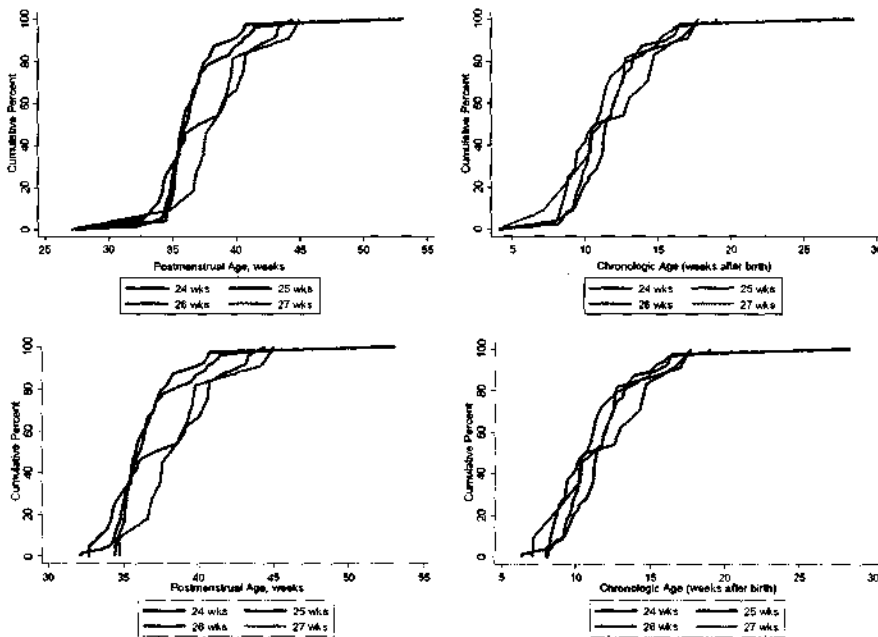
¹ Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.

² Min = minimum age at which designated severity of ROP was identified; max = maximum age.

³ Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 3.

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth



In contrast to prior studies, our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP.

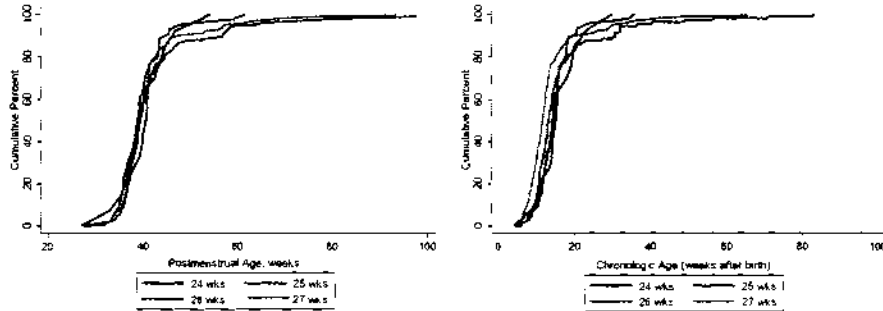
The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among

infants who had one exam without stage 3 ROP or plus disease and vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

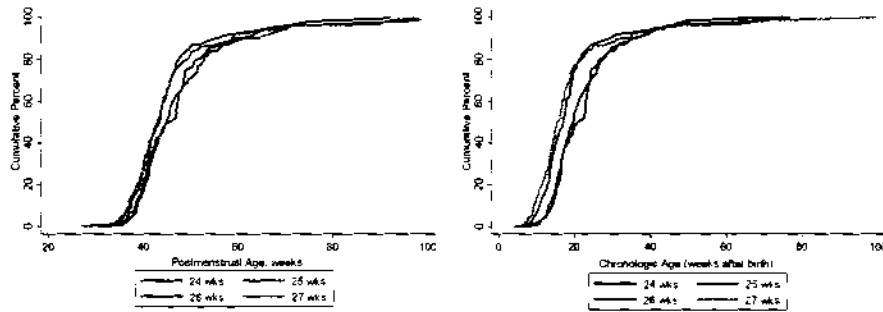
Comment [KKA9]: Added in response to Brad Yoder's comment. Need to verify.

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

No ROP on any exam



Mild/Moderate ROP



Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)

Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 infant (0.1%: 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%: or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge).

Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=I and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,⁹ so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,³ lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,¹ albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤ 1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.¹⁶ Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age¹⁷ and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,¹¹ which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al¹² included 23-27 week infants; infants ≤ 25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants >25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (23-24 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest age of onset of Type 1 ROP is more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian Network study,¹² the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al¹³ that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronological age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

Comment [KKA10]: Dale, I added this at Abbot's suggestion. I'm not that happy with it. Your thoughts?

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.¹⁶ The SUPPORT Trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.¹⁸

Conclusion

Current screening guidelines, published in 2006,¹ recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at ≥ 35 weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

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Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halford, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Geltner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children’s National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D’Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

From: [Kennedy, Kathleen A](#)
To: [Phelps, Dale](#)
Cc: [Wrage, Lisa Ann \(wrage@rti.org\)](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: comments on ROP manuscript
Date: Monday, October 29, 2012 4:35:39 PM

I don't think I'm as concerned as you about whether our findings "agree" with the CRYO findings. I think the most important conclusion is that our data do not warrant any changes in the screening recommendations that were based on the CRYO findings. As we've both said, the CRYO cohort was defined and stratified by BW rather than GA, so there are lots of potential differences in the populations that might explain why our curves for PMA of onset don't converge as tightly as the curves in the CRYO study did. We could plot ours as "up and down" instead of cumulative incidence but the curves still would not overlap. I think the cumulative incidence curves are more logical when you're trying to illustrate the timing when incidence begins and when it has achieved 100%.

We can decide how to proceed when you've had a chance to look at the most recent two versions of the manuscript.

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Saturday, October 27, 2012 9:51 AM
To: Kennedy, Kathleen A; 'Wrage, Lisa Ann'
Subject: RE: comments on ROP manuscript

Lisa and Kathleen,

I am adding some comments that I think will clarify Kathleen's request and/or make it easier to answer.

Please see below: I have marked [my comments in color and brackets: DLP]

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Friday, October 26, 2012 4:35 PM
To: Phelps, Dale
Cc: 'Wrage, Lisa Ann'
Subject: RE: comments on ROP manuscript

Thanks for helping me think through this. As I said in the previous email, I think it's really important that we correctly state what we did with the exams. It's possible that our findings could influence screening guidelines or practices and we don't want to say something that's potentially misleading.

About the vessels in zone III: Here's what I think we need to find out (it's not something we've asked

before).

Among infants who had a definitive ROP outcome (excluding those who were adjudicated) and excluding those who had severe ROP in zone I or zone II,

[I think this is a problem because you want to know if any went from zone III to severe ROP, I would keep them. --DLP], tabulate the following:

Based on the first exam with vessels in zone III in both eyes,

[In this case I would use either eye and keep analysis by eye. ... what if one is zone II and the other zone III, no ROP showing. The eye that was zone III should still be considered. --DLP]

Of the zone III eyes, the number on this first zone III exam that also had:

with plus disease (meeting treatment with vessels in zone III) if that ever happened
and the number with

no ROP,

stage 1

stage 2

or stage 3 ROP.

For the ones without plus disease at the time of the first exam with vessels in zone III, within each of the categories of ROP or no ROP, how many subsequently developed severe ROP? **Lisa**, could you work on this, please?

[Lisa, what we want to know is if one exam in zone III means you are safe from developing severe ROP. The belief in designing the study was "No", but that if you had 2 examinations in a row (consecutive) that were in zone III (without meeting criteria for severe ROP) that you would be 'safe' from subsequently developing severe ROP. So I would add to the question above: of those that did develop severe ROP (if any), did they have two examinations consecutively in zone III preceding the severe ROP? DLP]

Dale, I'm not sure what to do with your statement "I just can not accept this last sentence. I think there is something wrong with the way we are looking at the data." about the "What's new?" section. The Network data are different from what's been previously reported but it's really only the Cryo study that carefully looked at this and we've discussed a number of differences in the way that cohort was defined as compared to what the Network did. I don't see a different or better way to look at our data. What do you have in mind?

[The problem is kind of explained in comment [07], well maybe not well, but it is there.

CRYO-ROP plotted infants of <1250g BW and any gestation .. so they had a wider range of GA than SUPPORT. Their plots (see attached manuscript: Figure 5 A 5B 5C and 5D)

are chronologic age A and B (or postconceptual age that we now call PMA C and D)

vs.

percent of cases that developed ROP of severity 'prethreshold' (A and C) or

"threshold (B and D)

These four graphs would not have been interesting at all if they had not been further subdivided into the 3 lines on each. The three lines were for infants <750g BW, 750-999g BW and

1000-1250g BW. This is what brought out the difference in timing for small, medium and large size very low BW infants. CRYO-ROP assumed that the <750g infants were younger GA than the 750-999g BW infants and that those in turn were younger GA than the 1000-1250g BW infants. -- but I do not remember them publishing the mean sd of gestation for those 3 subgroups.

So we are having trouble comparing the CRYO-ROP graphs to the SUPPORT graphs because they are plotting different subgroups.

If we look at the CRYO Table 3B to get chrono age of onset of Threshold ROP

<750	11.3
750-999	10.3
1000-1250	8.6 weeks

for the median PMA that threshold occurred: I we see

<750 g	36.7
750-999g	37.0
1000-1250g	37.3 PMA (weeks)

That's quite a powerful convergence (within 0.6 weeks) of PMA over chronologic age (2.7 weeks spread)

What would be helpful (and we don't have) is the median GA of the 3 weight groups in CRYO. If I were a guessing person I'd guess that <750g are a week younger than the middle group and that the largest were 2 weeks older than that.

Another difference that makes it harder to compare is that "the percent of cases" plot from CRYO is an up down curve of proportions instead of a progressive accumulation curve like we have for SUPPORT.

I do not know what the best way is to ask the question of the SUPPORT data. One question is: does chronologic age or PMA better describe when serious ROP will occur? (if it occurs?)

or maybe a regression analysis?

Looking at our data from Table 3: The answers are 6 weeks chronologic and 32 weeks PMA. These agree with Palmer's Figure 5B and 5D.

So here is my problem. The SUPPORT table 3 agrees with CRYO-ROP. But at present, our paper concludes that it disagrees with CRYO-ROP data. (by the way, they have 3 times as many subjects as SUPPORT does).

If the CRYO-ROP data were plotted all together and accumulatively, would they look like the SUPPORT data? I don't think we have any way to know.

We just have not examined the potential differences in detail enough to definitively state that the SUPPORT data do not agree with the CRYO data.

I lack the skills to know how to do this, and am struggling here.

I am asking Lisa and RTI to help us figure this out. DLP]

Here is the breakdown that Lisa sent before (2/24) about the 10 babies with severe ROP and age of onset unknown:

1 infant had severe ROP at first

1 infant had old ROP scars in zone 2 on previous exam 15 days prior to first exam with Type 1/Treated ROP

the remaining 8 infants did not meet exam timing criteria outlined in your ROP Natural History document (based on info on most recent exam prior to first exam with severe ROP):

2 infants had no ROP on previous exam > 3 weeks prior (lowest zone of any vessels=2)

2 infants had ROP in zone 1 on previous exam > 1 week prior

4 infants had ROP in zone 2, > 2 weeks prior

For the 1 baby who had severe ROP on the first exam, the first exam was performed at 33 weeks. (It says that in the manuscript). So I thought it was ok to say that severe ROP was not observed before 32 weeks. Do you disagree?

[I would amend the last sentence to be explicit and reads: Severe ROP was not observed before 32 weeks, although 1 infant that did not meet the inclusion criteria had severe ROP at the first examination conducted at 33 weeks PMA, so the week of onset is not known.]

I've attached the latest revision with the most recent changes highlighted in gray.

[I will try to look at these soon. DLP]

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From: Roy Heyne
To: "Vohr, Betty"; Archer, Stephanie (NIH/NICHD) [E]; Neil Finer (nfiner@ucsd.edu); Wally Carlo (wacarlo@uab.edu); Michele Walsh (Michele.walsh@cwru.edu); Marie Gantz (mgantz@rti.org); Laptook, Abbot; Brad Yoder (bradley.yoder@hsc.utah.edu); Roger Faix (roger.faix@hsc.utah.edu); Jamie Newman (newman@rti.org); Abhik Das (adas@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Wade Rich (wrich@ucsd.edu); Nancy Newman (nxs5@cwru.edu); Richard Ehrenkranz (richard.ehrenkranz@yale.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Dee Wilson (b)(6)@aol.com); Kim Yolton (kimberly.yolton@cchmc.org); Patricia Evans (Patricia.W.Evans@uth.tmc.edu); Yvonne Vaucher (yvaucher@ucsd.edu); Ira Adams-Chapman (iadamsc@emory.edu); Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org); (b)(6)@gmail.com); Athina Pappas (apappas@med.wayne.edu); Susan Hintz (srhintz@stanford.edu); Mike Acarregui (Michael.Acarregui@providence.org); Janell Fuller (JaFuller@salud.unm.edu); Ricki Goldstein (golds005@mc.duke.edu); Charles Bauer (cbauer@peds.med.miami.edu); Mike O`Shea (moshea@wfubmc.edu); Gary Myers (gary_myers@URMC.Rochester.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu)
Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper
Date: Monday, October 29, 2012 2:35:52 PM
Attachments: Manuscript -Stevens BreathingOutcomes Edits BV 10-23-12_rh1029.docx

Tim, I agree with Betty's comments/edits and have added some of my own. Good work.

From: Vohr, Betty [mailto:BVohr@WIHRI.org]
Sent: Saturday, October 27, 2012 11:31 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Neil Finer (nfiner@ucsd.edu); Wally Carlo (wacarlo@uab.edu); Michele Walsh (Michele.walsh@cwru.edu); Marie Gantz (mgantz@rti.org); Laptook, Abbot; Brad Yoder (bradley.yoder@hsc.utah.edu); Roger Faix (roger.faix@hsc.utah.edu); Jamie Newman (newman@rti.org); Abhik Das (adas@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Wade Rich (wrich@ucsd.edu); Nancy Newman (nxs5@cwru.edu); Richard Ehrenkranz (richard.ehrenkranz@yale.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Dee Wilson (b)(6)@aol.com); Kim Yolton (kimberly.yolton@cchmc.org); Roy Heyne; Patricia Evans (Patricia.W.Evans@uth.tmc.edu); Yvonne Vaucher (yvaucher@ucsd.edu); Ira Adams-Chapman (iadamsc@emory.edu); Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org); (b)(6)@gmail.com); Athina Pappas (apappas@med.wayne.edu); Susan Hintz (srhintz@stanford.edu); Mike Acarregui (Michael.Acarregui@providence.org); Janell Fuller (JaFuller@salud.unm.edu); Ricki Goldstein (golds005@mc.duke.edu); Charles Bauer (cbauer@peds.med.miami.edu); Mike O`Shea (moshea@wfubmc.edu); Gary Myers (gary_myers@URMC.Rochester.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu)
Subject: RE: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Steve, Very nice. I have some edits and suggestions and queries in tracking. Best wishes. Betty

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Wednesday, October 24, 2012 1:00 PM
To: Neil Finer (nfiner@ucsd.edu); Wally Carlo (wacarlo@uab.edu); Michele Walsh (Michele.walsh@cwru.edu); Marie Gantz (mgantz@rti.org); Laptook, Abbot; Brad Yoder (bradley.yoder@hsc.utah.edu); Roger Faix (roger.faix@hsc.utah.edu); Jamie Newman (newman@rti.org); Abhik Das (adas@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Wade Rich (wrich@ucsd.edu); Nancy Newman (nxs5@cwru.edu); Richard Ehrenkranz (richard.ehrenkranz@yale.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Vohr, Betty; Dee Wilson (b)(6)@aol.com); Kim Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); Patricia Evans (Patricia.W.Evans@uth.tmc.edu); Yvonne Vaucher (yvaucher@ucsd.edu); Ira Adams-Chapman (iadamsc@emory.edu); Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org); (b)(6)@gmail.com); Athina Pappas (apappas@med.wayne.edu); Susan Hintz (srhintz@stanford.edu); Mike Acarregui (Michael.Acarregui@providence.org); Janell Fuller (JaFuller@salud.unm.edu); Ricki Goldstein (golds005@mc.duke.edu); Charles Bauer (cbauer@peds.med.miami.edu); Mike O`Shea (moshea@wfubmc.edu); Gary Myers (gary_myers@URMC.Rochester.edu); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu)

Subject: Author Review | Stevens, SUPPORT Breathing Outcomes paper

Attached is a draft of Tim's SUPPORT Breathing Outcomes paper for the coauthors to review.

Please send any comments back to Tim by **Wednesday, November 7th**.

Thank you,

Stephanie

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Tuesday, October 23, 2012 9:35 PM
To: Newman, Jamie <newman@rti.org> (newman@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: Breathing Outcomes

Hi Jamie and Rose,

Here is the next version of the manuscript. Barbara double checked the tobacco exposure and provided updated values.

Can you forward the manuscript to the reviewers?

Thanks

Tim

<hr>
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UT Southwestern Medical Center

The future of medicine, today.

Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

Timothy P. Stevens, MD MPH¹; Neil N. Finer, MD²; Waldemar A. Carlo, MD³; Peter G. Szilagyi, MD¹; Michele C. Walsh, MD MS⁴; Marie G. Gantz, PhD⁵; Abbot R. Lupton, MD⁶; Bradley A. Yoder, MD⁷; Roger G. Faix, MD⁸; Jamie E. Newman, PhD, MPH⁹; Abhik Das, PhD⁸; Barbara Do, MSPH⁸; Kurt Schibler, MD⁹; Wade Rich, RRT²; Nancy S. Newman, RN⁶; Richard A. Ehrenkranz, MD¹⁰; Myriam Peralta-Carcelen, MD MPH⁹; Betty R. Vohr, MD⁶; Deanne E. Wilson-Costello, MD⁴; Kimberly Yolton, PhD⁹; Roy J. Heyne, MD¹¹; Anna M. Dusick, MD FAAP¹²; Patricia W. Evans, MD¹³; Yvonne E. Vaucher, MD MPH²; Ira Adams-Chapman, MD¹⁴; Elisabeth C. McGowan, MD¹⁵; Anna Bodnar, MD⁷; Athina Pappas, MD¹⁶; Susan R. Hintz, MD MS Epi¹⁷; Michael J. Acarregui, MD¹⁸; Janell Fuller, MD¹⁹; Ricki F. Goldstein, MD²⁰; Charles R. Bauer, MD²¹; T. Michael O'Shea, MD MPH²²; Gary J. Myers, MD¹; Rosemary D. Higgins, MD²³ for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Word Count:

Text: MeSH terms:

Bronchopulmonary Dysplasia
Infant, Newborn
Infant, Low Birth Weight
Infant, Extremely Low Birth Weight
Infant, Premature
Infant, Extremely Low Gestational Age
Infant mortality
Respiratory morbidity
Intensive care, neonatal
Hospital Readmission
Oximetry
Randomized controlled trial
Retinopathy of prematurity (ROP)
Continuous Positive Airway Pressure
Intubation, intratracheal
Pulmonary surfactants/therapeutic use
Oxygen inhalation therapy/methods
Oxygen administration & dosage
Follow-up studies

ABSTRACT

BACKGROUND:

The NICHD SUPPORT Trial found no difference in the composite outcomes of death or BPD, death or ROP and death or neurodevelopmental impairment between infants treated with lower (85-89%) versus higher (91-95%) oxygen saturation targets or with CPAP versus early surfactant (Surfactant). Though the composite incidence of death or ROP was similar, infants treated with lower rather than higher saturation targets had less ROP but greater mortality.

METHODS:

The Breathing Outcomes Sub-Study assessed reported here followed infants 24-27 6/7 weeks' gestation, who were enrolled in SUPPORT, at 6 month intervals from hospital discharge to 18-22 months CA with using a series of 4 standardized parental interviews to assess respiratory-related symptoms, illnesses, medication use and health care utilization. Findings in the study arms of low and high saturation and CPAP and Surfactant were compared.

Comment [R1]: Commas added for clarity

RESULTS:

From a cohort of 922 eligible infants, All four interviews were completed on 873 (94.7%) of 922 eligible infants, completed the four part interview series. The two prespecified primary outcomes, incidences of recurrent wheezing and chronic cough, were 47.9% and 32.0%, respectively, and did not differ between study arms of either randomized intervention. Among secondary outcomes, infants in the lower saturation group had a lower incidence of wheezing (36.3% vs. 43.4%, $p < 0.05$) and nebulizer use at 6 months CA and of wheezing without a cold (28.4% vs. 36.3%, $p < 0.01$) at 18-22 months CA. CPAP compared with surfactant treated infants at 18-22 months CA had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p < 0.05$), fewer respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p = 0.02$) and fewer physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p < 0.05$).

CONCLUSION:

Treatment with lower rather than higher oxygen saturation targets may be associated with less wheezing by 18-22 months CA, a benefit which is insufficient to offset the higher mortality seen in this group as part of SUPPORT. We also conclude that CPAP and limited ventilation rather than intubation and surfactant for infants 24 - 27 6/7th weeks' is safe and results in less respiratory morbidity by 18-22 months CA.

Word count: 315

BACKGROUND

Extremely preterm infants are at greater risk of respiratory symptoms and need for pulmonary care in early childhood than later preterm or term infants [1-7] and contribute substantially to the public health burden of childhood respiratory disease in the United States. [8] Mechanical ventilation and supplemental oxygen use in the early neonatal period has each been identified as a major risk factor for development of BPD and pulmonary morbidity in infancy, childhood and beyond. [1, 2, 9, 10] Though infants with Bronchopulmonary Dysplasia (BPD) are at highest risk for poor pulmonary outcome, neonates without BPD are also at risk for airway dysfunction and pulmonary morbidity during infancy. [4, 11]

The multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) studied infants 24 0/7th-27 6/7th weeks' gestation treated with each of two respiratory strategies designed to minimize mechanical ventilation and supplemental oxygen exposure: 1) treatment with lower (85-89%) compared with higher (91-95%) oxygen saturation targets and 2) early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (Surfactant). Our Network previously reported results of SUPPORT demonstrating no difference in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants treated with either of the two respiratory interventions. [12, 13] (Vaucher when available) It is important to note that although the composite incidence of death or BPD was similar, infants treated with lower rather than higher saturation targets had a lower incidence of retinopathy of prematurity (ROP) but a higher risk of mortality. [13]

We now report on The Breathing Outcomes Study, a secondary outcome to the SUPPORT Trial, which sought to compare respiratory morbidity among extremely preterm infants treated with the SUPPORT study interventions as neonates. ~~It was~~ We hypothesized that infants treated with lower rather than higher oxygen saturation targets and CPAP rather than early surfactant will each have less frequent episodes of recurrent wheezing and cough and less need for outpatient pulmonary care at 18-22 months' corrected age (CA).

METHODS

Infants eligible for The Breathing Outcomes Study were ~~these~~ infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. One thousand three hundred sixteen [1316] infants from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009. Infants were eligible for SUPPORT if their gestational age was between 24 weeks 0 days to 27 completed weeks' (up to 27 6/7ths) by best obstetrical estimate and were born at a participating center, planned to receive full resuscitation if necessary, and without major congenital malformations. Because a goal of the Breathing Outcomes Study was to obtain health outcomes on as many of the SUPPORT subjects as possible, and because enrollment into the Breathing Outcomes Study

began after SUPPORT had begun enrollment, written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT Trial or separately for those patients already enrolled in SUPPORT. As a result, the Breathing Outcomes Study cohort was a subset of the SUPPORT cohort. The study was approved by the institutional review boards at all participating Network centers and by RTI International, the data center for the NICHD Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for both SUPPORT and Breathing Outcomes.[12, 13]

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned in the delivery room to receive CPAP after birth, followed by a limited ventilation strategy if intubation were needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age. Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with either a saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Randomization for both study interventions was accomplished using block randomization with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported.[13, 14]

Assessments of the Breathing Outcomes Study

For subjects enrolled in Breathing Outcomes, a parent or primary caregiver was interviewed by research staff either in person or by phone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at 6, 12 and 18-22 months corrected age. The study questionnaires were drafted based upon questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study.[15, 16] ~~Questions were added to~~ the Tucson questionnaires ~~were added questions~~ to more fully elicit the respiratory health and health service use specific to preterm infants (e.g. palivizumab injections). To standardize administration of the interview, a lead interviewer at each participating center underwent training consisting of a teleconference with 1 of 2 project trainers (Rochester site) to discuss each study question and the written interview script associated with it. Interview trainees then interviewed a standardized patient simulated by the project trainers. Lead interviewers at each center were then able to train additional interviewers at their sites as needed. To minimize misinterpretation of other respiratory sounds as wheezing, a verbal description of wheezing and a brief audio clip of wheezing were played for the interviewee at the beginning of the interview. Questionnaires originally written in English were translated into Spanish using a certified translation service (Cornell Translation Service, Ithaca, NY). Interviews were conducted in either English or Spanish as appropriate.

To minimize loss of recall over time, interviews were conducted at 6 month intervals beginning at the time of hospital discharge. Study personnel conducted the first parent interview using a questionnaire designed to collect information on family history of respiratory diseases and atopy, home environment including tobacco and pet exposures, and diet at discharge from the hospital. Based upon the preference of each participating center, the 6, 12 and 18-22 month interviews were conducted either by

Comment [R2]: Since the windows for these interviews spanned up to two months, may be better to say "at or near"

Comment [R3]: Though you reference the Tucson study, I think it would still be important to note that the two primary outcome questions (9-10) elicit history of cough or wheezing since the "last contact," i.e. over the last 6 months give or take.

Comment [R4]: Actually, since these children were not all discharged at 0 months corrected age, and since some were seen closer to 22 months adjusted age at the final interview, this is only approximately true. May suffice to qualify this with "approximately".

trained staff at the local center (15 centers) or by long distance telephone interview from the Rochester center (5 centers). At each of the 6, 12 and 18-22 month interviews, the parent or caregiver was asked to base their responses on the 6 month interval since the last interview. If an interview at one time point was not completed, interviewees were asked to base their responses during the next interview upon the interval history since the last completed interview. Taken together, the four questionnaire series administered by interviewing the parent or primary caregiver was designed to provide a complete respiratory history over the first 18-22 months' corrected age. In addition to reporting interview responses during the first 18-22 months corrected age, we report responses from the 6 month interview because preterm infants are at especially high risk of respiratory morbidity during the first 6 months of age. REF

The 6 and 12 month interviews were based on questionnaires designed to elicit the frequency and characteristics of respiratory symptoms, including wheezing and cough; incidence of physician-diagnosed asthma, reactive airway disease or "BPD flare-up"; incidence of bronchiolitis, bronchitis or pneumonia, croup; use of medications to treat respiratory illnesses including diuretics, nebulized bronchodilators, inhaled steroids, systemic steroids or oxygen; use of health services including respiratory related physician visits, emergency room visits and hospitalizations; use of preventive therapies including palivizumab and influenza immunization; and impact on the family including whether the parent or caregiver needed to change plans due their child's breathing. In addition to the questions above, the 18-22 month interview included additional questions to elicit whether the child had atopic symptoms or conditions, including eczema and food or medication allergy.

Outcomes

Primary Outcomes: Two primary outcomes were assessed by parental report: the incidence of recurrent wheezing and incidence of chronic cough. From these, the incidence of the combined outcome, recurrent wheezing or chronic cough, was also considered. The incidence of wheezing was ascertained using the primary question used and validated in the Tucson Study (a large prospective birth cohort study of term infants), "Has his/her chest sounded wheezy or whistling?". [15] Recurrent wheezing was defined as wheezing occurring more than twice in any week. The incidence of chronic cough ascertained using the Tucson question, "Has [your] child had a cough for 3 days or more when he/she did not have a cold?" [15].

Secondary outcomes and covariates: Secondary outcomes were interview responses to the 6, 12 and 18-22 month questionnaires for respiratory symptoms, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, the following covariates were evaluated: family history, environmental exposures including tobacco smoke, diet and use of preventive therapies as outlined above. In addition, each patient's outcomes from SUPPORT were available to the Breathing Outcomes Study analysis.

Statistical Analyses

The available subject pool for the Breathing Outcomes Study was limited to subjects enrolled in SUPPORT who survived to hospital discharge and consented to participation. For Breathing Outcomes, a

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Comment [T5]: Where is the data for 18-22 months shown for the 4 groups. In Table 1 the title is Neonatal and Demographic characteristics. Is it a combination of findings from all assessments?

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Comment [T6]: Already stated in Methods

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sample size of 817 subjects was calculated as necessary to detect an absolute risk difference of 0.1 in the incidence of recurrent wheezing between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of recurrent wheezing of 29%. Sample size calculations for SUPPORT have been reported. [12, 13] Based upon SUPPORT's target enrollment of 1310 patients and assuming a 22% mortality (NICHD historical data for calendar year 2000), we anticipated 1021 patients potentially eligible for the Breathing Outcomes Study.

Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. For categorical variables with low frequency ($n < 5$), Fisher exact tests were used. The two primary analyses used the number of patients with either recurrent wheezing or chronic cough as the numerator and the number of infants for whom that outcome was known as the denominator. Using Poisson regression models to adjust for gestational age strata, study center and familial clustering, adjusted relative risk (ARR) values and 95% confidence intervals were calculated and are reported. When Poisson models did not converge, relative risk adjusted for gestational age and center is reported (indicated in tables by †). When the two adjustment models failed to converge due to low prevalence (<5%), unadjusted relative risks are reported (indicated by †† in table). Results were considered statistically significant if the two-sided p value was less than 0.05; a trend towards significance was considered if the two sided p value was between 0.05 and 0.10 inclusive. No adjustments have been made for multiple comparisons. All calculations were performed using SAS software (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study (Figure 1). Follow up rates at each time point are listed in Figure 1; Parents of a total of 873 patients/infants completed the four questionnaire series (94.7%).

Comment [T7]: Should be clear that all of your data is for 837 infants.

Characteristics of the follow-up cohort:

Among the follow up cohort, the group managed with lower compared with higher saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with bronchopulmonary dysplasia (BPD) defined using the traditional criteria of supplemental oxygen uses at 36 weeks' post menstrual age (PMA). The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to surfactant (Table 1). There was no difference between groups in the proportion of infants with BPD defined using the physiologic definition. Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and surfactant groups (Table 2).

Primary Outcomes:

The overall incidences of the two primary outcomes for the 873 infants with complete data, episodes of wheezing more than twice per week and cough lasting more than 3 days, in the follow up cohort during the first 18-22 months corrected age were 47.3% and 33.0%, respectively. There was no difference in incidence of these outcomes between either the subcohort of infants treated with lower compared with higher oxygen saturation targets nor between the subcohort infants treated with CPAP rather than

surfactant (Tables 3 and 4, respectively). The combined outcome of episodes of wheezing more than twice per week or cough lasting more than 3 days for the total cohort was 64.6% and did not differ significantly between subcohorts treated with lower rather than higher saturation target or CPAP rather than surfactant (Tables 3 and 4, respectively).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months corrected age, infants randomized to lower compared with higher saturation targets had a lower incidence of wheezing and in use of nebulized medications since NICU discharge (36.3% vs. 43.4%, $p < 0.05$ and 1.2% vs. 3.9%, $p = 0.02$, respectively) (Table 3). Supporting these differences in wheezing was a trend toward a lower incidence of recurrent wheezing defined as wheezing episodes occurring more than twice per week (22.0% vs. 27.7%, $p = 0.06$) (Table 3). Over the first 18-22 months of corrected age (listed as 6-22 months in Tables 3 and 4), infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (28.4% vs. 36.3%, $p = 0.01$) (Table 3).

Early CPAP Intervention

At 6 months corrected age, infants treated with CPAP rather than surfactant were reported to have fewer asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor since NICU discharge (12.3% vs. 17.2%, $p < 0.05$) and a trend toward fewer hospitalizations for wheezing or breathing problems (16.5% vs. 27.0%, $p = 0.09$). Perhaps related to these differences, parents or primary caregivers of infants treated with CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (12.8% vs. 20.4%, $p < 0.01$) (Table 4).

During the first 6-22 months corrected age, infants receiving early CPAP versus surfactant were significantly less likely to have wheezing episodes occurring without a cold (28.9% vs. 36.5%, $p = 0.01$), respiratory illnesses diagnosed by a doctor (one or more episodes of asthma, reactive airway disease or BPD flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, $p = 0.02$), wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, $p < 0.05$). Compared with those of surfactant treated infants, parents or guardians of CPAP treated infants were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, $p < 0.05$).

DISCUSSION

We report respiratory outcomes during the first 18-22 months' corrected age for a cohort of extremely premature infants (24-27 6/7 weeks' gestation) treated in the NICHD-SUPPORT Trial. We found no significant differences in reported respiratory outcomes at 18-22 months corrected age between patients treated with lower rather than higher saturation targets or with CPAP rather than surfactant in either of the two primary outcomes, incidence of recurrent wheezing and incidence of cough lasting more than 3 days without a cold.

Comment [R8]: For children with a positive hx of wheezing is this based on the secondary question which asks about wheezing "on average" rather than the one re the "worst two weeks"?

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Comment [T9]: Confusing. Tables say 6,12 and 22 m

Comment [R10]: Agree this is confusing. The headings of the table notes 6,12, 18-22; but the rows in the table specify 6 and 6-22. Think you need to specify under methods how the "6-22 month" data points were calculated to show how they reflect "the first 18-22 months of corrected age." Moreover, since each of these interviews reflect events "since the last contact" the 6 month interview presumably reflects the time period since NICU discharge. So does the "6-22 month" data point reflect the 12 and 18-22 month interviews or 6, 12, and 18-22 month. If the latter then it would come close reflecting the "first 18-22 months of corrected age," though I think the suggested rewording by Betty below ("between discharge and 18-22 months corrected age") is more accurate. However, if it does not include the 6 month interview, then would reflect the first 6 to 18-22 months of corrected age, which is what you describe two paragraphs below for Early CPAP

Comment [R11]: See preceding comment.

In secondary analyses, extremely preterm infants managed with low compared with high saturation targets were less likely to have wheezing or use a home nebulizer at 6 months corrected age and to have wheezing apart from a cold ~~between discharge and during the first 18-22 months corrected age~~. In the main SUPPORT trial, patients managed with lower compared with higher saturation targets were exposed to lower concentration of inspired oxygen. Several pulmonary outcome studies have found an association between neonatal oxygen exposure and expiratory flow dysfunction and airway hyperreactivity among infants with or without BPD. [2, 7, 17-19] Our results, taken together with current literature, suggest that lower oxygen exposure in the neonatal period may be associated with reduced wheezing in infancy. However, based upon the findings of greater mortality among patients in SUPPORT treated with lower rather than higher saturation targets, the benefit of reduced wheezing and nebulizer use does not justify management patients 24-27 6/7 weeks' gestation with lower oxygen saturation targets. If oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant injury other than targeting lower oxygen saturations will be needed. [20, 21]

Patients treated with CPAP and limited ventilation rather than intubation and surfactant administration within 1 hour had fewer asthma, reactive airway disease or BPD flare-up episodes at 6 months corrected age and a trend toward fewer hospitalizations for respiratory problems. Perhaps related to these findings was a significant reduction in the proportion of parents reporting that they needed to change plans due to their child's breathing difficulties. During the first 18-22 months corrected age, patients receiving early CPAP rather than surfactant were significantly less likely to have had wheezing episodes occurring without a cold, respiratory illnesses diagnosed by a physician or physician or emergency room visits for breathing or wheezing problems. Parents of CPAP compared with surfactant treated infants were less likely to report changing their plans due to the child's breathing problems. These respiratory benefits were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria, was similar between CPAP and surfactant arms in the SUPPORT study and in the Breathing Outcomes' follow-up cohort. Our data are consistent with follow up data from The COIN Trial, which despite finding no difference in the incidence of death or BPD among 610 infants randomized to either CPAP or conventional management, found better pulmonary function at 8 weeks corrected among a 39 patient subcohort of study infants treated with CPAP. [22, 23] These observations suggest that treatment of infants 24-27 6/7 weeks gestation at risk for RDS with CPAP is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone and that longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions in randomized clinical trials.

We found that regardless of treatment arm, respiratory symptoms and health care usage are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months corrected age. Overall in the Breathing Outcomes cohort, recurrent wheezing occurred in 47.9% of patients and asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor in 34.5%. Treatment of these conditions prompted not only frequent physician visits (63.8% of children), emergency room visits (46.6%) and hospitalizations (42.5%), which have the potential to add to health care costs [8] but also to frequent use of both inhaled (26.3%) and systemic (9.4%) steroids which have potential long term effects on growth and development. [24, 25]

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Comment [T12]: This data is not shown or discussed in the results section. Do you need a column on your tables for total cohort. You could combine tables 3 and 4 in landscape and add a total cohort column ??

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The strengths of this study include the large number of extremely preterm infants enrolled. This is the largest respiratory follow up study of a randomized clinical trial. Other strengths include the high follow up rates for enrolled patients and use of comprehensive respiratory questionnaires administered in a scripted interview by trained personnel. Though not as objective as pulmonary function testing, respiratory history was used as outcome measures due to clinical and financial concerns associated with use of invasive pulmonary testing and potential complications of sedation in former preterm infants. In addition, parental report of wheezing has been shown to correlate with pulmonary function testing and data extracted from office records and provides an estimate of the burden of respiratory morbidity to the patient and family as well as the health care system. [26, 27] Among potential weaknesses, respiratory history data were taken by parental report, which has the potential for classification and recall bias. To minimize classification bias, all primary and follow up study data of this randomized trial were collected in a blinded manner. Hence, though it may affect the precision of point estimates, classification bias is unlikely to have introduced systematic bias into our study that favors one study arm over another. To reduce recall bias, parent interviews were conducted at 6 month intervals.[27] Because the Breathing Outcomes Study was approved and began enrollment after SUPPORT had begun and because we wished to follow all available SUPPORT subjects, study results are not reported as competing outcomes (e.g. death or recurrent wheezing) but rather as respiratory outcomes of the cohort of SUPPORT subjects that survived to hospital discharge. As has been previously reported, the results of SUPPORT and thereby potentially the follow up studies associated with it may not be fully generalizable to all extremely preterm infants because the need for antenatal consent resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort. [28]

In summary, we found no significant differences in the incidence of recurrent wheezing or chronic cough at 18-22 months corrected age between extremely preterm survivors who were randomized at delivery to either lower or higher saturation targets and early CPAP or surfactant. In secondary analyses, we found reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months corrected age in the lower saturation group. However, because management with lower saturation targets was associated with greater mortality in SUPPORT [13], we conclude that the benefit of reduced wheezing and nebulizer use seen in the Breathing Outcomes Study does not justify treatment with lower saturation targets in patients 24-27 6/7 weeks' gestation. Also in secondary analyses, we report fewer respiratory symptoms, physician diagnosed respiratory problems and reduced health care use among infants treated with CPAP rather than early surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over surfactant. [12, 13](add Vaucher reference when available). Those findings coupled with the respiratory outcomes identified in this report reported here suggest that treatment of extremely premature infants with CPAP and limited ventilation rather than intubation and early surfactant administration is safe and may result in less respiratory morbidity during the first 18-22 months corrected age. The findings also clearly demonstrate the increased risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation and the need for close medical monitoring post-discharge.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

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Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

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From: Susan Hintz
To: Vaucher, Yvonne
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; "Wally Carlo, M.D."; Gantz, Marie; "Kurt Schibler"; "mcw3@cwru.edu"; "ROGER.FADX@HSC.UTAH.EDU"; "Laptook, Abbot"; Bradley.Yoder@hsc.utah.edu; "Myriam Peralta, M.D."; "nancy.newman"; Rich, Wade; "Das, Abhik"; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, October 26, 2012 5:35:34 PM

Looks great - thanks for all your work on this analysis!

Susan

On Oct 26, 2012, at 12:42 PM, Vaucher, Yvonne wrote:

> All,
>
> Here is the final antenatal enrollment abstract I have sent to Rose.
>
> Yvonne
> <Antenatal enrollment SUPPORTPAS2013FINALtoNRN102612.docx>

From: Wally Carlo, M.D.
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie; "Kurt Schibler"; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; "Laptook, Abbot"; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; "nancy newman"; Rich, Wade; "Das, Abhik"; Susan Hintz
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, October 26, 2012 5:15:58 PM

Yvonne:

Great job leading this abstract!!!

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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Cell: 205 (b)(6)

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]
Sent: Friday, October 26, 2012 2:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Susan Hintz
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

All,

Here is the final antenatal enrollment abstract I have sent to Rose.

Yvonne

From: [Vaucher, Yvonne](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Antenatal Enrollment ND Outcomes Abstract PAS 2013
Date: Friday, October 26, 2012 3:43:02 PM
Attachments: [Antenatal enrollment SUPPORTPAS2013FINALtoNRN102612.docx](#)

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

Title: ANTENATAL ENROLLMENT IN CLINICAL TRIALS: IS NEURODEVELOPMENTAL OUTCOME REPRESENTATIVE?

Yvonne E Vaucher, MD, MPH¹, Susan R Hintz, MD, MS², Wade Rich, BS, MS, RRT¹, Marie G Gantz, PhD³ and Neil N Finer, MD¹. ¹Dept. of Pediatrics, University of California, San Diego, CA, United States; ²Dept. of Pediatrics, Stanford University, Palo Alto, CA, United States and ³Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States.

Background: Antenatal enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) was associated with differences in demographic, antenatal and neonatal characteristics between the enrolled vs. non-enrolled extremely preterm infants. Mothers of eligible/non-enrolled infants were less likely to be White/non-Hispanic, insured, have prenatal care (PNC), or receive antenatal steroids (ANS). Eligible/non-enrolled infants were more likely to have lower gestational age (GA), birthweight (BW) and Apgar Scores, require DR resuscitation, develop BPD and severe IVH and die before discharge.

Objective: To determine whether antenatal enrollment in SUPPORT was associated with differences in Death and Neurodevelopmental Impairment (NDI) in enrolled vs. eligible/non-enrolled children.

Design/Methods: We included 24-26 week GA infants at Neonatal Research Network (NRN) sites with BW >400 g, born from 1/2006 to 2/2009, who were eligible for SUPPORT. A comprehensive neurodevelopmental evaluation was performed at 18-22 mo corrected age (CA) using standardized neuromotor assessment and the cognitive scale of the BSID-III. Outcomes compared for enrolled vs. eligible/non-enrolled children were Death or NDI, individual components of NDI [cognitive BSID-III score <70, Gross Motor Function Classification System Score (GMFCS) \geq 2, moderate-severe cerebral palsy, blind, deaf] and levels of cognitive delay. Logistic regression models controlled for center, sex, race, GA, BW, insurance, PNC, ANS, Apgar scores and DR resuscitation.

Results: The primary composite SUPPORT outcome (Death or NDI) was determined for 95.3% (695/729) of children enrolled in SUPPORT vs. 90.9% (1471/1618) of children eligible/non-enrolled ($p < .001$). In unadjusted analyses, eligible/non-enrolled children were more likely to have Death or NDI (41.4% vs. 33.4%, $p < .001$), to die before 18-22 mo CA (31.7% vs. 24.8%, $p < .001$), and to have cognitive scores <80 (19.9% vs. 15.5%, $p = .038$). No other outcomes were significantly different. In adjusted models, antenatal and neonatal risk factors predicted outcomes while enrollment did not.

Conclusions: Compared to children enrolled in SUPPORT, those who were eligible but not enrolled were more likely to die, to have Death or NDI and to have lower cognitive scores. These differences are attributed to demographic, antenatal and neonatal differences that favored those who were enrolled.

From: Luc Brion
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: (b)(6)@gmail.com; Wrage, Lisa Ann
Subject: FW: Issues with PAS website
Date: Thursday, October 25, 2012 2:43:11 PM
Attachments: PAS 2013_750229_preview.pdf

Stephanie;
Here is Jackie's abstract
Luc

From: c4asupport [c4asupport@coetruman.com]
Sent: Thursday, October 25, 2012 9:55 AM
To: Luc Brion
Subject: RE: Issues with PAS website

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Sandra Varley

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, October 22, 2012 11:03 AM
To: c4asupport
Cc: Wrage, Lisa Ann; 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: Issues with PAS website

To whom it may concern:

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The abstract number is 750229.

On Friday it generated hieroglyphs; today it only shows up to the award section, not the abstract

itself.

Please could you advise me on how to proceed.

Sincerely,

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
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First Author: Jaclyn LeVan, DO
Presenting Author: Jaclyn LeVan DO
Contact Author: Luc P Brion, MD **Email:** luc.brion@utsouthwestern.edu

Filename: 750229

2013 PAS Annual Meeting

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Theme: Neonatal - Disease-Oriented Research

Presenting Author: Jaclyn LeVan DO
Department/Institution/Address: Pediatrics, Univ Texas Southwestern, 5323 Harry Hines Blvd, Dallas, TX, 75390-9063, United States
Phone: 817-360-7552 **Fax:** 214-648-2481

Presenting Author E-mail: doctorlevan@gmail.com

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Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR

Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, August 1-4, 2013

Research Type: Clinical

Presentation Sabbath Conflict on: N/A

APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS abstract:

Sponsor Name: Luc P Brion

Email: luc.brion@utsouthwestern.edu

Is the Sponsor an Author? Yes

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Title: CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn LeVan, DO¹, Luc P Brion, MD¹ and Lisa A Wrage². ¹Univ Texas Southwestern, Dallas, TX and ²RTI International, Research Triangle Park, NC; on behalf of the NICHD NRN.

Background: In the NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure and Oxygenation Randomized Trial (SUPPORT) preterm neonates 24-27^{6/7} weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) and subsequent limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85 to 89% or 91 to 95%. The interventions did not affect the primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks), and death or severe retinopathy of prematurity (ROP). However, randomization to low O₂ saturation targets increased deaths and decreased severe ROP. We hypothesized that the odds of DR intubation would decrease after dissemination of the SUPPORT results, without affecting BPD/death and severe ROP/death.

Objective: To compare DR intubation, BPD/death at 36 weeks, and severe ROP/death by discharge in time periods before SUPPORT and after its publication.

Design/Methods: This was a retrospective cohort study using the prospective NRN generic database. We included infants 24-27 6/7 weeks GA born before (2003-04) and after SUPPORT (2010-11) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes/major malformations and those receiving comfort care.

Results: The % of DR intubation, ROP/death, BPD/death, and death by discharge significantly decreased after SUPPORT (Table). After adjustment for baseline variables, the odds ratios (OR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.

Conclusions: The adjusted odds of DR intubation and ROP/death, but not those of BPD/death and death by discharge, significantly decreased after dissemination of SUPPORT results in NRN centers involved in the trial.

Parameters	Pre-SUPPORT	Post-SUPPORT	p-value	Adjusted OR (95% CI)	Adjusted p-value
DR Intubation	1313/1617 (81%)	1082/1534 (71%)	<0.0001	0.55 (0.46-0.67)	<0.0001
BPD/death	970/1617 (60%)	824/1522 (54%)	0.0009	1.09 (0.91-1.30)	0.37
Severe ROP/death	515/1581 (33%)	406/1501 (27%)	0.0011	0.73 (0.60-0.87)	0.0007
Death by discharge	358/1614 (22%)	285/1519 (19%)	0.017	0.85 (0.69-1.04)	0.11

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 Questions about the **2013 Eastern Society for Pediatric Research Annual Meeting**? Contact the ESPR Secretary at michael.posencheg@uphs.upenn.edu or espr-info@espr.org.

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From: [Wrage, Lisa Ann](#)
To: [Kennedy, Kathleen A](#)
Cc: dale_phelps@urmc.rochester.edu; [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: Another revision
Date: Wednesday, October 24, 2012 2:19:07 PM

Hi Kathleen,

Thanks for reviewing. I'll have Marie help clear up/verify information in #1. And I'll work some more on the figures & will verify Table 3.

Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Wednesday, October 24, 2012 12:40 PM
To: Wrage, Lisa Ann
Cc: dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD)
Subject: RE: Another revision

Lisa, thanks again for your work on this.

Remaining questions for Lisa:

- 1) I'm still not clear on how a favorable study endpoint was defined. Was it two eye exams with vessels in Zone 3 or two eye exams with no ROP and vessels in Zone 3? The manual just says "Vessels in zone III for two sequential eye examinations". I don't know if that's because it was considered "favorable" if they had exams with mild ROP in zone 3 or if it was assumed that the ophthalmologist would keep following them if that occurred. Or maybe it just never happens. I think we should be very clear about this in the manuscript.
- 2) I like the new Figure 2. I think it would look better if you could make the fonts bolder (as they were on the previous version) and the titles on the x-axis need to be centered below the appropriate group of bars. I think it would look a little better if the bars for each week were slightly closer together but that's a minor point and it probably won't look better if you have to move them too close to each other.
- 3) I've relabeled the title for Table 3 to say that these are "95% confidence intervals". The tracking changes made it a little hard to see some of the numbers in the revised table. Please verify.
- 4) I don't think the new Figure 3 really solves the problem of the figure appearing to be different from the data in the table. You just can't see where the line starts departing from zero. I also like the original colors better. The light yellow is hard to see.

Dale,

I never got a response to the email I sent on 9/12. Here's a copy of the part that was directed to you: "The attached revision is my attempt to do what everyone asked whenever feasible. The changes that I made in response to other people's suggestions are highlighted in yellow. I'd appreciate it if you'd look at those parts to see if you agree with the changes. I wasn't able to make all the changes that you suggested to the What's new? and the Abstract because of the word limits. The biggest changes have to do with incorporating 2 new similar papers (we really need to get this done and published before there are more) and trying to clarify the Discussion about postmenstrual vs chronologic age. It didn't even make sense to me after I'd taken a break from it for a while. We may need to tweak the wording some more when Lisa finishes the analyses but I don't think there will be major changes. As always, I look forward to your comments on this."

The most recent changes to the manuscript (based on Lisa's responses to the 9/12 email) are highlighted in gray in the attachment.

All,

When these questions are resolved, I think we will have done everything that's reasonable to respond to the subcommittee's comments. (I asked Wally and Neil for clarification of some of their comments and never got a response so I think we can go with what we have). I'd really like to send this to Bill Truog for internal review soon. I think we're very close.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 19, 2012 2:18 PM
To: Kennedy, Kathleen A
Cc: Das, Abhik
Subject: RE: Another revision

Hi Kathleen,

Here's an updated version of the paper. I've addressed most of the issues you brought up. Some of the graphs may need more tweaking, I've added in a couple of new ones along with some comments to see how you like them. I have not found an obvious way to put confidence intervals around the cumulative distribution of age of onset graphs, I'll be double checking that, but I wanted to get you the rest of these updates to look at. Please see below for additional comments (In red) (as well is in the update).

Thanks and have a nice weekend.

Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Tuesday, October 16, 2012 3:36 PM
To: Wrage, Lisa Ann
Subject: RE: Another revision

I like the configuration/arrangement of the bars. To my eye at least, it would look better if all the components of the ROP bar were shades of blue and the gray or black colors were used for death and death or ROP.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 16, 2012 10:11 AM
To: Kennedy, Kathleen A
Subject: FW: Another revision

Hi Kathleen,

Could you take a look at this (unfinished draft) of the bar figure now with stacked bars for the ROP groups and please let me know if you think you are going to like an updated version with the stacked bar vs. the old version.

I am finishing up the rest of the other updates as well.

Thanks.

Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 02, 2012 10:43 AM
To: 'Kennedy, Kathleen A'; dale_phelps@urmc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Another revision

Hi, I have not forgotten about this, I just have been busy with PAS, I'm getting started with this now.

Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Wednesday, September 12, 2012 8:26 PM
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Another revision

Lisa, here's a summary of what we "discussed" yesterday and the additional comments/requests from the other reviews.

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Director, MS in Clinical Research Degree Program

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Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, September 11, 2012 11:13 AM
To: Kennedy, Kathleen A
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)

Hi Kathleen,
See below:

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Tuesday, September 11, 2012 11:41 AM
To: Wrage, Lisa Ann
Subject: FW: Onset of ROP Observational Study (SUPPORT Secondary)

Could you please take a look at Abhik's comments #5 and #7?

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Lisa: It should be able to be dotted. I am assuming that you mean to include all infants with any ROP in that line??

Thanks.
Lisa

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From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Friday, July 27, 2012 12:28 PM
To: Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)

Kathleen:

This looks very good. I only have a few minor comments/suggestions in the attached.

Thanks

Abhik

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Sent: Friday, July 27, 2012 9:53 AM
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Archer, Stephanie
Subject: Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

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From: Kennedy, Kathleen A
To: Wrage, Lisa Ann
Cc: dale_phelps@urne.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Another revision
Date: Wednesday, October 24, 2012 12:40:39 PM
Attachments: ROP_Natural_History_Study_Manuscript_(revised_for_internal_review).doc

Lisa, thanks again for your work on this.

Remaining questions for Lisa:

- 1) I'm still not clear on how a favorable study endpoint was defined. Was it **two eye exams with vessels in Zone 3** or **two eye exams with no ROP and vessels in Zone 3**? The manual just says "Vessels in zone III for two sequential eye examinations". I don't know if that's because it was considered "favorable" if they had exams with mild ROP in zone 3 or if it was assumed that the ophthalmologist would keep following them if that occurred. Or maybe it just never happens. I think we should be very clear about this in the manuscript.
- 2) I like the new Figure 2. I think it would look better if you could make the fonts bolder (as they were on the previous version) and the titles on the x-axis need to be centered below the appropriate group of bars. I think it would look a little better if the bars for each week were slightly closer together but that's a minor point and it probably won't look better if you have to move them too close to each other.
- 3) I've relabeled the title for Table 3 to say that these are "95% confidence intervals". The tracking changes made it a little hard to see some of the numbers in the revised table. Please verify.
- 4) I don't think the new Figure 3 really solves the problem of the figure appearing to be different from the data in the table. You just can't see where the line starts departing from zero. I also like the original colors better. The light yellow is hard to see.

Dale,

I never got a response to the email I sent on 9/12. Here's a copy of the part that was directed to you: "The attached revision is my attempt to do what everyone asked whenever feasible. The changes that I made in response to other people's suggestions are highlighted in yellow. I'd appreciate it if you'd look at those parts to see if you agree with the changes. I wasn't able to make all the changes that you suggested to the What's new? and the Abstract because of the word limits. The biggest changes have to do with incorporating 2 new similar papers (we really need to get this done and published before there are more) and trying to clarify the Discussion about postmenstrual vs chronologic age. It didn't even make sense to me after I'd taken a break from it for a while. We may need to tweak the wording some more when Lisa finishes the analyses but I don't think there will be major changes. As always, I look forward to your comments on this."

The most recent changes to the manuscript (based on Lisa's responses to the 9/12 email) are highlighted in gray in the attachment.

All,

When these questions are resolved, I think we will have done everything that's reasonable to respond to the subcommittee's comments. (I asked Wally and Neil for clarification of some of their comments and never got a response so I think we can go with what we have). I'd really like to send this to Bill Truong for internal review soon. I think we're very close.

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 19, 2012 2:18 PM
To: Kennedy, Kathleen A
Cc: Das, Abhik
Subject: RE: Another revision

Hi Kathleen,

Here's an updated version of the paper. I've addressed most of the issues you brought up. Some of the graphs may need more tweaking, I've added in a couple of new ones along with some comments to see how you like them. I have not found an obvious way to put confidence intervals around the cumulative distribution of age of onset graphs, I'll be double checking that, but I wanted to get you the rest of these updates to look at. Please see below for additional comments (In red) (as well is in the update).

Thanks and have a nice weekend.

Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Tuesday, October 16, 2012 3:36 PM
To: Wrage, Lisa Ann
Subject: RE: Another revision

I like the configuration/arrangement of the bars. To my eye at least, it would look better if all the components of the ROP bar were shades of blue and the gray or black colors were used for death and death or ROP.

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, October 16, 2012 10:11 AM
To: Kennedy, Kathleen A
Subject: FW: Another revision

Hi Kathleen,

Could you take a look at this (unfinished draft) of the bar figure now with stacked bars for the ROP groups and please let me know if you think you are going to like an updated version with the stacked bar vs. the old version.

I am finishing up the rest of the other updates as well.

Thanks.

Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 02, 2012 10:43 AM
To: 'Kennedy, Kathleen A'; dale_phelps@urmc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Another revision

Hi, I have not forgotten about this, I just have been busy with PAS, I'm getting started with this now.
Lisa

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Wednesday, September 12, 2012 8:26 PM
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD)
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Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy, MD MPH¹; Lisa A. Wraga, MPH²; Rosemary D. Higgins, MD³; Neil N. Finer, MD⁴; Waldemar A. Carlo, MD⁵; Michele C. Walsh, MD MS⁶; Abbot R. Lupton, MD⁷; Roger G. Faix, MD⁸; Bradley A. Yoder, MD⁹; Kurt Schibler, MD⁹; Marie G. Gantz, PhD²; Abhik Das, PhD¹⁰; Nancy S. Newman, RN⁸; Wade Rich, RRT⁴; Dale L. Phelps, MD¹¹; for the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

Comment [KKA1]: 2907 words excluding title page, abstract, tables, subtitles, figures, figure legends, and references; needs to be <=3000

Abbreviations:

GA – gestational age
PMA – postmenstrual age
ROP – retinopathy of prematurity
SUPPORT – Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

Keywords

retinopathy of prematurity, screening, extremely preterm infants

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⁶ Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

⁷ Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

⁸ Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT

⁹ Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH

¹⁰ RTI International, Rockville, MD

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Corresponding author:
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What's Known on this Subject

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

Comment [KKA2]: 40/40 words

What This Study Adds

Our data support the timing of examinations in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. We did not replicate the observation that the onset of ROP is more closely correlated with postmenstrual than chronological age.

Comment [KKA3]: 40/40 words

Abstract

Objective: Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997 and treated for threshold ROP. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

Patients and Methods: Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was a primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

Results: 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had a final ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

Conclusions: Our contemporary data support continued use of the 2006 guidelines. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines^{1,2} are based on natural history data from the CRYO-ROP³ and LIGHT-ROP⁴ studies. The CRYO-ROP study⁵ remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.⁶ Over the past two decades, survival of lower birth weight infants has increased.^{7,8} For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.⁷ The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.⁴ Based on the results of the ET-ROP study, earlier treatment is now recommended.⁹ With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP, defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP Study¹⁰ and a population-based cohort study of infants born 2004-2007 in Sweden¹¹ reported the age of onset of stages 1, 2, and 3 ROP; the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from the Canadian Neonatal Network reported the age of onset of Type 1 ROP in a cohort of 214 infants \leq 27 weeks gestation;¹² this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort¹³ reported that "No preterm infants required treatment before the 33th postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for treatable ROP so that appropriate follow-up can be arranged (particularly

Comment [KKA4]: 249 words, needs to be \leq 250 Dale, I can't add anything more to the abstract without removing something.

Comment [KKA5]: Dale, I've searched before for newer references for this statement. If we want a reference to support a statement that survival has improved, we need a report of survival for the same cohort (by either BW or GA) in two different time periods. This is the most recent report of that kind that I could find. I added the newer reference even though it doesn't support this statement because it reports survival of ELGA infants during the time of the SUPPORT trial.

for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 ⁶/₇ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)¹⁴ to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O₂ saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24 ⁰/₇ - 27 ⁶/₇ weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab); or no severe ROP (full vascularization to the ora serrata or vascularization in zone III on 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up was curtailed at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

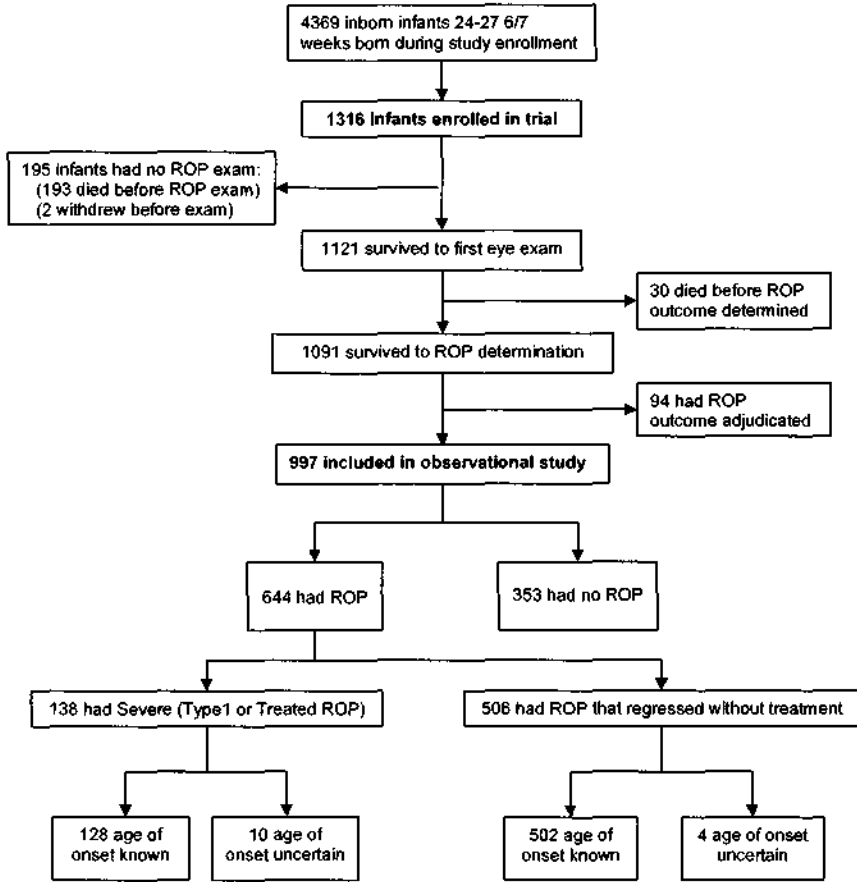
Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in the either eye.

Classification of ROP was compared using Chi-square tests. All analyses were completed using SAS (SAS Institute, Cary, NC).

Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-five percent (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of subjects in the original trial and current analysis



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP ¹	Severe (Type 1 or Treated) ROP

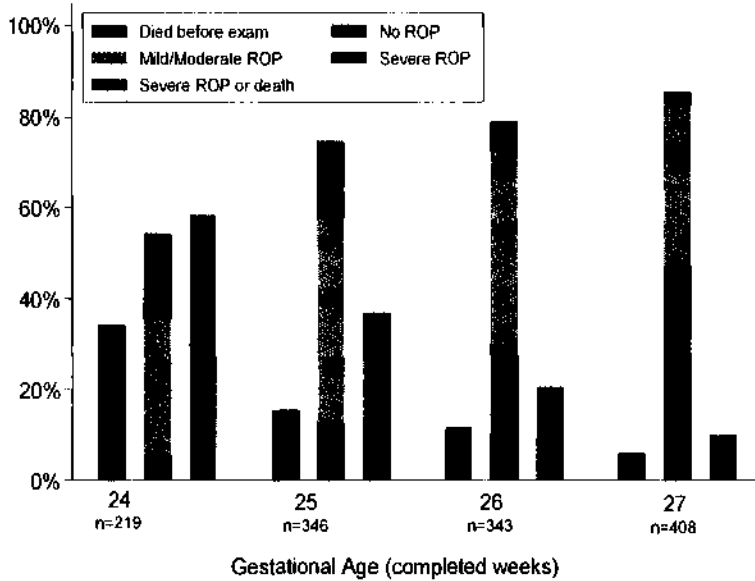
n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA ² [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

¹ Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

² based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all 1316 infants in SUPPORT Trial



Comment [KKA6]: This came from Lisa on 10/19. I've asked if she can make the fonts bold and align the labels on the x-axis.

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP).

Table 2. Risk factors for ROP

Risk Factor	No ROP	Any ROP ¹	Severe (Treated or Type 1) ROP
n	353	644	138
Days on supplemental oxygen (mean [SD])	32.7 (17.9)	42.9 (20.0)	64.1 (22.7)
Late-onset sepsis (+ culture) [n (%)]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23 ² (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98 ² (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

¹ Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

² missing data for 1 infant

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

Table 3. Postmenstrual and chronological age of onset¹ (with 95% confidence intervals (CI)) of any stage ROP (among infants with ROP age of onset determined)

ROP type	n	Postmenstrual Age (weeks)									
		min ²	1%	5%	25%	50%	75%	95%	99%	Max ²	
Any ROP (95%CI)	635	29.3	30.0 (29.6-30.6)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.6-34.2)	35.1 (34.8-35.4)	36.0 (35.7-36.3)	36.9 (36.6-37.2)	37.7 (37.4-38.0)	46.7
Type 2 ROP ³ (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.8-31.1)	34.3 (33.8-34.9)	36.1 (35.6-36.6)	37.1 (36.6-37.7)	38.4 (37.9-38.9)	39.4 (38.9-39.9)	40.4 (39.9-40.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-33.7)	33.8 (32.7-34.3)	35.1 (34.7-35.4)	36.1 (35.6-36.6)	37.1 (36.6-37.6)	38.1 (37.6-38.6)	39.1 (38.6-39.6)	40.1 (39.6-40.6)	53.1

ROP type	n	Chronological Age (weeks)									
		min	1%	5%	25%	50%	75%	95%	99%	max	
Any ROP (95%CI)	635	4.0	4.8 (4.6-5.0)	5.4 (5.0-6.0)	6.9 (6.8-6.8)	8.0 (8.7-8.1)	9.4 (9.7-9.0)	11.0 (11.3-10.7)	12.3 (12.4-12.2)	13.3 (14.1-12.5)	19.7
Type 2 ROP ³ (95%CI)	158	4.4	4.6 (4.4-5.0)	5.3 (4.9-5.8)	6.7 (7.4-6.0)	8.0 (8.7-7.3)	9.6 (10.3-8.9)	11.0 (12.2-9.7)	12.0 (13.1-10.9)	13.0 (14.2-11.8)	22.7
Severe (Type 1 /treated) ROP (95% CI)	128	6.4	7.0 (6.4-7.6)	8.4 (7.7-9.0)	9.8 (10.5-9.1)	11.0 (12.2-9.7)	12.1 (13.3-10.9)	13.1 (14.3-11.9)	14.0 (15.2-12.8)	15.0 (16.2-13.8)	28.4

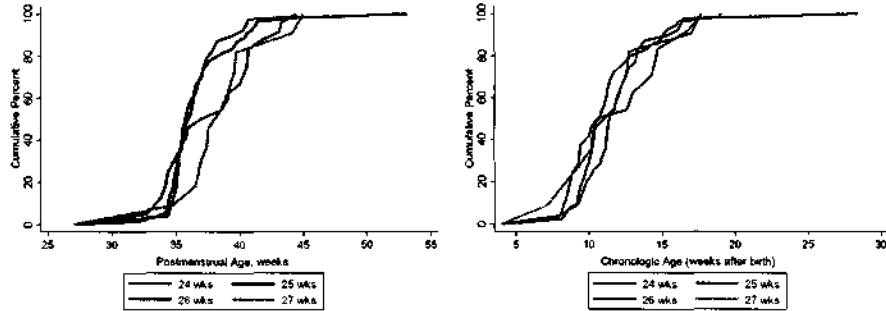
¹ Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.

² Min = minimum age at which designated severity of ROP was identified; max = maximum age.

³ Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 3.

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth

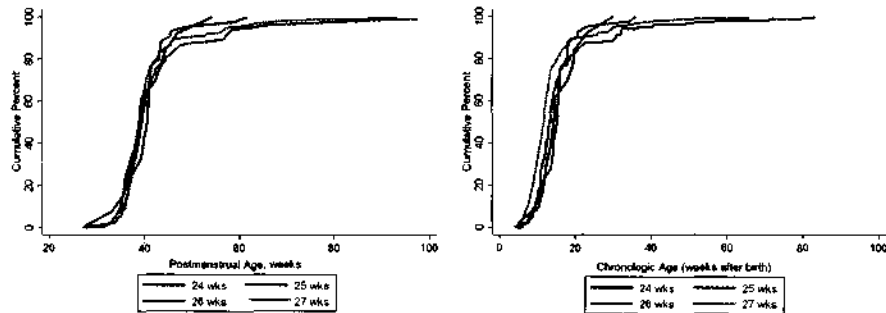


In contrast to prior studies, our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. [REDACTED] The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam without stage 3 ROP or plus disease and vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

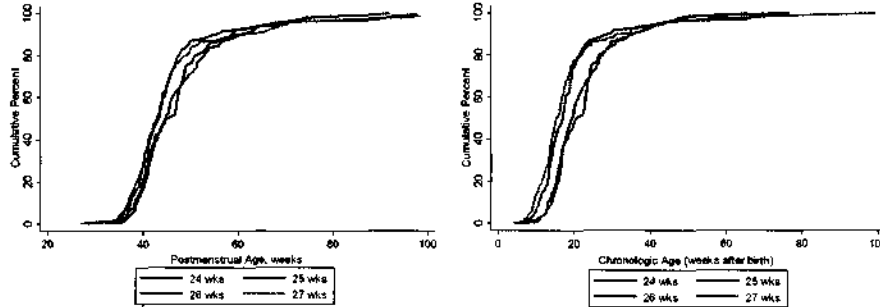
Comment [KKA7]: Added in response to Brad Yoder's comment. Need to verify with Lisa and Dale.

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

No ROP on any exam



Mild/Moderate ROP



Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge).

Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)

Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,⁹ so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,³ lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,¹ albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ($\leq 1250g$) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.¹⁶ Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely

Comment [KKA8]: Dale, I added this at Abbot's suggestion. I'm not that happy with it. Your thoughts?

that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age¹⁷ and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum (<750g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

Comment [KKA9]: They didn't stratify randomization but they stratified by BW when they reported the timing of onset of ROP in the natural history paper.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,¹¹ which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al¹² included 23-27 week infants; infants ≤ 25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants >25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (23-24 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest age of onset of Type 1 ROP is more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian Network study,¹² the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al¹³ that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronological age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.¹⁸ The SUPPORT Trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.¹⁸

Conclusion

Current screening guidelines, published in 2006,¹ recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at ≥ 35 weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at

onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

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Acknowledgments

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Dr. Marie Gantz, and Ms. Wrage (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – William Oh, MD; Betty R. Vohr, MD; Angelita M. Hensman, RN BSN; Bonnie E. Stephens, MD; Barbara Alksninis, PNP; Dawn Andrews, RN; Kristen Angela, RN; Susan Barnett, RRT; Bill Cashore, MD; Melinda Caskey, MD; Kim Francis, RN; Dan Gingras, RRT; Regina A. Gargus, MD FAAP; Katharine Johnson, MD; Shabnam Lainwala, MD; Theresa M. Leach, MEd CAES; Martha R. Leonard, BA BS; Sarah Lillie, RRT; Kalida Mehta; James R. Moore, MD; Lucy Noel; Suzy Ventura; Rachel V. Walden; Victoria E. Watson, MS CAS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Deanne E. Wilson-Costello, MD; Bonnie S. Siner, RN; Arlene Zadel RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kimberly Yolton, PhD; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki F. Goldstein, MD; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ira Adams-Chapman, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Comment [KKA10]: May need to be moved to after Corresponding Author for Pediatrics submission.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; Anna M. Dusick, MD FAAP; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; Susan R. Hintz, MD MS Epi; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; Elisabeth C. McGowan, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD; Myriam Peralta-Carcelen, MD MPH; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN; Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Yvonne E. Vaucher, MD MPH; Kathy Amell, RNC; Rene Barbieri-Welge; Ayala Ben-Tali; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Elaine Ito; Meghan Lukasik; Deborah Pontillo; Donna Posin, OTR/L MPA; Cheryl Runyan; James Wilkes; Paul Zlotnik.

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Michael J. Acarregui, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroeger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Janell Fuller, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Gary David Markowitz, MD; Gary J. Myers, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augustino; Julie Babish Johnson, MSW; Erica Burnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Roy J. Heyne, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Jon E. Tyson, MD MPH; Patricia W. Evans, MD; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Anna Bodnar, MD; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Manlee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised protocol for Jackie LeVan's protocol
Date: Wednesday, October 24, 2012 5:16:14 AM

Thanks a lot for your help and advice.

Best regards

Luc

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 23, 2012 12:37 PM
To: Luc Brion
Subject: RE: Revised protocol for Jackie LeVan's protocol

Not at this point

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, October 23, 2012 1:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised protocol for Jackie LeVan's protocol

Thanks a lot

Do I need to do anything else at this point?

Luc

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, October 23, 2012 8:50 AM
To: Luc Brion
Cc: 'Barbara Stoll'; 'Wally Carlo, M.D.'; 'nfiner@ucsd.edu'; Pablo Sanchez; Roy Heyne; Myra Wyckoff; (b)(6)@gmail.com; 'Das, Abhik'; Gantz, Marie; 'Wrage, Lisa Ann'; Mambarambath Jaleel
Subject: RE: Revised protocol for Jackie LeVan's protocol

Luc

The GDB subcommittee will need to meet and formally review as the next step. I will have a call set up.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Monday, October 22, 2012 3:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Barbara Stoll'; 'Wally Carlo, M.D.'; 'nfiner@ucsd.edu'; Pablo Sanchez; Roy Heyne; Myra Wyckoff; (b)(6)@gmail.com; 'Das, Abhik'; Gantz, Marie; 'Wrage, Lisa Ann'; Mambarambath Jaleel
Subject: Revised protocol for Jackie LeVan's protocol

Rose:

Here is the revised version of Jackie LeVan's protocol. This version has addressed comments from Lisa and Roy and was approved by Barbara. I changed CN into CNN, the official name of the Canadian Neonatal Network.

Please let me know whether this revised protocol should be submitted to all of the following committees and in which order: the Steering Committee, the GDB Committee, the SUPPORT Committee.

Please let me know at what stage I should contact the Canadian Network and whom:

Network Director: Dr. Shoo K. Lee, University of Toronto
Associate Director: Dr. Prakesh Shah, University of Toronto?

Thanks and best regards,
Luc

Luc P. Brion, MD
Professor of Pediatrics
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Michele Walsh (mcw3@cwru.edu); Wally Carlo (wcarlo@uab.edu); Ed Bell (edward-bell@uiowa.edu); Abbot Laptook; Pablo Sanchez@UTSouthwestern.edu; Seetha Shankaran.; Krisa Van Meurs (vanmeurs@stanford.edu); Bethany Ball (mbball@stanford.edu); Ellen Hale (ehale@emory.edu); nxs5@case.edu; Abhik Das (adas@rti.org)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org); Jenna Gabrio (jgabrio@rti.org)
Subject: Revised Jackie LeVan Protocol 5 4 10-22-12
Date: Tuesday, October 23, 2012 9:51:00 AM
Attachments: Revised Jackie LeVan Protocol 5 4 10-22-12.docx

Hi

Jenna will set up a call to discuss this study as well as another study (Will forward) from Ed's group.

Thanks

Rose

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From: [Finer, Neil](#)
To: [Gantz, Marie](#); [Wally Carlo, M.D.](#); [Vaucher, Yvonne](#); [Kurt Schibler](#); mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; [Laptook, Abbot](#); Bradley.Yoder@hsc.utah.edu; [Myriam Peralta, M.D.](#); [nancy newman](#); [Rich, Wade](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]
Cc: [Archer, Stephanie \(NIH/NICHD\)](#) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Monday, October 22, 2012 4:28:23 PM

Agree and thanks Marie
Neil

On 10/22/12 12:55 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

>With respect to the discussion of what comparator group we should be
>using, the aim of this proposal was to "compare the frequency of death
>and the neurodevelopmental outcome of surviving 24-26 weeks gestation
>children at 18-22 months corrected age... who were eligible and enrolled
>in the SUPPORT trial to similar outcomes of surviving 24-26 week
>gestation children who born during the same time period and who were
>eligible but were not enrolled in the SUPPORT trial." This aim is
>consistent with the previous Antenatal Consent paper that compared
>neonatal outcomes between the enrolled and non-enrolled groups. These
>papers really seek to describe the impact of the antenatal consent
>process, and the current comparator group is most appropriate for doing
>that. Comparing children in SUPPORT to those whose parents refused
>consent would address an entirely different aim that was not in the
>original proposal.

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org

>828-254-6255

>

>

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

>From: [Wally Carlo, M.D. \[mailto:WCarlo@peds.uab.edu\]](mailto:WCarlo@peds.uab.edu)

>Sent: Thursday, October 18, 2012 1:42 PM

>To: [Vaucher, Yvonne](#); [Finer, Neil](#); [Gantz, Marie](#); 'Kurt Schibler';

>mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook, Abbot';

>Bradley.Yoder@hsc.utah.edu; [Myriam Peralta, M.D.](#); 'nancy newman'; [Rich,](#)

>[Wade](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]

>Cc: [Archer, Stephanie \(NIH/NICHD\)](#) [E]

>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:

>Enrolled vs. Eligible/Nonenrolled

>

>We need to be careful to undermine SUPPORT results based on the incorrect

>comparator group.

>

>We need to make sure the baseline characteristics were comparable to

>prevent likely biases.

>

>Wally

>

>Wally Carlo, M.D.
>Edwin M. Dixon Professor of Pediatrics
>University of Alabama at Birmingham
>Director, Division of Neonatology
>Director, Newborn Nurseries
>1700 6th Avenue South
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>Phone: 205 934 4680
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>

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

>From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]
>Sent: Thursday, October 18, 2012 11:53 AM
>To: Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt
>Schibler'; 'mew3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot';
>Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman'; Rich,
>Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled

>

>All,

>

>Here is the latest version with Abhiks's suggestions incorporated.

>Yvonne

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Barbara Stoll"; "Wally Carlo, M.D."; "nfiner@ucsd.edu"; Pablo Sanchez; Roy Heyne; Myra Wyckoff; (b)(6)@gmail.com"; "Das, Abhik"; Gantz, Marie; "Wrage, Lisa Ann"; Mambarambath Jaleel
Subject: Revised protocol for Jackie LeVan's protocol
Date: Monday, October 22, 2012 3:36:48 PM
Attachments: Revised Jackie LeVan Protocol 5.4.10-22-12.docx

Rose:

Here is the revised version of Jackie LeVan's protocol. This version has addressed comments from Lisa and Roy and was approved by Barbara. I changed CN into CNN, the official name of the Canadian Neonatal Network.

Please let me know whether this revised protocol should be submitted to all of the following committees and in which order: the Steering Committee, the GDB Committee, the SUPPORT Committee.

Please let me know at what stage I should contact the Canadian Network and whom:

Network Director: Dr. Shoo K. Lee, University of Toronto
Associate Director: Dr. Prakesh Shah, University of Toronto?

Thanks and best regards,
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Pennatal Medicine
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From: Gantz, Marie
To: Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy.newman; Rich, Wade; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Monday, October 22, 2012 3:08:18 PM
Attachments: Antenatal enrollment SUPPORTPAS2012rev_MG.docx

My suggested edits are attached. Note that this version is slightly shorter than the one sent by Yvonne.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, October 18, 2012 12:53 PM
To: Vaucher, Yvonne; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy.newman'; Rich, Wade; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

All,

Here is the latest version with Abhiks's suggestions incorporated.
Yvonne

Title: ANTENATAL ENROLLMENT IN CLINICAL TRIALS: IS NEURODEVELOPMENTAL OUTCOME REPRESENTATIVE?

Yvonne E Vaucher, MD, MPH¹, Susan R Hintz, MD, MS², Wade Rich, BS, MS, RRT¹, Marie G Gantz, PhD³ and Neil N Finer, MD¹. ¹Dept. of Pediatrics, University of California, San Diego, CA, United States; ²Dept. of Pediatrics, Stanford University, Palo Alto, CA, United States and ³Statistics and Epidemiology, RTI International, Rockville, MD Research Triangle Park, NC, United States.

Background: Antenatal enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) was associated with differences in demographic, antenatal and neonatal characteristics between the enrolled vs. non-enrolled extremely preterm infants. Mothers of eligible/non-enrolled infants were less likely to be White/non-Hispanic, insured, have prenatal care (PNC), or receive antenatal steroids (ANS). Eligible/non-enrolled infants were more likely to have lower gestational age (GA), birthweight (BW) and Apgar Scores, require DR resuscitation, develop BPD and severe IVH and die before discharge.

Objective: To determine whether antenatal enrollment in SUPPORT was associated with differences in Death and Neurodevelopmental Impairment (NDI) in enrolled vs. eligible/non-enrolled children.

Design/Methods: We identified all included 24-26 week gestation GA infants at 18 Neonatal Research Network (NRN) sites with BW > 5400 g, born from 1/2006 to 2/2009, who were eligible for inclusion in SUPPORT. A comprehensive neurodevelopmental evaluation was performed at 18-22 mo corrected age (CA) using standardized neuromotor assessment and the cognitive scale of the BSID-III. Outcomes compared for enrolled vs. eligible/non-enrolled children included were Death or NDI, individual components of NDI [cognitive BSID-III score < 70, Gross Motor Function Classification System Score (GMFCS) ≥ 2, moderate-severe cerebral palsy, blind, deaf] and levels of cognitive delay. Analyses were adjusted for gestational age, center and multiple birth. Logistic regression models controlled for center, sex, race, GA, BW, insurance, PNC, ANS, Apgar scores and DR resuscitation.

Results: The primary composite SUPPORT outcome (Death or NDI) was determined for 95.3% (695/729) of children enrolled in SUPPORT vs. 90.9% (1471/1618) of children eligible/non-enrolled ($p < .001$). Compared to enrolled children, in unadjusted analyses, eligible/non-enrolled children were more likely to have Death or NDI (41.4% vs. 33.4%, $p < .001$), to die before 18-22 mo CA (31.7% vs. 24.8%, $p < .001$), and to have cognitive scores < -80 (19.9% vs. 15.5%, $P = .038$). There were no differences between groups in NDI or the individual components of NDI. No other outcomes were significantly different. By multiple regression analyses predictors of adverse outcomes were BW, gender, center, ANS (any), Apgar score < 3 at 5 min, severe IVH/PVL, BPD and severe ROP. In adjusted models, antenatal and neonatal risk factors predicted outcomes while enrollment did not.

Conclusions: Compared to children enrolled in SUPPORT, those who were eligible but not enrolled were more likely to die, to have Death or NDI and to have lower cognitive scores. These differences are attributed to demographic, antenatal and neonatal differences that favored those who were enrolled.

[99.08%]

From: Luc Brion
To: "Barbara Stoll"; "Wally Carlo, M.D."; "nfiner@ucsd.edu"; Pablo Sanchez; Roy Heyne; Myra Wyckoff; (b)(6)@gmail.com"; "Das, Abhik"; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; "Wrage, Lisa Ann"; Mambarambath, Jaleel
Subject: Version 5.3
Date: Monday, October 22, 2012 2:52:51 PM
Attachments: Revised Jackie LeVan Protocol 5.3 10-22-12.docx

This version incorporates additional comments from Roy Heyne and from Lisa Wrage.

Best regards,

Luc

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From: Luc Brion
To: "Barbara Stoll"; "Wally Carlo, M.D."; "nfiner@ucsd.edu"; Pablo Sanchez; Roy Heyne; Myra Wyrkoff; (b)(6)@gmail.com"; "Das, Abhik"; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; "Wrage, Lisa Ann"; Mambarambath Jaleel
Subject: Updated protocol for Jackie LeVan" study
Date: Monday, October 22, 2012 2:28:19 PM
Attachments: Revised Jackie LeVan Protocol rev 10-22-12.docx

Here is the updated version, incorporating suggestions from Lisa Wrage.

Best regards,

Luc

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From: Finer, Neil
To: Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [F]; Newman, Jamie <newman@rti.org> (newman@rti.org)
Subject: Re: Breathing Outcomes
Date: Monday, October 22, 2012 1:36:26 PM
Attachments: Breathing Outcomes first version Tim Oct 22 2012 - 10-22-12.docx

Hi Tim

An excellent first draft

I have made a few corrections and added some comments

Can we look at the 4 groups – Hi Sat, CPAP, HI Sat Surf, Low Sat CPAP, Low SatSurf

I know we do not have the power but I was interested in what this would reveal.

Overall the message is clear, the problem is also clear – what to do now- The assumption being with higher SpO2 limits – we will see more morbidity – and you have now provided a possible magnitude for that effect

Very nice

Neil

From: <Stevens>, Timothy Stevens
<Timothy_Stevens@URMC.Rochester.edu<mailto:Timothy_Stevens@URMC.Rochester.edu>>
Date: Monday, October 22, 2012 10:09 AM
To: Rosemary Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, Jamie Newman
<newman@rti.org<mailto:newman@rti.org>>, UCSD Pediatrics <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Subject: Breathing Outcomes

Hi Jamie, Rose and Neil,

Attached is a first draft of the Breathing Outcomes manuscript.

I look forward to your thoughts.

Thanks

Tim

Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

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Word Count:

Text: MeSH terms:

Bronchopulmonary Dysplasia
Infant, Newborn
Infant, Low Birth Weight
Infant, Extremely Low Birth Weight
Infant, Premature
Infant, Extremely Low Gestational Age
Infant mortality
Respiratory morbidity
Intensive care, neonatal
Hospital Readmission
Oximetry
Randomized controlled trial
Retinopathy of prematurity (ROP)
Continuous Positive Airway Pressure
Intubation, intratracheal
Pulmonary surfactants/therapeutic use
Oxygen inhalation therapy/methods
Oxygen administration & dosage
Follow-up studies

ABSTRACT

BACKGROUND:

The NICHD SUPPORT Trial found no difference in the composite outcomes of death or BPD, death or ROP and death or neurodevelopmental impairment between infants treated with lower (85-89%) versus higher (91-95%) oxygen saturation targets or with CPAP versus early surfactant (Surfactant). Though the composite incidence of death or ROP was similar, infants treated with lower rather than higher saturation targets had less ROP but greater mortality.

METHODS:

The Breathing Outcomes Study reported here followed infants 24-27 6/7 weeks' gestation who were enrolled in SUPPORT at 6 month intervals from hospital discharge to 18-22 months CA using a series of 4 parental interviews to assess respiratory-related symptoms, illnesses, medication use and health care utilization.

RESULTS:

From a cohort of 922 eligible infants, 873 (94.7%) completed the four part interview series. The two prespecified primary outcomes, incidences of recurrent wheezing and chronic cough, were 47.9% and 32.0%, respectively, and did not differ between study arms of either randomized intervention. Among secondary outcomes, infants in the lower saturation group had a lower incidence of wheezing (36.3% vs. 43.4%, $p < 0.05$) and nebulizer use at 6 months CA and of wheezing without a cold (28.4% vs. 36.3%, $p < 0.01$) at 18-22 months CA. CPAP compared with surfactant treated infants at 18-22 months CA had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p < 0.05$), fewer respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p = 0.02$) and fewer physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p < 0.05$).

CONCLUSION:

Treatment with lower rather than higher oxygen saturation targets may be associated with less wheezing by 18-22 months CA, a benefit which is insufficient to offset the higher mortality seen in this group as part of SUPPORT. We also conclude that CPAP and limited ventilation rather than intubation and surfactant in infants 24 – 27 6/7th weeks' is safe and results in less respiratory morbidity by 18-22 months CA.

Word count: 315

BACKGROUND

Extremely preterm infants are at greater risk of respiratory symptoms and need for pulmonary care in early childhood than later preterm or term infants [1-7] and contribute substantially to the public health burden of childhood respiratory disease in the United States. [8] Mechanical ventilation and supplemental oxygen use in the early neonatal period has each been identified as a major risk factor for development of BPD and pulmonary morbidity in infancy, childhood and beyond. [1, 2, 9, 10] Though infants with Bronchopulmonary Dysplasia (BPD) are at highest risk for poor pulmonary outcome, neonates without BPD are also at risk for airway dysfunction and pulmonary morbidity during infancy. [4, 11]

The multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) studied infants 24 0/7th -26 6/7th weeks' gestation treated with each of two respiratory strategies designed to minimize mechanical ventilation and supplemental oxygen exposure: 1) treatment with lower (85-89%) compared with higher (91-95%) oxygen saturation targets and 2) early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (Surfactant). Our Network previously reported results of SUPPORT demonstrating no difference in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants treated with either of the two respiratory interventions. [12, 13] (Vaucher when available) It is important to note that although the composite incidence of death or BPD was similar, infants treated with lower rather than higher saturation targets had a lower incidence of retinopathy of prematurity (ROP) but a higher risk of mortality. [13]

We now report on The Breathing Outcomes Study, a Secondary outcome of the SUPPORT Trial~~follow-on to SUPPORT~~, which sought to compare respiratory morbidity among extremely preterm infants treated with the SUPPORT study interventions as neonates. We hypothesized that infants treated with lower rather than higher oxygen saturation targets and CPAP rather than early surfactant will each have less frequent episodes of recurrent wheezing and cough and less need for outpatient pulmonary care at 18-22 months' corrected age (CA).

METHODS

Infants eligible for The Breathing Outcomes Study were those infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. One thousand three hundred sixteen infants from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009. Infants were eligible for SUPPORT if their gestational age was between 24 weeks 0 days to 27 completed weeks' (up to 27 6/7ths) by best obstetrical estimate and were born at a participating center, planned to receive full resuscitation if necessary, and without major congenital malformations. Because a goal of the Breathing Outcomes Study was to obtain health outcomes on as many of the SUPPORT subjects as possible, and because enrollment into the Breathing Outcomes Study

began after SUPPORT had begun enrollment, written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT Trial or separately for those patients already enrolled in SUPPORT. As a result, the Breathing Outcomes Study cohort was a subset of the SUPPORT cohort. The study was approved by the institutional review boards at all participating Network centers and by RTI International, the data center for the NICHD Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for both SUPPORT and Breathing Outcomes.[12, 13]

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned in the delivery room to receive CPAP after birth, followed by a limited ventilation strategy if intubation were needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age. Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with either a saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Randomization for both study interventions was accomplished using block randomization with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported.[13, 14]

Assessments of the Breathing Outcomes Study

For subjects enrolled in Breathing Outcomes, a parent or primary caregiver was interviewed by research staff either in person or by phone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at 6, 12 and 18-22 months corrected age. The study questionnaires were drafted based upon questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study.[15, 16] To the Tucson questionnaires were added questions to more fully elicit the respiratory health and health service use specific to preterm infants (e.g. palivizumab injections). To standardize administration of the interview, a lead interviewer at each participating center underwent training consisting of a teleconference with 1 of 2 project trainers (Rochester site) to discuss each study question and the written interview script associated with it. Interview trainees then interviewed a standardized patient simulated by the project trainers. Lead interviewers at each center were then able to train additional interviewers at their sites as needed. To minimize misinterpretation of other respiratory sounds as wheezing, a verbal description of wheezing and a brief audio clip of wheezing were played for the interviewee at the beginning of the interview. Questionnaires originally written in English were translated into Spanish using a certified translation service (Cornell Translation Service, Ithaca, NY). Interviews were conducted in either English or Spanish as appropriate.

To minimize loss of recall over time, interviews were conducted at 6 month intervals beginning at the time of hospital discharge. Study personnel conducted the first parent interview using a questionnaire designed to collect information on family history of respiratory diseases and atopy, home environment including tobacco and pet exposures, and diet at discharge from the hospital. Based upon the preference of each participating center, the 6, 12 and 18-22 month interviews were conducted either by

trained staff at the local center (15 centers) or by long distance telephone interview from the Rochester center (5 centers). At each of the 6, 12 and 18-22 month interviews, the parent or caregiver was asked to base their responses on the 6 month interval since the last interview. If an interview at one time point was not completed, interviewees were asked to base their responses during the next interview upon the interval history since the last completed interview. Taken together, the four questionnaire series administered by interviewing the parent or primary caregiver was designed to provide a complete respiratory history over the first 18-22 months' corrected age. In addition to reporting interview responses during the first 18-22 months corrected age, we report responses from the 6 month interview because preterm infants are at especially high risk of respiratory morbidity during the first 6 months of age.

The 6 and 12 month interviews were based on questionnaires designed to elicit the frequency and characteristics of respiratory symptoms, including wheezing and cough; incidence of physician-diagnosed asthma, reactive airway disease or "BPD flare-up"; incidence of bronchiolitis, bronchitis or pneumonia, croup; use of medications to treat respiratory illnesses including diuretics, nebulized bronchodilators, inhaled steroids, systemic steroids or oxygen; use of health services including respiratory related physician visits, emergency room visits and hospitalizations; use of preventive therapies including palivizumab and influenza immunization; and impact on the family including whether the parent or caregiver needed to change plans due their child's breathing. In addition to the questions above, the 18-22 month interview included additional questions to elicit whether the child had atopic symptoms or conditions, including eczema and food or medication allergy.

Outcomes

Primary Outcomes: Two primary outcomes were assessed by parental report: the incidence of recurrent wheezing and incidence of chronic cough. From these, the incidence of the combined outcome, recurrent wheezing or chronic cough, was also considered. The incidence of wheezing was ascertained using the primary question used and validated in the Tucson Study (a large prospective birth cohort study of term infants), "Has his/her chest sounded wheezy or whistling?". [15] Recurrent wheezing was defined as wheezing occurring more than twice in any week. The incidence of chronic cough ascertained using the Tucson question, "Has [your] child had a cough for 3 days or more when he/she did not have a cold?"[15].

Secondary outcomes and covariates: Secondary outcomes were interview responses to the 6, 12 and 18-22 month questionnaires for respiratory symptoms, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, the following covariates were evaluated: family history, environmental exposures including tobacco smoke, diet and use of preventive therapies as outlined above. In addition, each patient's outcomes from SUPPORT were available to the Breathing Outcomes Study analysis.

Statistical Analyses

The available subject pool for the Breathing Outcomes Study was limited to subjects enrolled in SUPPORT who survived to hospital discharge and consented to participation. For Breathing Outcomes, a

sample size of 817 subjects was calculated as necessary to detect an absolute risk difference of 0.1 in the incidence of recurrent wheezing between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of recurrent wheezing of 29%. Sample size calculations for SUPPORT have been reported. [12, 13] Based upon SUPPORT's target enrollment of 1310 patients and assuming a 22% mortality (NICHD historical data for calendar year 2000), we anticipated 1021 patients potentially eligible for the Breathing Outcomes Study.

Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. For categorical variables with low frequency ($n < 5$), Fisher exact tests were used. The two primary analyses used the number of patients with either recurrent wheezing or chronic cough as the numerator and the number of infants for whom that outcome was known as the denominator. Using Poisson regression models to adjust for gestational age strata, study center and familial clustering, adjusted relative risk (ARR) values and 95% confidence intervals were calculated and are reported. When Poisson models did not converge, relative risk adjusted for gestational age and center is reported (indicated in tables by †). When the two adjustment models failed to converge due to low prevalence ($< 5\%$), unadjusted relative risks are reported (indicated by †† in table). Results were considered statistically significant if the two-sided p value was less than 0.05; a trend towards significance was considered if the two sided p value was between 0.05 and 0.10 inclusive. No adjustments have been made for multiple comparisons. All calculations were performed using SAS software (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study (Figure 1). Follow up rates at each time point are listed in Figure 1; a total of 873 patients completed the four questionnaire series (94.7%).

Characteristics of the follow-up cohort:

Among the follow up cohort, the group managed with lower compared with higher saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with bronchopulmonary dysplasia (BPD) defined using the traditional criteria of supplemental oxygen uses at 36 weeks' post menstrual age (PMA). The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to surfactant (Table 1). There was no difference between groups in the proportion of infants with BPD defined using the physiologic definition. Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and surfactant groups (Table 2).

Primary Outcomes:

The overall incidences of the two primary outcomes, episodes of wheezing more than twice per week and cough lasting more than 3 days, in the follow up cohort during the first 18-22 months corrected age were 47.3% and 33.0%, respectively. There was no difference in incidence of these outcomes between either the subcohort of infants treated with lower compared with higher oxygen saturation targets nor between the subcohort infants treated with CPAP rather than surfactant (Tables 3 and 4, respectively).

The combined outcome of episodes of wheezing more than twice per week or cough lasting more than 3 days was 64.6% and did not differ significantly between subcohorts treated with lower rather than higher saturation target or CPAP rather than surfactant (Tables 3 and 4, respectively).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months corrected age, infants randomized to lower compared with higher saturation targets had a lower incidence of wheezing and in use of nebulized medications (36.3% vs. 43.4%, $p < 0.05$ and 1.2% vs. 3.9%, $p = 0.02$, respectively) (Table 3). Supporting these differences in wheezing was a trend toward a ~~higher~~ lower incidence of recurrent wheezing defined as wheezing episodes occurring more than twice per week (22.0% vs. 27.7%, $p = 0.06$) (Table 3). Over the first 18-22 months of corrected age (listed as 6-22 months in Tables 3 and 4), infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (28.4% vs. 36.3%, $p = 0.01$) (Table 3).

Early CPAP Intervention

At 6 months corrected age, infants treated with CPAP rather than surfactant were reported to have fewer asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor (12.3% vs. 17.2%, $p < 0.05$) and a trend toward fewer hospitalizations for wheezing or breathing problems (16.5% vs. 27.0%, $p = 0.09$). Perhaps related to these differences, parents or primary caregivers of infants treated with CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (12.8% vs. 20.4%, $p < 0.01$) (Table 4).

During the first 6-22 months corrected age, infants receiving early CPAP ~~rather than~~ versus - (many surfactant infants did get surfactant) surfactant were significantly less likely to have wheezing episodes occurring without a cold (28.9% vs. 36.5%, $p = 0.01$), respiratory illnesses diagnosed by a doctor (one or more episodes of asthma, reactive airway disease or BPD flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, $p = 0.02$), wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, $p < 0.05$). Compared with those of surfactant treated infants, parents or guardians of CPAP treated infants were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, $p < 0.05$).

Can we look at the 4 groups - ie Low sat+CPAP, Low sat with Surf, Hi Sat with CPAP Hi Sat with Surf?? I know we are not powered to do this!

DISCUSSION

We report respiratory outcomes during the first 18-22 months' corrected age for a cohort of extremely premature infants (24-27 6/7 weeks' gestation) treated in the NICHD SUPPORT Trial. We found no significant difference at 18-22 months corrected age between patients treated with lower rather than

higher saturation targets or with CPAP rather than surfactant in either of the two primary outcomes, incidence of recurrent wheezing and incidence of cough lasting more than 3 days without a cold.

In secondary analyses, extremely preterm infants managed with low compared with high saturation targets were less likely to have wheezing or use a home nebulizer at 6 months corrected age and to have wheezing apart from a cold during the first 18-22 months corrected age. In SUPPORT, patients managed with lower compared with higher saturation targets were exposed to lower concentration of inspired oxygen. Several pulmonary outcome studies have found an association between neonatal oxygen exposure and expiratory flow dysfunction and airway hyperreactivity among infants with or without BPD. [2, 7, 17-19] Our results, taken together with current literature, suggest that lower oxygen exposure in the neonatal period may be associated with reduced wheezing in infancy. However, based upon the findings of greater mortality among patients in SUPPORT treated with lower rather than higher saturation targets, the benefit of reduced wheezing and nebulizer use does not justify management patients 24-27 6/7 weeks' gestation with lower oxygen saturation targets. If oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant injury other than targeting lower oxygen saturations will be needed. [20, 21]

Patients treated with CPAP and limited ventilation rather than intubation and surfactant administration within 1 hour had fewer asthma, reactive airway disease or BPD flare-up episodes at 6 months corrected age and a trend toward fewer hospitalizations for respiratory problems. Perhaps related to these findings was a significant reduction in the proportion of parents reporting that they needed to change plans due to their child's breathing difficulties. During the first 18-22 months corrected age, patients receiving early CPAP rather than surfactant were significantly less likely to have had wheezing episodes occurring without a cold, respiratory illnesses diagnosed by a physician or physician or emergency room visits for breathing or wheezing problems. Parents of CPAP compared with surfactant treated infants were less likely to report changing their plans due to the child's breathing problems. These respiratory benefits were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria, was similar between CPAP and surfactant arms in the SUPPORT study and in the Breathing Outcomes' follow-up cohort. Our data are consistent with follow up data from The COIN Trial, which despite finding no difference in the incidence of death or BPD among 610 infants randomized to either CPAP or conventional management, found better pulmonary function at 8 weeks corrected among a 39 patient subcohort of study infants treated with CPAP. [22, 23] These observations suggest that treatment of infants 24-27 6/7 weeks gestation at risk for RDS with CPAP is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone and that longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions in randomized clinical trials.

We found that regardless of treatment arm, respiratory symptoms and health care usage are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months corrected age. Overall in the Breathing Outcomes cohort, recurrent wheezing occurred in 47.9% of patients and asthma, reactive airway disease or BPD flare-up episodes diagnosed by a doctor in 34.5%. Treatment of these conditions prompted not only frequent physician visits (63.8% of children), emergency room visits (46.6%) and hospitalizations (42.5%), which have the potential to add to health care costs [8] but also to frequent

use of both inhaled (26.3%) and systemic (9.4%) steroids which have potential long term effects on growth and development. [24, 25]

The strengths of this study include the large number of extremely preterm infants enrolled. This is the largest respiratory follow up study of a randomized clinical trial. Other strengths include the high follow up rates for enrolled patients and use of comprehensive respiratory questionnaires administered in a scripted interview by trained personnel. Though not as objective as pulmonary function testing, respiratory history was used as outcome measures due to clinical and financial concerns associated with use of invasive pulmonary testing and potential complications of sedation in former preterm infants. In addition, parental report of wheezing has been shown to correlate with pulmonary function testing and data extracted from office records and provides an estimate of the burden of respiratory morbidity to the patient and family as well as the health care system. [26, 27] Among potential weaknesses, respiratory history data were taken by parental report, which has the potential for classification and recall bias. To minimize classification bias, all primary and follow up study data of this randomized trial were collected in a blinded manner. Hence, though it may affect the precision of point estimates, classification bias is unlikely to have introduced systematic bias into our study that favors one study arm over another. To reduce recall bias, parent interviews were conducted at 6 month intervals.[27] Because the Breathing Outcomes Study was approved and began enrollment after SUPPORT had begun and because we wished to follow all available SUPPORT subjects, study results are not reported as competing outcomes (e.g. death or recurrent wheezing) but rather as respiratory outcomes of the cohort of SUPPORT subjects that survived to hospital discharge. As has been previously reported, the results of SUPPORT and thereby potentially the follow up studies associated with it may not be fully generalizable to all extremely preterm infants because the need for antenatal consent resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort. [28]

In summary, we found no significant differences in the incidence of recurrent wheezing or chronic cough at 18-22 months corrected age between extremely preterm survivors who were randomized at delivery to either lower or higher saturation targets and early CPAP or surfactant. In secondary analyses, we found reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months corrected age in the lower saturation group. However, because management with lower saturation targets was associated with greater mortality in SUPPORT [13], we conclude that the benefit of reduced wheezing and nebulizer use seen in the Breathing Outcomes Study does not justify treatment with lower saturation targets in patients 24-27 6/7 weeks' gestation. Also in secondary analyses, we report fewer respiratory symptoms, physician diagnosed respiratory problems and reduced health care use among infants treated with CPAP rather than early surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over surfactant. [12, 13](add Vaucher reference when available). Those findings coupled with the respiratory outcomes reported here suggest that treatment of extremely premature infants with CPAP and limited ventilation rather than intubation and early surfactant administration is safe and may result in less respiratory morbidity during the first 18-22 months corrected age.

Acknowledgements

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The National Institutes of Health, the *Eunice Kennedy Shriver* NICHD provided grant support for the Breathing Outcomes Study (Grant number: HD050646, Grant PI – T.P. Stevens, MD, MPH), a follow on study to the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We wish to acknowledge the Tucson Children's Respiratory Study (Marilyn Lindell, RN), Tucson, Az for support of this project by sharing respiratory symptom questionnaires which were adapted for use in this study.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

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From: Luc Brion
To: Archer, Stephanie (NIH/NICHD) [E]; Wraga, Lisa Ann
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Issues with PAS website
Date: Monday, October 22, 2012 12:18:24 PM

FYI

Luc

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From: c4asupport [mailto:c4asupport@coetruman.com]
Sent: Monday, October 22, 2012 11:17 AM
To: Luc Brion
Subject: RE: Issues with PAS website

Dr. Brion,

We are currently experiencing some technical difficulties with the PAS submission site and hope to have a resolution later today.

I apologize for the inconvenience this may have caused.

Best regards,

Sandra Varley
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From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Monday, October 22, 2012 11:03 AM
To: c4asupport
Cc: Wrage, Lisa Ann; 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: Issues with PAS website

To whom it may concern:

I am having trouble with previewing my PAS abstract and creating a readable PDF file to share with my colleagues.

The abstract number is 750229.

On Friday it generated hieroglyphs; today it only shows up to the award section, not the abstract itself.

Please could you advise me on how to proceed.

Sincerely,

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From: Luc Brion
To: Finer, Neil; Barbara Stoll; Wally Carlo, M.D.; Pablo Sanchez; Roy Heyne; Myra Wyckoff; doctorlevan@gmail.com; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann; Mambarambath Jaleel
Subject: RE: Revised protocol
Date: Monday, October 22, 2012 12:14:04 PM

Neil:
Thanks a lot for your help and for your comments.
Best regards,
Luc

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From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Monday, October 22, 2012 11:13 AM
To: Luc Brion; Barbara Stoll; Wally Carlo, M.D.; Pablo Sanchez; Roy Heyne; Myra Wyckoff; doctorlevan@gmail.com; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann; Mambarambath Jaleel
Subject: Re: Revised protocol

Hello Luc

This is very detailed, and should provide unique information - I am pleased that it includes the oximeter question as well I fully support moving ahead with this proposal Let me know if I can help Be well Neil

From: "Luc.Brion@UTSouthwestern.edu<<mailto:Luc.Brion@UTSouthwestern.edu>>"
<Luc.Brion@UTSouthwestern.edu<<mailto:Luc.Brion@UTSouthwestern.edu>>>
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Subject: Revised protocol

Hi everyone;

Here is a revised proposed protocol based on multiple discussions during abstract preparation, during and after the latest NRN meeting.

Rose told me I should submit a revised protocol to ask the Steering Committee for permission to approach another network; she suggested me to contact the Canadian Network.

Please review before I submit this protocol to the NRN Steering Committee.

Thanks for your collaboration.

Best regards,

Luc

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From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Barbara Stoll
Subject: FW: Proposed update for the protocol
Date: Sunday, October 21, 2012 11:43:13 PM

Rose:

Please see Barbara's email.

Could you please provide me with some advice about how to proceed.

Thanks

Luc

Luc P. Brion, MD
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From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Sunday, October 21, 2012 10:42 PM
To: Luc Brion
Cc: "(b)(6)" <(b)(6)@gmail.com> <@ws-mr1.cc.emory.edu>
Subject: Re: Proposed update for the protocol

I would think you should have some preliminary contact with someone at the CN before the submission-- ?? would ask Rose about this

BJS Luc Brion <Luc.Brion@utsouthwestern.edu> writes:

Barbara [Marker]

Thanks a lot for your comments.

In response to your questions,

We plan to send a survey to all centers, which was part of the December submission. I inserted a revised version into the current version of this protocol.

I do not know if the Canadian Network will agree to collaborate or has the data of interest (or in another form). Rose told I should first submit a request to the NRN Steering Committee. Once this is authorized I will go ahead.

If the Canadian Network refuses or does not have the data we could ask VON. I will include this in the protocol.

Thanks for your help and your suggestions.

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From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Sunday, October 21, 2012 9:13 PM
To: Luc Brion
Cc: Winge, Lisa Ann [mailto:lwinge@nhi.org]; NIH/NICHD; Rosemary
Subject: Re: Proposed update for the protocol

Luc

Reread and had some comments/questions and a few edits(attached)

I do think it is ready to move forward

THANKS

BJSLuc Brion <Luc.Brion@utsouthwestern.edu> writes:
Barbara et al.
Thank for all the comments. [Marker]

Here is a proposed revised version of the protocol, taking into account all our previous discussions.

Please let me know if you have any comments or suggestion, and whether this version is ready to be submitted to a larger group including Neil & Wally.

Thanks for your collaboration

Best regards,

Luc

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From: Barbara Stoll [<mailto:Barbara.Stoll@oz.ped.emory.edu>]
Sent: Tuesday, October 16, 2012 10:56 PM
To: Lou Brion
Cc: Wang, Lisa Ann; "Dan@ndb-mc1.ce.emory.edu"; Abhik; "Higgins@ndb-mc3.ce.emory.edu"; NIH/NICHD
Subject: Re: Proposed update for the protocol

Whatever we do - can only report changes rather than causality - cannot know if the change resulted from the SUPPORT study or other temporal changes in the care of ELBW infants

BIS Lou Brion <Lou.Brion@utsouthwestern.edu> writes:
Lisa

I agree with you, it would be best to include the 2012 data.

Barbara and Rose:

Please could you let me know your thoughts about using the intervening years during

SUPPORT

Thanks

Dr.

Lawrence H. Frank, MD

Professor of Pediatrics

Director Fellowship Training Program in Neonatal Perinatal Medicine

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hlfrank@utsouthwestern.edu

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From: Wraga, Lisa Ann [mailto:wraga@nrc.org]
Sent: Monday, October 15, 2012 12:52 PM
To: Luc Brion; doctorleyan@gmail.com; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD)
Subject: RE: Proposed update for the protocol

Hi Luc,

I am going to look at the documents you've sent in more detail, but in general I don't see how we can really get a grasp on whether or not changes in our outcomes are potentially due to dissemination of SUPPORT results or some other general trend if we don't include the intervening years (and analyze the data such that we are looking year by year or something like that) and I don't see how we can include the intervening years and not take into consideration (for the NRN data) the fact that SUPPORT was in process, although if the emphasis is still on the 2nd question this does not have to be the focus. So while there may be some limitations to using the intervening years of NRN data to me it seems it may be more of a limitation to not use them at all. As Abhik has suggested we can potentially think of ways to adjust for the differences between SUPPORT enrolled/non-enrolled babies. I'll take some more thought because it is not a simplistic analysis, but it is worth considering. At the moment I don't have an opinion on which network to use, but I am thinking that we should use as much post SUPPORT data as we can, is there some reason why we are not yet including 2012 data? I think we should.

Thanks,

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, October 12, 2012 7:10 PM
To: Wraga, Lisa Ann; doctorleyan@gmail.com; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD)
Subject: FW: Proposed update for the protocol

Here is a reference on cohort study, which talks about the before-after study design. [Marker]

Please let me know how to proceed from now

Thanks

Luc

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From: Luc Brien
Sent: Friday, October 12, 2012 2:32 PM
To: Winge, Lisa Ann; Das, Abhik; rose higgins; barbara stoll
Cc: dofontevan@gmail.com
Subject: RE: Proposed update for the protocol

Lisa and Abhik:

Thanks a lot for all your suggestions and comments.

Lisa, Abhik, Barbara, Rose:

I think I told all of you that when I spoke with Rose at the latest NKN meeting about comparing NRN data with VON, she told me I should prepare a request to the Steering Committee if I wish to ask for comparison of NRN data with national/international data. She recommended me to consider the Canadian Network.

Please advise so I can further develop a revised proposal.

Our initial proposal (attached) was a cohort study with before/after design to study changes during SUPPORT recruitment. I attach the summary statement of the GDB subcommittee 2-5-10. We were asked to re-write the protocol to analyze changes after SUPPORT publication.

At least two questions about changes in practice can be asked about changes in practice in relationship with a trial:

1. Do any changes in practice occur in non-enrolled patients during a RCT and before publication of the results? These changes cannot be based on results of the trials but other factors. We have commenced and almost completed the study of changes during and immediately after SUPPORT recruitment (before publication) at Parkland. For this study we analyzed secular trends by using (1) social changes, (2) internal controls (ineligible, larger OA group) and (3) external controls (VON).

2. Is publication of the results of a trial followed by changes in practice? If I understood

correctly, this is the question the GDB was interested in

For both questions, we need a cohort study with before/after design, and secular trends can be addressed by serial changes and by comparison with internal controls and comparable external controls.

I have a few questions for you:

Are we going to dilute the NRN manuscript by adding a biased group (not enrolled in SUPPORT) to the study?

Should we re-write this protocol to also address the first question? If so, could this be potentially considered as duplicate publication (using the same Parkland patients twice for the same question)?

Do we have internal controls in some or all centers like at Parkland to correct for this?

Should we limit our request to the Canadian Network, as suggested by Rees, to avoid using MON data for two studies?

Best regards,

Luc

Luc P. D'Elia, MD

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 12, 2012 8:49 AM
To: Lis, Annie; Eric Brown, (b)(6)@gmail.com
Subject: RE: Proposed update for the protocol

I also think that we could use intervening years from other network data, could we not?

Thanks

Lisa

From: Das, Abhik
Sent: Friday, October 12, 2012 9:48 AM
To: Wraga, Lisa Ann; Luc Brion; [redacted] (b)(6) @gmail.com
Subject: RE: Proposed update for the protocol

I understand this, but it seems to be that there should still be a way to use these data, and we can adjust for the factors that were different between the SUPPORT enrolled and non-enrolled babies, because we know them. I know that GDB may not have liked this before, but I think it still may be worth some further thought because looking year by year does afford us the opportunity to separate long term time trends from any sudden dip attributable to SUPPORT and avoid some of the pitfalls of this before/after study.

Thanks

Abhik

From: Wraga, Lisa Ann
Sent: Friday, October 12, 2012 9:38 AM
To: Luc Brion; Das, Abhik; [redacted] (b)(6) @gmail.com
Subject: RE: Proposed update for the protocol

Makes sense, thanks

Ersa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]

Sent: Thursday, October 11, 2012 5:02 PM

To: Wang, Lisa Ann, Das, Abhil, (b)(6) @gmail.com

Subject: FW: Proposed update for the protocol

Lisa,

I forgot to mention we can't use the data during SUPPORT because

1. One fifth of the babies were randomized to CPAP intubation in SUPPORT

2. There was a selection bias, the other 4/5 of the babies were different from those enrolled in SUPPORT, this is why the GDB subcommittee rejected the first draft of our proposal to look into data during SUPPORT.

Luc

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FOIA(b)(7) - (D)

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[REDACTED]

From: Luc Brion
Sent: Thursday, October 11, 2012 3:57 PM
To: 'Wraga, L. M. Ann'
Cc: (b)(6) in@gmail.com
Subject: RE: Proposed update for the protocol

Lisa,
Thanks for your comments and suggestions.

I developed the plan further accordingly.

I also split the analysis by GA stratum. I expect a difference in DR intubations between the two strata.

Luc

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From: Wrage, Lisa Ann [mailto:Wrage@utsouthwestern.edu]
Sent: Thursday, October 11, 2012 12:02 PM
To: Luc Brión
Subject: RE: Proposed update for the protocol

Hi Luc,

I have added a few comments to your proposal. Primarily I think you should add detail on this proposed analysis of data from another network. I also forwarded your proposal to Abhik and Marie as an FYI and for their comments. As to ROC curve analysis, I don't see how it fits here and Abhik confirmed (it is not a prediction problem).

Thanks

Eisa

From: Luc Brión [mailto:Luc.Brión@UTSouthwestern.edu]

Sent: Thursday, October 11, 2012 10:11 AM
To: Winge, Lisa Ann, (b)(6) @gmail.com
Subject: FW: Proposed update for the protocol

Lisa,

Should we do an ROC curve instead of using the baseline 80% DR intubation rate cutoff for the chi-square analysis of DR intubation pre vs post?

Luc

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From: Luc Biron
Sent: Wednesday, October 10, 2012 5:02 PM
To: Wiage, Lisa Ann, (b)(6) @gmail.com
Cc: Pablo Sanchez
Subject: Proposed update for the protocol

Jackie, Lisa:

Based on all our discussions we need to submit to the Steering Committee a justified request for comparing our data with either Vermont-Oxford Network or with the Canadian Network.

Here is the first draft of a revised protocol, which includes the above and other changes that took place during the writing of the abstract.

PYL, a multivariate analysis of death was actually planned, it should also include other variables as described.

Please review and comment before I submit to Ross.

Thanks

Luc

Eric P. Brass, MD

Professor of Pediatrics

Director, Fellowship Training Program in Neonatal-Perinatal Medicine

University of Texas Southwestern Medical School Program

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6411 11/08/2012 11:04:11 AM

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From: Luc Brion
To: Barbara Stoll; Wally Carlo, M.D.; nfiner@ucsd.edu; Pablo Sanchez; Roy Heyne; Myra Wyckoff; (b)(6)@gmail.com; Das, Abhik; Higgins, Rosemary (NIH/NICHD); [E]; Wraga, Lisa Ann; Mambambath Jajeel
Subject: Revised protocol
Date: Sunday, October 21, 2012 11:16:03 PM
Attachments: Revised Jackie LeVan Protocol rev 10-21-12 bjs lpb clean.docx

Hi everyone;

Here is a revised proposed protocol based on multiple discussions during abstract preparation, during and after the latest NRN meeting.

Rose told me I should submit a revised protocol to ask the Steering Committee for permission to approach another network; she suggested me to contact the Canadian Network.

Please review before I submit this protocol to the NRN Steering Committee.

Thanks for your collaboration.

Best regards,

Luc

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From: [Susan Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Gina Touse \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Subject: Re: Response Requested: Invitation: Pediatric Clinical Research Networks Conference
Date: Friday, October 19, 2012 5:47:52 AM

No
I am taking my mother to AZ

-----Original Message-----
From: Raju, Touse (NIH/NICHD) [E]
Sent: Friday, October 19, 2012 03:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Response Requested: Invitation: Pediatric Clinical Research Networks Conference

Do either of you will be attending the one? I can attend the 9th.

Touse N K, Raju, MD, DCH
PHD/MD
Phone: 301-402-1872

-----Original Message-----
From: Donna Harris (<mailto:DHarris@aacp.org>)
Sent: Friday, October 19, 2012 2:20 PM
To: Raju, Touse (NIH/NICHD) [E]
Cc: Alison Bocian
Subject: Response Requested: Invitation: Pediatric Clinical Research Networks Conference

Dear Dr Raju

I'm following up on the invitation to the Pediatric Clinical Research Networks Conference to be held November 8th and 9th at the Hilton Garden Inn in Bethesda. The meeting is described below and the response form is attached below.

Will you be able to join us?

Hope to see you there!

Donna Harris

Hello, Dr Raju

I am thanking you because of your involvement as a scientific officer with the Eunice Kennedy Shriver National Institute of Child Health and Human Development to invite you to our fourth conference of pediatric clinical research network leaders

As you may know, in the previous three years, this meeting was funded under Grant # 1R15CY019972-01A1, Pediatric Clinical Research Networks: Optimizing Effectiveness Through Cooperation, to the American Academy of Pediatrics from the National Eye Institute and the National Center for Research Resources. This year, while we are waiting for a final decision on our competing continuation of that grant, the meeting is being funded by the American Academy of Pediatrics.

The theme of this year's meeting is "Building Pediatric Research for the 21st Century." The conference will take place Thursday, November 8, 2012 (noon to 7:00 pm) & Friday, November 9 (8:00 am to 3:00 pm) at the Hilton Garden Inn, Bethesda, MD. As you're probably aware, we cannot support travel or meal expenses of federal employees, but we hope that substantial numbers of program and project officers from the federal government and foundations can attend to provide their vital perspectives and insights to the meeting.

The original objectives of this conference series were:

1. Bring together network leaders to identify shared interests and identify barriers common to inter-institutional collaborations.
2. Provide mechanisms for network leaders to exchange strategies and share best practices to promote efficient and effective network research.
3. Help networks explore opportunities for cross-network collaboration, including the possibility of a stable coalition of networks that would enhance research network function.
4. Link networks to entities within the AAP (e.g. committees, subcommittee sections, chapters) and partnering organizations to expand venues for pursuing collaborative research.

Last year's meeting yielded a variety of concrete ideas from network leaders addressing these objectives, and the ideas conceived at the meeting were carried forward at the Pediatric Academic Society's Pediatric Clinical Research Network Special Interest Group. This year's meeting will, like last year's, be a working meeting, focusing on the objectives listed above.

If you have any questions about the conference, please contact Alison Bocian at 800/433-5016, extension 7620 alocian@aacp.org (<mailto:alocian@aacp.org>) please email me at rwasserm@uvm.edu (alocian@aacp.org)

For conference planning purposes, please let us know as soon as possible if you can or cannot attend and complete the attached fax-back sheet.

If you personally are unable to attend, we would appreciate your suggesting another individual who reflects your area of expertise and/or point of view.

I look forward to seeing you at the conference.

Sincerely,
Mort Wasserman

R. "Mort" Wasserman, MD, MPH
Professor of Pediatrics, University of Vermont Director, Pediatric Research in Office Settings (PROS), American Academy of Pediatrics

Alison Bocian, MS
Senior Research Associate
Division of Primary Care Research

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American Academy of Pediatrics

847/434-7620

Doune Harris, MA
PROS Research Database Analyst
Phone: 847/434-4362
Email: dharris@aap.org

From: [Vaucher, Yvonne](#)
To: [Wally Carlo, M.D.](#)
Cc: "Das, Abhik"; [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [Vaucher, Yvonne](#)
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 3:51:35 PM

The comparator group is different. That is the point. We can't make them the same. The message of this abstract is that demographic, antenatal and neonatal differences in the groups, not enrollment itself, were associated with differences in outcome....fortunately. SUPPORT results are generalizable if you take into account these differences. Perhaps Abhik can help state this more clearly so people will not be misled.

Yvonne

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Thursday, October 18, 2012 12:21 PM
To: Vaucher, Yvonne
Cc: 'Das, Abhik'; [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#)
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Yvonne:

I am still deeply concerned as the comparator group is so different to the enrolled babies. We should exclusively report data on comparable groups as otherwise too much bias can distort the results.

We need to be careful as the wrong analysis can undermine SUPPORT by implying that the results are not generalizable.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]
Sent: Thursday, October 18, 2012 2:03 PM
To: Wally Carlo, M.D.
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

I don't think this undermines the SUPPORT RCT results. It just says that process of antenatal enrollment results in a selection bias already described in Wade's papers and that the outcomes of enrolled vs. non enrolled are different-unrelated to enrollment per se but rather to differences in baseline characteristics which are known to be associated with worse outcome. So in that way it strengthens the SUPPORT results. I hope this addresses your question. It will be interesting to look at the characteristics of the different groups who were not enrolled, especially those who refused. I would imagine the same factors would apply to those who refuse enrollment postnatally.

On 10/18/12 10:41 AM, <WCarlo@peds.uab.edu> wrote:

>We need to be careful to undermine SUPPORT results based on the
>incorrect comparator group.
>
>We need to make sure the baseline characteristics were comparable to
>prevent likely biases.
>
>Wally
>
>Wally Carlo, M.D.
>Edwin M. Dixon Professor of Pediatrics
>University of Alabama at Birmingham
>Director, Division of Neonatology
>Director, Newborn Nurseries
>1700 6th Avenue South
>176F Suite 9380R
>Birmingham, AL 35233-7335
>Phone: 205 934 4680
>FAX: 205 934 3100
>Cell: 205 (b)(6)

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

>From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]
>Sent: Thursday, October 18, 2012 11:53 AM
>To: Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie;
>'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook,
>Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy
>newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled
>
>All,
>
>Here is the latest version with Abhiks's suggestions incorporated.
>Yvonne

From: Walsh, Michele
To: Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 3:10:42 PM

I agree: need to convey this message more clearly-
It is not quite clear now.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

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

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, October 18, 2012 10:38 AM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

This is important information that is not easy to glean from the current write-up.

Thanks

Abhik

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

From: Gantz, Marie
Sent: Thursday, October 18, 2012 10:26 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Vaucher, Yvonne'; Finer, Neil; 'Wally Carlo, M.D.'; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Although children enrolled in SUPPORT had better outcomes (especially with respect to mortality), we don't have evidence to conclude that enrollment in and of itself was the reason. Children who were not enrolled were worse off at birth, and after controlling for risk factors at birth, there is not a significant difference in the outcomes of the enrolled and non-enrolled groups.

The 587 who were excluded from analysis were 27 weeks GA (408) or born before 2006 when the Bayley III came into use for general FU (177) or <401 g and born before 2008 so not eligible for GDB at the time (2).

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International

mgantz@rti.org
828-254-6255

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 18, 2012 9:01 AM
To: 'Vaucher, Yvonne'; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Two comments -

Can we speculate that children enrolled in trials may have a better outcome?
Can we check the numbers - we have a denominator of 729 for the SUPPORT infants (total n was 1316, so were the 587 which includes the 27 week infants as well as the lost to FU)?? Just want to be sure

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, October 18, 2012 2:13 AM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

All,

Still 10/17 here on the west coast. Appended is the "final" enrolled vs. eligible/non-enrolled ND Outcome abstract for PAS with independent predictors added. Not enough room to add the p values for the regressions so just said "significant". Presently at 99.81% of allowable space. Your comments/thoughts are appreciated.
Thanks.

Yvonne

From: Vaucher, Yvonne [yvaucher@ucsd.edu]
Sent: Thursday, September 27, 2012 6:32 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.';

Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT subcommittee:

PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs. Eligible/Nonenrolled attached. (97% full) Please send comments.

Thanks.

Yvonne

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From: Myriam Peralta, M.D.
To: "Vaucher, Yvonne"; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; "Kurt Schibler"; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; "Laptook, Abbot"; Bradley.Yoder@hsc.utah.edu; "nancy newman"; Rich, Wade; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 2:16:12 PM

In your conclusion you are stating that the differences are because of the differences in predictor variables in the two groups, can you say this?. I am not clear on this from the information on the abstract. Also can more of these variables be used for adjusting in the analysis?.

Thanks.

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, October 18, 2012 11:53 AM
To: Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

All,

Here is the latest version with Abhiks's suggestions incorporated.

Yvonne

From: [Vaucher, Yvonne](#)
To: [Vaucher, Yvonne](#); [Einer, Neil](#); ["Wally Carlo, M.D."](#); [Gantz, Marie](#); ["Kurt Schibler"](#); ["mcw3@cwru.edu"](#); ["ROGER.FAIX@HSC.UTAH.EDU"](#); ["Lantook, Abbot"](#); [Bradley.Yoder@hsc.utah.edu](#); ["Myriam Peralta, M.D."](#); ["nancy newman"](#); [Rich, Wade](#); ["Das, Abhik"](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]
Cc: [Archer, Stephanie \(NIH/NICHD\)](#) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 12:55:11 PM
Attachments: [Antenatal enrollment SUPPORTPAS2012rev.docx](#)

All,

Here is the latest version with Abhik's suggestions incorporated.
Yvonne

Title: ANTENATAL ENROLLMENT IN CLINICAL TRIALS: IS NEURODEVELOPMENTAL OUTCOME REPRESENTATIVE?

Yvonne E Vaucher, MD, MPH¹, Susan R Hintz, MD, MS², Wade Rich, BS, MS, RRT¹, Marie G Gantz, PhD³ and Neil N Finer, MD¹. ¹Dept. of Pediatrics, University of California, San Diego, CA, United States; ²Dept. of Pediatrics, Stanford University, Palo Alto, CA, United States and ³Statistics and Epidemiology, RTI International, Rockville, MD, United States.

Background: Antenatal enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) was associated with differences in demographic, antenatal and neonatal characteristics between the enrolled vs. non-enrolled extremely preterm infants. Mothers of eligible/non-enrolled infants were less likely to be White/non-Hispanic, insured, have prenatal care, or receive antenatal steroids (ANS). Eligible/non-enrolled infants were more to have lower gestational age (GA), birthweight (BW) and Apgar Scores, require DR resuscitation, develop BPD and severe IVH and die before discharge.

Objective: To determine whether antenatal enrollment in SUPPORT was associated with differences in Death and Neurodevelopmental Impairment (NDI) in enrolled vs. eligible/non-enrolled children.

Design/Methods: We identified all 24-26 week gestation infants at 18 Neonatal Research Network (NRN) sites with BW > 500 g, born from 1/2006 to 2/2009, who were eligible for inclusion in SUPPORT. A comprehensive neurodevelopmental evaluation was performed at 18-22 mo corrected age using standardized neuromotor assessment and the cognitive scale of the BSID-III. Outcomes compared for enrolled vs. eligible/non-enrolled children included Death or NDI, individual components of NDI [cognitive BSID-III score < 70, Gross Motor Function Classification System Score (GMFCS) ≥ 2, moderate-severe cerebral palsy, blind, deaf] and levels of cognitive delay. Analyses were adjusted for gestational age, center and multiple birth.

Results: The primary composite SUPPORT outcome (Death or NDI) was determined for 95% (695/729) of children enrolled in SUPPORT vs. 90.9% (1471/1618) of children eligible/non-enrolled ($p < .001$). Compared to enrolled children, eligible/non-enrolled children were more likely to have Death or NDI (41.4% vs. 33.4%, $p < .001$), to die before 18-22mo CA (31.7% vs. 24.8%, $p < .001$), and to have cognitive scores < 80 (19.9% vs. 15.5%, $P = .038$). There were no differences between groups in NDI or the individual components of NDI. By multiple regression analyses predictors of adverse outcomes were BW, gender, center, ANS (any), Apgar score < 3 at 5 min, severe IVH/PVL, BPD and severe ROP.

Conclusions: Compared to children enrolled in SUPPORT, those who were eligible but not enrolled were more likely to have Death or NDI and to have lower cognitive scores due to demographic, antenatal and neonatal differences that favored those who were enrolled.

[99.08%]

From: Vaucher, Yvonne
To: Das, Abhik; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 11:12:43 AM

OK

From: Das, Abhik [adas@rti.org]
Sent: Thursday, October 18, 2012 5:30 AM
To: Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

I think the methods section needs some allusion to adjusted analyses and what adjustments were made. The last 2 sentences in the results section were unclear to me. I suggest you substitute them for just stating whether the differences in outcomes observed among the enrolled and non enrolled babies were still significant upon adjustment.

Thanks

Abhik

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, October 18, 2012 2:13 AM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

All,

Still 10/17 here on the west coast. Appended is the "final" enrolled vs. eligible/non-enrolled ND Outcome abstract for PAS with independent predictors added. Not enough room to add the p values for the regressions so just said "significant". Presently at 99.81% of allowable space. Your comments/thoughts are appreciated.

Thanks.

Yvonne

From: Vaucher, Yvonne [yvaucher@ucsd.edu]
Sent: Thursday, September 27, 2012 6:32 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT subcommittee:

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.

PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs. Eligible/Nonenrolled attached. (97% full) Please send comments.

Thanks.

Yvonne

From: Vaucher, Yvonne
To: Gantz, Marie; Finer, Neil; Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 11:05:36 AM

See Marie's breakdown below for reasons not enrolled. There is an assortment of reasons and for 33% no reason is given. We can look at this for the paper but I don't think it belongs in this abstract which is already at max space. Our message is that the outcomes are different based on differences in demographic (BW, GA), antenatal (ANC) and postnatal (BPD, ROP, IVH) factors, not enrollment per se. I could try to squeeze in a statement that enrollment was not one of the independent predictors of outcome.

Yvonne

From: Gantz, Marie [mgantz@rti.org]
Sent: Friday, October 05, 2012 9:10 AM
To: Vaucher, Yvonne; Finer, Neil; Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Here is the breakdown of the information we have on consent for the 1618 in the non-enrolled group (from SUPPORT form SUPP02).

537 (33%) We do not have information
63 (4%) 'Not eligible' because born during a time when equipment or personnel were not available
31 (2%) Consented to SUPPORT but not randomized
194 (12%) Parent unavailable
391 (24%) Parent refused consent
395 (24%) Consent not requested
7 (0.4%) Physician refused consent

What was the Steering Committee interested in looking at, specifically?

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, October 05, 2012 11:40 AM
To: Finer, Neil; Walsh, Michele; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

The primary question we are asking is whether having to obtain antenatal consent (regardless of the reason for lack of consent) biases outcome. It does. The adjusted models show the predictors for the differential effect on outcome. My take on this is that ANS and the fetal/maternal stabilization that goes with it are the critical factors which result in the difference in death reflected in poor condition at delivery and low Apgar score.

Yvonne

On 10/5/12 8:23 AM, "Finer, Neil" <nfiner@ucsd.edu> wrote:

>I agree
>Its how you look
>Neil
>
>-----Original Message-----
>From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
>Sent: Friday, October 05, 2012 7:13 AM
>To: Vaucher, Yvonne; Gantz, Marie; Higgins, Rosemary (NIH/NICHHD) [E];
>Wally Carlo, M.D.; Finer, Neil
>Cc: Archer, Stephanie (NIH/NICHHD) [E]
>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled
>
>I agree with the issue raised by others- The imbalance in antenatal
>steroid and abx administration In those enrolled may be the causative
>factor rather Than being in a trial, so the adjusted are critical.
>Refused is a better comparator than not approached Who may have been
>ineligible on the basis of time in hospital prior to delivery. Can
>this be in the abstract Not just the paper?
>
>Michele Walsh, MD
>Chief, Division of Neonatology
>216.844.3759
>
>It's not what you look at that matters, it's what you see. Thoreau
>
>
>
>-----Original Message-----
>From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
>Sent: Friday, October 05, 2012 9:42 AM
>To: Gantz, Marie; Higgins, Rosemary (NIH/NICHHD) [E]; Wally Carlo, M.D.;
>Finer, Neil; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU;
>Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy
>newman; Rich, Wade; Das, Abhik
>Cc: Archer, Stephanie (NIH/NICHHD) [E]
>Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled
>
>That (refused vs. not approached) would be interesting to look at also.
>We
>can do that for the paper.
>
>Marie, Please run the models for death and death or NDI with severe
>Grade
>3-4 IVH (if possible separated from PVL) since IVH occurs in the first
>few days after birth and it may be an significant factor in early death
>for the 24-25 week infants, particularly when care is withdrawn.
>Different situation for PVL so if there is much more PVL it may dilute
>the effect of IVH if there is one when the two are combined.

>

>Thanks.

>

>Yvonne

>

>On 10/5/12 6:28 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

>

>>Rose, we have not looked at that. I'm not sure what the numbers would

>>look like for refused consent and consent not sought, but I can check

>to

>>see what they would be.

>>

>>Marie

>>

>>Marie Gantz, Ph.D.

>>Senior Research Statistician

>>RTI International

>>mgantz@rti.org

>>828-254-6255

>>

>>

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

>>From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

>>Sent: Tuesday, October 02, 2012 11:19 AM

>>To: 'Wally Carlo, M.D.'; Vaucher, Yvonne; Finer, Neil; Gantz, Marie;

>>'Kurt Schibler'; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook,

>>Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy

>newman';

>>Rich, Wade; Das, Abhik

>>Cc: Archer, Stephanie (NIH/NICHD) [E]

>>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:

>>Enrolled vs. Eligible/Nonenrolled

>>

>>One item from a steering committee discussion - Have we looked at the

>>eligible, but not enrolled and divided them by refused consent and

>>consent not sought?? There may be some differences between these two

>>groups.

>>

>>ROse

>>

>>Rosemary D. Higgins, MD

>>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal

>Research

>>Network Pregnancy and Perinatology Branch CDBPM, NIH

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>>301-496-5575

>>301-496-3790 (FAX)

>>higginsr@mail.nih.gov

>>

>>

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

>>From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]

>>Sent: Friday, September 28, 2012 7:13 AM

>>To: Vaucher, Yvonne; Finer, Neil; Gantz, Marie; 'Kurt Schibler';
>>mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook, Abbot';
>>Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman';
>>Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
>>Cc: Archer, Stephanie (NIH/NICHD) [E]
>>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>>Enrolled vs. Eligible/Nonenrolled

>>

>>Yvonne:

>>

>>Very good as a descriptive study in which we knew the baselines differ
>>were huge.

>>

>>However, with so many differences in baseline characteristics that are
>>associated with outcomes, it would be ideal to adjust for baseline
>>differences. With the adjusted model, it would then be important to
>>assess how good the model is to assure that at least 50% of the
>>variance

>>in the model is accounted for. This would reassure that the
>>differences in outcomes were not due to baseline differences although
>>I understand that this was not necessarily your intended analytical approach.

>>

>>An alternative is to match patients for the expected outcome based on
>>the

>>baseline risk and then assess whether enrollment modified their
>>outcome,

>>but again, this was not necessarily what you intended to do.

>>

>>In summary, as a descriptive study, I think it is ok although to make
>>sure readers are aware of your insight, you could state the
>>conclusions in a slightly different way such as: "Compared to
>>children enrolled in SUPPORT, those eligible but not enrolled were
>>more likely to die or
>>have

>>NDI, due to substantial baseline differences that favored those
>>enrolled."

>>

>>Hope this helps.

>>

>>Wally

>>

>>Wally Carlo, M.D.

>>Edwin M. Dixon Professor of Pediatrics University of Alabama at

>>Birmingham Director, Division of Neonatology Director, Newborn

>>Nurseries

>>1700 6th Avenue South

>>176F Suite 9380R

>>Birmingham, AL 35233-7335

>>Phone: 205 934 4680

>>FAX: 205 934 3100

>>Cell: 205 (b)(6)

>>

>>

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

>>From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]

>>Sent: Thursday, September 27, 2012 8:32 PM

>>To: Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler';

>>'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot';
>>Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; Vaucher, Yvonne;
>'nancy
>>newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
>>Cc: Archer, Stephanie (NIH/NICHD) [E]
>>Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled
>>vs. Eligible/Nonenrolled
>>
>>SUPPORT subcommittee:
>>
>>PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs.
>>Eligible/Nonenrolled attached. (97% full) Please send comments.
>>
>>Thanks.
>>
>>Yvonne
>
>
>
>
>
>Visit us at www.UHhospitals.org.
>
>The enclosed information is **STRICTLY CONFIDENTIAL** and is intended for
>the use of the addressee only. University Hospitals and its affiliates
>disclaim any responsibility for unauthorized disclosure of this
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>
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>psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions,
>alcohol, and/or drug_dependence or abuse disclosed in this email.
>Federal regulation (42 CFR Part 2) and Ohio Revised Code section
>5122.31 and
>3701.243 prohibit disclosure of this information without the specific
>written consent of the person to whom it pertains, or as otherwise
>permitted by law.
>

From: Vaucher, Yvonne
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 10:55:28 AM

I think we stated this clearly in the conclusion. In Marie's outcome models for Death, Death and NDI, NDI and cognitive score < 80, "enrollment" was not near significance.

Yvonne

From: Gantz, Marie [mgantz@rti.org]
Sent: Thursday, October 18, 2012 7:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Although children enrolled in SUPPORT had better outcomes (especially with respect to mortality), we don't have evidence to conclude that enrollment in and of itself was the reason. Children who were not enrolled were worse off at birth, and after controlling for risk factors at birth, there is not a significant difference in the outcomes of the enrolled and non-enrolled groups.

The 587 who were excluded from analysis were 27 weeks GA (408) or born before 2006 when the Bayley III came into use for general FU (177) or <401 g and born before 2008 so not eligible for GDB at the time (2).

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 18, 2012 9:01 AM
To: 'Vaucher, Yvonne'; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman'; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Two comments -

Can we speculate that children enrolled in trials may have a better outcome?

Can we check the numbers - we have a denominator of 729 for the SUPPORT infants (total n was 1316, so were the 587 which includes the 27 week infants as well as the lost to FU)?? Just want to be sure

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and
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301-496-5575
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-----Original Message-----

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, October 18, 2012 2:13 AM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mew3@cwru.edu';
'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.';
'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

All,

Still 10/17 here on the west coast. Appended is the "final" enrolled vs. eligible/non-enrolled ND Outcome abstract for PAS with independent predictors added. Not enough room to add the p values for the regressions so just said "significant". Presently at 99.81% of allowable space. Your comments/thoughts are appreciated.

Thanks.

Yvonne

From: Vaucher, Yvonne [yvaucher@ucsd.edu]
Sent: Thursday, September 27, 2012 6:32 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu';
'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.';
Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT subcommittee:

PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs. Eligible/Nonenrolled attached. (97% full) Please send comments.

Thanks.

Yvonne

From: [Wally Carlo, M.D.](#)
To: [Das, Abhik](#); [Vaucher, Yvonne](#); [Finer, Neil](#); [Gantz, Marie](#); [Kurt Schibler](#); mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; [Laptook, Abbot](#); Bradley.Yoder@hsc.utah.edu; [Myriam Peralta, M.D.](#); [nancy newman](#); [Rich, Wade](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]
Cc: [Archer, Stephanie \(NIH/NICHD\)](#) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 8:38:11 AM

What happened about the effort to limiting the comparator group to infants whose parents refused consent rather than those never approached? This is the least biased analysis.

Wally

Wally Carlo, M.D.
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176F Suite 9380R
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Cell: 205 (b)(6)

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

From: [Das, Abhik \[mailto:adas@rti.org\]](mailto:adas@rti.org)
Sent: Thursday, October 18, 2012 7:31 AM
To: [Vaucher, Yvonne](#); [Finer, Neil](#); [Wally Carlo, M.D.](#); [Gantz, Marie](#); [Kurt Schibler](#); mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; [Laptook, Abbot](#); Bradley.Yoder@hsc.utah.edu; [Myriam Peralta, M.D.](#); [nancy newman](#); [Rich, Wade](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]
Cc: [Archer, Stephanie \(NIH/NICHD\)](#) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

I think the methods section needs some allusion to adjusted analyses and what adjustments were made. The last 2 sentences in the results section were unclear to me. I suggest you substitute them for just stating whether the differences in outcomes observed among the enrolled and non enrolled babies were still significant upon adjustment.

Thanks

Abhik

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

From: [Vaucher, Yvonne \[mailto:yvaucher@ucsd.edu\]](mailto:yvaucher@ucsd.edu)
Sent: Thursday, October 18, 2012 2:13 AM
To: [Finer, Neil](#); ['Wally Carlo, M.D.'](#); [Gantz, Marie](#); ['Kurt Schibler'](#); ['mcw3@cwru.edu'](mailto:mcw3@cwru.edu); 'ROGER.FAIX@HSC.UTAH.EDU'; ['Laptook, Abbot'](#); Bradley.Yoder@hsc.utah.edu; ['Myriam Peralta, M.D.'](#); ['nancy newman'](#); [Rich, Wade](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; [Vaucher, Yvonne](#)
Cc: [Archer, Stephanie \(NIH/NICHD\)](#) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

All,

Still 10/17 here on the west coast. Appended is the "final" enrolled vs. eligible/non-enrolled ND Outcome abstract

for PAS with independent predictors added. Not enough room to add the p values for the regressions so just said "significant". Presently at 99.81% of allowable space. Your comments/thoughts are appreciated.
Thanks.

Yvonne

From: Vaucher, Yvonne [yvaucher@ucsd.edu]
Sent: Thursday, September 27, 2012 6:32 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT subcommittee:

PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs. Eligible/Nonenrolled attached. (97% full) Please send comments.

Thanks.

Yvonne

From: [Vaucher, Yvonne](#)
To: [Finer, Neil](#); ["Wally Carlo, M.D."](#); [Gantz, Marie](#); ["Kurt Schibler"](#); ["mcw3@cwru.edu"](#); ["ROGER.FAIX@HSC.UTAH.EDU"](#); ["Laptook, Abbot"](#); [Bradley.Yoder@hsc.utah.edu](#); ["Myriam Peralta, M.D."](#); ["nancy newman"](#); [Rich, Wade](#); ["Das, Abhik"](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; [Vaucher, Yvonne](#)
Cc: [Archer, Stephanie \(NIH/NICHD\)](#) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, October 18, 2012 2:13:08 AM
Attachments: [Antenatal enrollment SUPPORTPAS2012.docx](#)

All,

Still 10/17 here on the west coast. Appended is the "final" enrolled vs. eligible/non-enrolled ND Outcome abstract for PAS with independent predictors added. Not enough room to add the p values for the regressions so just said "significant". Presently at 99.81% of allowable space. Your comments/thoughts are appreciated.

Thanks.

Yvonne

From: Vaucher, Yvonne [yvaucher@ucsd.edu]
Sent: Thursday, September 27, 2012 6:32 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT subcommittee:

PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs. Eligible/Nonenrolled attached. (97% full)

Please send comments.

Thanks.

Yvonne

Title: ANTENATAL ENROLLMENT IN CLINICAL TRIALS: IS NEURODEVELOPMENTAL OUTCOME REPRESENTATIVE?

Yvonne E Vaucher, MD, MPH¹, Susan R Hintz, MD, MS², Wade Rich, BSHS, RRT¹, Marie G Gantz, PhD³ and Neil N Finer, MD¹. ¹Dept. of Pediatrics, University of California, San Diego, CA, United States; ²Dept. of Pediatrics, Stanford University, Palo Alto, CA, United States and ³Statistics and Epidemiology, RTI International, Rockville, MD, United States.

Background: Antenatal enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) was associated with differences in demographic, antenatal and neonatal characteristics between the enrolled vs. non-enrolled extremely preterm infants. Mothers of eligible/non-enrolled infants were less likely to be White/non-Hispanic, insured, have prenatal care, or receive antenatal steroids (ANS). Eligible/non-enrolled infants were more likely to have lower gestational age (GA), birthweight (BW) and Apgar Scores, require DR resuscitation, develop BPD and severe IVH and die before discharge.

Objective: To determine whether antenatal enrollment in SUPPORT was associated with differences in Death and Neurodevelopmental Impairment (NDI) in enrolled vs. eligible/non-enrolled children.

Design/Methods: We identified all 24-26 week gestation infants at 18 Neonatal Research Network (NRN) sites with BW > 500 g, born from 1/2006 to 2/2009, who were eligible for inclusion in SUPPORT. A comprehensive neurodevelopmental evaluation was performed at 18-22 mo corrected age using standardized neuromotor assessment and the cognitive scale of the BSID-III. Outcomes compared for enrolled vs. eligible/non-enrolled children included Death or NDI, individual components of NDI [cognitive BSID-III score < 70, Gross Motor Function Classification System Score (GMFCS) ≥ 2, moderate-severe cerebral palsy, blind, deaf] and levels of cognitive delay.

Results: The primary composite SUPPORT outcome (Death or NDI) was determined for 95% (695/729) of children enrolled in SUPPORT vs. 90.9% (1471/1618) of children eligible/non-enrolled ($p < .001$). Compared to enrolled children, eligible/non-enrolled children were more likely to have Death or NDI (41.4% vs. 33.4%, $p < .001$), more likely to die before 18-22mo CA (31.7% vs. 24.8%, $p < .001$), and more likely to have cognitive scores < 80 (19.9% vs. 15.5%, $P = .038$). There were no differences between groups in NDI or the individual components of NDI. Significant independent predictors of death were GA, BW, gender, center and Apgar < 3 at 5min. Significant independent predictors of a cognitive score < 80 were BW, gender, center, ANS(any), severe IVH/PVL, BPD and severe ROP.

Conclusions: Compared to children enrolled in SUPPORT, those who were eligible but not enrolled were more likely to have Death or NDI and to have lower cognitive scores due to demographic, antenatal and neonatal differences that favored those who were enrolled.

[99.81%]

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: [Tolivaia, Susan \(NIH/NICHD\) \[E\]](#)
Subject: My talk for Friday
Date: Wednesday, October 17, 2012 11:58:00 AM
Attachments: [10.20.2012 MFMJ UPDATE.pptx](#)

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



NICHD

NEONATAL RESEARCH NETWORK

NEONATAL RESEARCH NETWORK

2011-2016



NICHD NRN History

25th award year

1986 - 1991:	7 centers
1991 - 1996:	12 centers
1996 - 2001:	14 centers
2001 - 2006:	16 centers
2006 - 2011:	16 centers
2011 - 2016:	18 centers

Data Coordinating Center

Funding by:

NICHD

Specific studies may be co-funded by other NIH Institutes or government agencies (NHLBI, NEI, NIDA, CDC)

NATIONAL RESEARCH NETWORK



Re-competition Statistics

13 sites re-competed successfully

Case Western	UT Southwestern at Dallas
Wayne State	Emory
Cincinnati	Indiana
Iowa	Brown
Stanford	Alabama
UT Houston	New Mexico
Duke	

NATIONAL RESEARCH NETWORK



Re-competition Statistics

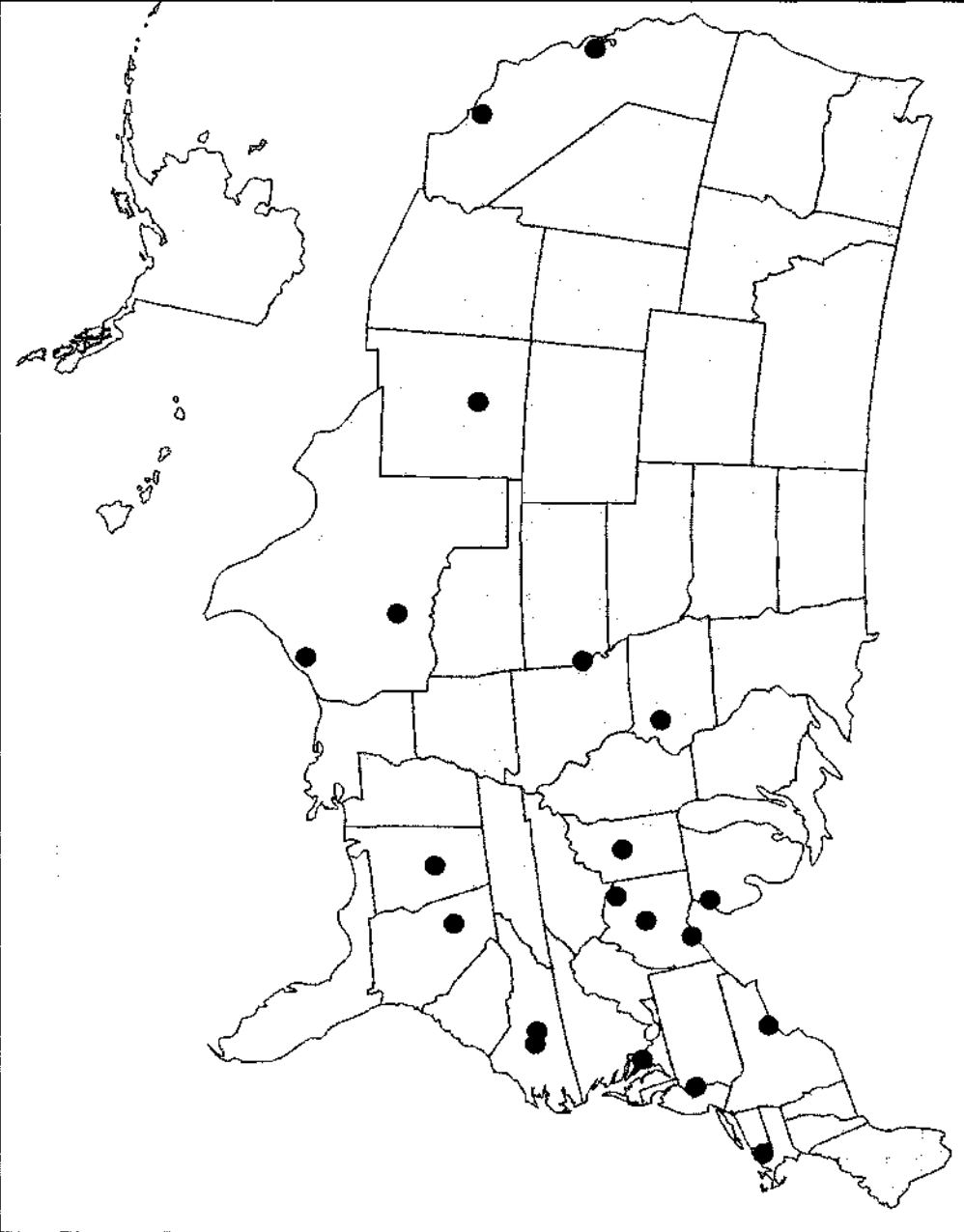
5 new sites

- Nationwide Children's Hospital (Ohio State)
- University of California – Los Angeles
- University of Rochester/University of Buffalo
- CHOP/University of Pennsylvania
- Children's Mercy Medical Center (University of Missouri)

NATIONAL RESEARCH NETWORK



NICHD NRN 2011-2016



NATIONAL RESEARCH NETWORK



Whole Body Cooling Trial School Age Follow up

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Childhood Outcomes after Hypothermia for Neonatal Encephalopathy

Seetha Shankaran, M.D., Athina Pappas, M.D., Scott A. McDonald, B.S.,
Betty R. Vohr, M.D., Susan R. Hintz, M.D., M.S.Fpi., Kimberly Yolton, Ph.D.,
Kathryn E. Gustafson, Ph.D., Theresa M. Leach, M.Ed., Charles Green, Ph.D.,
Rebecca Bara, R.N., B.S.N., Carolyn M. Petrie Huitema, M.S.,
Richard A. Ehrenkranz, M.D., Jon E. Tyson, M.D., M.P.H., Abhik Das, Ph.D.,
Jane Hammond, Ph.D., Myriam Peralta-Carcelen, M.D., M.P.H.,
Patricia W. Evans, M.D., Roy J. Heyne, M.D., Deanne E. Wilson-Costello, M.D.,
Yvonne E. Vaucher, M.D., M.P.H., Charles R. Bauer, M.D., Anna M. Dusick, M.D.,
Ira Adams-Chapman, M.D., Ricki F. Goldstein, M.D., Ronnie Guillet, M.D., Ph.D.,
Lu-Ann Papile, M.D., and Rosemary D. Higgins, M.D.
for the Eunice Kennedy Shriver NICHD Neonatal Research Network*

ABSTRACT

NEONATAL RESEARCH NETWORK



Ongoing Observational Studies

Generic Database (GDB)

Moderate Preterm Registry

Follow up (FU)

NATIONAL RESEARCH NETWORK



NRN Generic Database

To provide baseline and outcome data for infants 22-28 weeks EGA

Prospective cohort study

Inborn only

Baseline evaluation

Outcome evaluation – pulmonary, cardiac, neurological, infection, GI, Hearing, ophthalmology, syndromes, growth, LOS, cause of death

36 week physiologic definition of BPD

PERINATAL RESEARCH NETWORK



Moderate Preterm Registry

To provide baseline and outcome data for infants 29-33 weeks EGA

Prospective cohort study

Inborn and outborn infants (< 72 hours)

Baseline evaluation

Outcome evaluation – pulmonary, cardiac, neurological, infection, GI, Hearing, ophthalmology, syndromes, growth, LOS, cause of death

Time limited – March 1, 2012 – February 28, 2013

N = 1701 as of 9/30/12

NATIONAL RESEARCH NETWORK



NRRN Follow Up

Follow up at 24 months corrected age of infants with birth weights 401-1000g

Follow up rate >80% (have been > 90%)

Development assessed by Bayley III exams

Neurological exam

FU PI's meet at 2 Steering Committee meeting per year

PERINATAL RESEARCH NETWORK



Ongoing Interventional Trials

SUPPORT (Follow-up only)
Necrotizing Enterocolitis Surgery Trial (NEST)
Late Hypothermia for HIE
Optimizing Cooling (longer/deeper hypothermia)
Hydrocortisone for Extubation
Inhaled Prostaglandin E1 for Hypoxemic Respiratory Failure
Inositol for Retinopathy of Prematurity
Donor Milk vs. Preterm Formula for ELBWS
Transfusion of Prematures (TOP)

PERINATAL RESEARCH NETWORK



Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

- Hypothesis:** 1) Survival without BPD at 36 weeks will be greater in infants managed with early CPAP and a permissive ventilatory strategy than with prophylactic/early surfactant and conventional ventilation
- 2) Survival without threshold ROP and/or need for surgical intervention will be greater in infants managed with a higher SpO₂ range (91-95%) than with a lower range (85-89%)
- Design:** RCT 2x2 factorial design
- Intervention:** Early Surfactant vs. CPAP; higher vs. lower SpO₂ range
- Status:** Recruitment and 18-22 Month FU completed
- 6-7 Year FU of Neuroimaging secondary study cohort ongoing



Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 27, 2010

VOL. 362 NO. 23

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

*The authors are listed in the Appendix. The affiliations of the authors and other

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early CPAP versus Surfactant in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

ABSTRACT

BACKGROUND

*The authors are listed in the Appendix. The affiliations of members of the Writing Committee and other investigators in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

There are limited data to inform the choice between early treatment with continuous positive airway pressure (CPAP) and early surfactant treatment as the initial support for extremely-low-birth-weight infants.

NICHD
NEONATAL RESEARCH NETWORK



Necrotizing Enterocolitis Surgery Trial (NEST)

Hypothesis: Survival without NDI at 18-22 months will be greater with initial laparotomy than with initial drainage

Design: RCT

Intervention: Laporatomy vs. drain

Inclusion: Birth weight <1,000 g

Decision to perform surgery for suspected NEC or intestinal perforation

Infant \leq 8 weeks of age

At a center able to perform both laparotomy and drainage

Endpoint: Death or NDI at 18-22 months

Sample size: 300 infants

Status: Recruiting (127 enrolled as of 9/30/12)

PAEDIATRIC RESEARCH NETWORK



Inositol to Prevent ROP

- Hypothesis:** Survival without threshold ROP and/or need for surgical intervention will be greater in infants given prophylactic Inositol than in those given a placebo
- Design:** RCT (details are being finalized with the FDA and Abbot Nutrition)
- Intervention:** Inositol (IV or enteral) vs. placebo daily from < 48 hrs until 34 wks
- Inclusion:** < 28weeks gestational age
<48 hours of age at time of randomization and drug administration
- Endpoint:** Death or surgical ROP at 55 weeks of age
- Sample size:** ~1760 infants
- Co-funded:** NEI
- Partner:** Abbott Nutritional
- Status:** Pilot studies completed; submitting IND updates to FDA;
Main trial to start in early 2013



Late Hypothermia for HIE

Hypothesis: In infants 6-24 hours of age with HIE, death or disability at 18-22 months will be reduced for those managed with whole-body hypothermia for 96 hours than in those managed at normothermia

Design: RCT

Intervention: Cooling to 33.5°C vs. normothermia

Inclusion: ≥ 36 weeks gestational age
Cord or neonatal pH < 7.0 OR Base deficit > 16 mEq/L OR
History of an acute perinatal event AND 10 min. Apgar < 5 OR continued need for ventilation

AND
Signs of encephalopathy at 6-24 hours of age

Endpoint: Death or NDI at 18-22 months

Sample size: 168 infants

Status: Recruiting (114 enrolled as of 9/30/12)

PERINATAL RESEARCH NETWORK



Optimizing Cooling

- Hypothesis:** In infants <6 hours of age with HIE cooled with whole-body hypothermia, death or disability will be reduced for those cooled:
- 1) for 120 hours than those cooled for 72 hours
 - 2) to 32.0°C than for those cooled to 33.5°C
- Design:** RCT 2x2 factorial design
- Intervention:** Cooling for 120 vs. 72 hours; Cooling to 32.0°C vs. 33.5°C
- Inclusion:** ≥36 weeks gestational age
Cord or neonatal pH <7.0 OR Base deficit >16mEq/L OR
History of an acute perinatal event AND 10 min. Apgar <5 OR continued need for ventilation
AND
Signs of encephalopathy by 6 hours of age
- Endpoint:** Death or NDI at 18-22 months
- Sample size:** 726 infants
- Status:** Recruiting (201 enrolled as of 9/30/12)



Optimizing Cooling – Secondary Studies

Prediction of Outcome in HIE using aEEG

Hypothesis: aEEG will predict mortality or moderate to severe disability at 18-22 months in infants with HIE treated with hypothermia

Procedure: aEEG recording started as soon as feasible after initiation of hypothermia until 144 hours after target temperature is achieved

Systematic Monitoring of aEEG during Rewarming Trial (SMART) Secondary Study

Hypothesis: Rewarming initiated at 72 hours is associated with an increase in electrical seizure activity compared to rewarming at 120 hours.

Procedure: aEEG recordings will be done from 56-88 hours (for both duration arms) and 104-136 hours (for the 120-hour duration arm).
N = 38 enrolled as of 9/30/12



Hydrocortisone for Extubation

Hypothesis:

In infants <30 weeks GA who remain on mechanical ventilation at 14 -28 days of age:

- 1) Survival without moderate or severe BPD will be greater for those treated with hydrocortisone than for those treated with a placebo
- 2) Survival without NDI at 18-22 months will be greater for those treated with hydrocortisone than for those treated with a placebo

Design:

RCT

Intervention:

Hydrocortisone sodium succinate vs. saline placebo

Inclusion:

<30 weeks estimated gestational age

Inborn or admitted to an NRN site \leq 72 hours postnatal age

Have received \geq 7days of mechanical ventilation and are receiving mechanical ventilation through an endotracheal tube

Endpoint:

Death or BPD at 36 weeks of age

Sample size:

800 infants

Status:

Recruiting (120 enrolled as of 9/30/12)

PERINATAL RESEARCH NETWORK



Inhaled PGE1 (IPGE) in Neonates with Sub-optimal Response to iNO

- Hypothesis:** Feasibility and safety of prolonged IPGE1 administration and determination of optimal dose
- Design:** RCT pilot study
- Intervention:** Inhaled PGE1 vs. placebo
- Inclusion:** ≥ 34 weeks gestational age and ≤ 7 days (168 hours) of age
Receiving assisted ventilation for hypoxemic respiratory failure
Receiving iNO for 1-72 hours
Oxygenation Index = 15 on any 2 arterial blood gases 15 minutes to 12 hours apart while on iNO
Indwelling arterial line present
- Endpoint:** Death or NDI at 18-22 months
- Sample size:** 50 infants recruited within 9 months
- Status:** Halted for low recruitment



ALPS aEEG Secondary Study

Hypothesis: *Primary:* Ante-natal administration of corticosteroids to mothers of 34⁰ – 34⁶ weeks gestation is associated with an aEEG pattern consistent with increased maturity as demonstrated by more periods of quiet sleep compared to administration of placebo.

Hypothesis: *Secondary:* Ante-natal administration of corticosteroids is associated with more rapid resolution of morbidities whether they be CNS or non-CNS in origin compared to infants born to mothers given placebo.

Design: Cohort study

Intervention: aEEG recording at < 72 hours and 5-7 days of age

Inclusion: 34 0/7 to 35 6/7 weeks gestational age recruited in parent ALPS

Endpoint: Frequency of quiet sleep intervals (number/hour) in an aEEG recorded at less than 72 hours

Sample size: 99 infants

Status: Recruiting (n = 13 as of 9/30/12)



Donor Human Milk vs. Preterm Formula in ELBW infants

Hypothesis: In ELBW infants who receive no or minimal maternal milk, survival without NDI will be greater in those fed donor human milk than those fed formula

Design: RCT

Intervention: Donor human milk vs. formula

Inclusion: ≥ 36 weeks gestation

≤ 1000 g birth weight and survival to 12 hours of age
Inborn or admitted prior to enteral feeding (no > 72 hours of age), recruited up to day 21 of age

Endpoint: Death or NDI at 24 months

Sample size: 670 infants

Status: Recruiting (just started n = 1)



Transfusion Of Prematures (TOP)

Hypothesis: In ELBW infants, higher hemoglobin levels will lead to improvement in the primary outcome of survival and rates of neurodevelopmental impairment (NDI) at 22-26 months of age, using standardized assessments

Design: RCT

Intervention: High (liberal) versus low (restrictive) transfusion threshold

Inclusion: 22 to 28 weeks gestation

< 1000g birth weight

Inborn or admitted prior 48 hours of age

Endpoint: Death or NDI at 24 months

Sample size: 1824 infants

Status: Recruitment to begin in next few months

NATIONAL RESEARCH NETWORK

LOOKING AHEAD

Number of births – 150,749

NICU admissions – 33,276

< 29 weeks – 3,885

< 1000 grams – 3,027

Threshold ROP – 319 (total ROP = 1,984)

NEC Surgery – 397

HIE – 451

HIE + Cooling – 319

NATIONAL RESEARCH NETWORK



Food for thought



“An ounce of patience is sometimes better than a bushel full of brains”

PERINATAL RESEARCH NETWORK



From: Luc Brion
To: Wrage, Lisa Ann; (b)(6)@gmail.com; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Proposed update for the protocol
Date: Monday, October 15, 2012 1:56:11 PM

Lisa:

I agree with you, it would be best to include the 2012 data.

Barbara and Rose:

Please could you let me know your thoughts about using the intervening years during SUPPORT.

Thanks

Luc

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, October 15, 2012 12:52 PM
To: Luc Brion; (b)(6)@gmail.com; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD)
Subject: RE: Proposed update for the protocol

Hi Luc,

I am going to look at the documents you've sent in more detail, but in general I don't see how we can really get a grasp on whether or not changes in our outcomes are potentially due to dissemination of SUPPORT results or some other general trend if we don't include the intervening years (and analyze the data such that we are looking year by year or something like that) and I don't see how we can include the intervening years and not take into consideration (for the NRN data) the fact that SUPPORT was in process, although if the emphasis is still on the 2nd question this does not have to be the focus. So while there may be some limitations to using the intervening years of NRN data to me it seems it may be more of a limitation to not use them at all. As Abhik has suggested we can potentially think of ways to adjust for the differences between SUPPORT enrolled/non-enrolled babies. It'll take some more thought because it is not a simplistic analysis, but it is worth considering. At the moment I don't have an opinion on which network to use, but I am thinking that we should use as much post SUPPORT data as we can, is there some reason why we are not yet

including 2012 data? I think we should.

Thanks.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, October 12, 2012 7:10 PM
To: Wraga, Lisa Ann; (b)(6)@gmail.com; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD)
Subject: FW: Proposed update for the protocol

Here is a reference on cohort study, which talks about the before-after study design.

Please let me know how to proceed from now.

Thanks

Luc

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From: Luc Brion
Sent: Friday, October 12, 2012 2:32 PM
To: Wraga, Lisa Ann; Das, Abhik; rose higgins; barbara stoll
Cc: (b)(6)@gmail.com
Subject: RE: Proposed update for the protocol

Lisa and Abhik;

Thanks a lot for all your suggestions and comments.

Lisa, Abhik, Barbara, Rose:

I think I told all of you that when I spoke with Rose at the latest NRN meeting about comparing NRN data with VON, she told me I should prepare a request to the Steering Committee if I wish to ask for comparison of NRN data with national/international data. She recommended me to consider the Canadian Network.

Please advise so I can further develop a revised proposal.

Our initial proposal (attached) was a cohort study with before/after design to study changes during SUPPORT recruitment. I attach the summary statement of the GDB subcommittee 2-5-10. We were asked to re-write the protocol to analyze changes after SUPPORT publication.

At least two questions about changes in practice can be asked about changes in practice in relationship with a trial:

1. Do any changes in practice occur in non-enrolled patients during a RCT and before publication of the results? These changes cannot be based on results of the trials but other factors. We have continued and almost completed the study of changes during and immediately after SUPPORT recruitment (before publication) at Parkland. For this study we analyzed secular trends by using (1) serial changes, (2) internal controls (ineligible, larger GA group) and (3) external controls (VON).
2. Is publication of the results of a trial followed by changes in practice? If I understood correctly, this is the question the GDB was interested in.

For both questions, we need a cohort study with before/after design, and secular trends can be addressed by serial changes and by comparison with internal controls and comparable external controls.

I have a few questions for you.

Are we going to dilute the NRN manuscript by adding a biased group (not enrolled in SUPPORT) to the study?

Should we re-write this protocol to also address the first question? If so, could this be potentially considered as duplicate publication (using the same Parkland patients twice for the same question)?

Do we have internal controls in some or all centers like at Parkland to correct for this?

Should we limit our request to the Canadian Network, as suggested by Rose, to avoid using VON data for two studies?

Best regards,

Luc

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 12, 2012 8:49 AM
To: Das, Abhik; Luc Brion; [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com)
Subject: RE: Proposed update for the protocol

I also think that we could use intervening years from other network data, could we not?
Thanks.
Lisa

From: Das, Abhik
Sent: Friday, October 12, 2012 9:48 AM
To: Wrage, Lisa Ann; 'Luc Brion'; [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com)
Subject: RE: Proposed update for the protocol

I understand this, but it seems to be that there should still be a way to use these data, and we can adjust for the factors that were different between the SUPPORT enrolled and non-enrolled babies, because we know them. I know that GDB may not have liked this before, but I think it still may be worth some further thought because looking year by year does afford us the opportunity to separate long term time trends from any sudden dip attributable to SUPPORT and avoid some of the pitfalls of this before/after study.

Thanks

Abhik

From: Wrage, Lisa Ann
Sent: Friday, October 12, 2012 9:38 AM
To: 'Luc Brion'; Das, Abhik; doctorlevan@gmail.com
Subject: RE: Proposed update for the protocol

Makes sense, thanks.
Lisa

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Thursday, October 11, 2012 5:02 PM
To: Wrage, Lisa Ann; Das, Abhik; [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com)

Subject: FW: Proposed update for the protocol

Lisa:

I forgot to mention we can't use the data during SUPPORT because

1. One fifth of the babies were randomized to CPAP/intubation in SUPPORT
2. There was a selection bias: the other 4/5 of the babies were different from those enrolled in SUPPORT; this is why the GDB subcommittee rejected the first draft of our proposal to look into data during SUPPORT.

Luc

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From: Luc Brion
Sent: Thursday, October 11, 2012 3:57 PM
To: 'Wrage, Lisa Ann'
Cc: (b)(6)@gmail.com
Subject: RE: Proposed update for the protocol

Lisa;

Thanks for your comments and suggestions.

I developed the plan further, accordingly.

I also split the analysis by GA stratum. I expect a difference in DR intubations between the two strata.

Luc

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Thursday, October 11, 2012 12:02 PM
To: Luc Brion
Subject: RE: Proposed update for the protocol

Hi Luc,

I have added a few comments to your proposal. Primarily I think you should add detail on this proposed analysis of data from another network. I also forwarded your proposal to Abhik and Marie as an fyi and for their comments. As to ROC curve analysis, I don't see how it fits here and Abhik confirmed (it is not a prediction problem).

Thanks.

Lisa

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Thursday, October 11, 2012 10:11 AM
To: Wrage, Lisa Ann (b)(6) @gmail.com
Subject: FW: Proposed update for the protocol

Lisa:

Should we do an ROC curve instead of using the baseline 80% DR intubation rate cutoff for the chi-square analysis of DR intubation pre vs post?

Luc

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From: Luc Brion
Sent: Wednesday, October 10, 2012 5:02 PM
To: Wrage, Lisa Ann; (b)(6) @gmail.com
Cc: Pablo Sanchez

Subject: Proposed update for the protocol

Jackie, Lisa:

Based on all our discussions we need to submit to the Steering Committee a justified request for comparing our data with either Vermont-Oxford Network or with the Canadian Network.

Here is the first draft of a revised protocol, which includes the above and other changes that took place during the writing of the abstract.

FYI, a multivariate analysis of death was actually planned; it should also include other variables as described.

Please review and comment before I submit to Rose.

Thanks

Luc

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UT Southwestern Medical Center
The future of medicine, today.

From: Luc Brion
To: Wraga, Lisa Ann; (b)(6)@gmail.com; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Proposed update for the protocol
Date: Friday, October 12, 2012 7:15:57 PM
Attachments: Review by GDB 2-5-10 Proposal.rtf
Concept proposal 123109 - Luc P Brion.doc
Cohort studies - marching towards outcomes Grimes.pdf

Here is a reference on cohort study, which talks about the before-after study design.

Please let me know how to proceed from now.

Thanks

Luc

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From: Luc Brion
Sent: Friday, October 12, 2012 2:32 PM
To: Wraga, Lisa Ann; Das, Abhik; rose higgins; barbara stoll
Cc: (b)(6)@gmail.com
Subject: RE: Proposed update for the protocol

Lisa and Abhik;

Thanks a lot for all your suggestions and comments.

Lisa, Abhik, Barbara, Rose:

I think I told all of you that when I spoke with Rose at the latest NRN meeting about comparing NRN data with VON, she told me I should prepare a request to the Steering Committee if I wish to ask for

comparison of NRN data with national/international data. She recommended me to consider the Canadian Network.

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Should we limit our request to the Canadian Network, as suggested by Rose, to avoid using VON data for two studies?

Best regards,

Luc

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Friday, October 12, 2012 8:49 AM
To: Das, Abhik; Luc Brion; (b)(6)@gmail.com
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Thanks.

Lisa

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Sent: Friday, October 12, 2012 9:48 AM
To: Wrage, Lisa Ann; 'Luc Brion'; (b)(6)@gmail.com
Subject: RE: Proposed update for the protocol

I understand this, but it seems to be that there should still be a way to use these data, and we can adjust for the factors that were different between the SUPPORT enrolled and non-enrolled babies, because we know them. I know that GDB may not have liked this before, but I think it still may be worth some further thought because looking year by year does afford us the opportunity to separate long term time trends from any sudden dip attributable to SUPPORT and avoid some of the pitfalls of this before/after study.

Thanks

Abhik

From: Wrage, Lisa Ann
Sent: Friday, October 12, 2012 9:38 AM
To: 'Luc Brion'; Das, Abhik; (b)(6)@gmail.com
Subject: RE: Proposed update for the protocol

Makes sense, thanks.

Lisa

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Thursday, October 11, 2012 5:02 PM
To: Wrage, Lisa Ann; Das, Abhik; (b)(6)@gmail.com
Subject: FW: Proposed update for the protocol

Lisa:

I forgot to mention we can't use the data during SUPPORT because

1. One fifth of the babies were randomized to CPAP/intubation in SUPPORT
2. There was a selection bias: the other 4/5 of the babies were different from those enrolled in SUPPORT; this is why the GDB subcommittee rejected the first draft of our proposal to look into data during SUPPORT.

Luc

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From: Luc Brion
Sent: Thursday, October 11, 2012 3:57 PM
To: 'Wrane, Lisa Ann'
Cc: (b)(6)@gmail.com
Subject: RE: Proposed update for the protocol

Lisa;

Thanks for your comments and suggestions.

I developed the plan further, accordingly.

I also split the analysis by GA stratum. I expect a difference in DR intubations between the two strata.

Luc

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From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Thursday, October 11, 2012 12:02 PM
To: Luc Brion
Subject: RE: Proposed update for the protocol

Hi Luc,

I have added a few comments to your proposal. Primarily I think you should add detail on this proposed analysis of data from another network. I also forwarded your proposal to Abhik and Marie as an fyi and for their comments. As to ROC curve analysis, I don't see how it fits here and Abhik confirmed (it is not a prediction problem).

Thanks.

Lisa

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Thursday, October 11, 2012 10:11 AM
To: Wrage, Lisa Ann; (b)(6)@gmail.com
Subject: FW: Proposed update for the protocol

Lisa:

Should we do an ROC curve instead of using the baseline 80% DR intubation rate cutoff for the chi-square analysis of DR intubation pre vs post?

Luc

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From: Luc Brion
Sent: Wednesday, October 10, 2012 5:02 PM
To: Wrage, Lisa Ann; (b)(6)@gmail.com
Cc: Pablo Sanchez
Subject: Proposed update for the protocol

Jackie, Lisa:

Based on all our discussions we need to submit to the Steering Committee a justified request for comparing our data with either Vermont-Oxford Network or with the Canadian Network.

Here is the first draft of a revised protocol, which includes the above and other changes that took place during the writing of the abstract.

FYI, a multivariate analysis of death was actually planned; it should also include other variables as described.

Please review and comment before I submit to Rose.

Thanks

Luc

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Epidemiology series

Cohort studies: marching towards outcomes

David A Grimes, Kenneth F Schulz

A cohort study tracks two or more groups forward from exposure to outcome. This type of study can be done by going ahead in time from the present (prospective cohort study) or, alternatively, by going back in time to comprise the cohorts and following them up to the present (retrospective cohort study). A cohort study is the best way to identify incidence and natural history of a disease, and can be used to examine multiple outcomes after a single exposure. However, this type of study is less useful for examination of rare events or those that take a long time to develop. A cohort study should provide specific definitions of exposures and outcomes: determination of both should be as objective as possible. The control group (unexposed) should be similar in all important respects to the exposed, with the exception of not having the exposure. Observational studies, however, rarely achieve such a degree of similarity, so investigators need to measure and control for confounding factors. Reduction of loss to follow-up over time is a challenge, since differential losses to follow-up introduce bias. Variations on the cohort theme include the before-after study and nested case-control study (within a cohort study). Strengths of a cohort study include the ability to calculate incidence rates, relative risks, and 95% CIs. This format is the preferred way of presenting study results, rather than with p values.

The term cohort has military, not medical, roots. A cohort was a 300–600-man unit in the Roman army; ten cohorts formed a legion (figure 1). The etymology of the term provides a useful mnemonic: a cohort study consists of bands or groups of persons marching forward in time from an exposure to one or more outcomes.

This analogy might be helpful, since cohort studies have a bevy of confusing synonyms: incidence, longitudinal, forward-looking, follow-up, concurrent, and prospective study.^{1,2} Although the terminology can seem daunting, the cohort study is easy for clinicians to understand, since it flows in a logical direction (unlike the case-control study). Here, we explain the terminology, describe the strengths and weaknesses of cohort studies, consider several logistical concerns, mention two permutations of cohort studies, and summarise their analysis.

Data collection: forwards and backwards

A cohort study follows-up two or more groups from exposure to outcome. In its simplest form, a cohort study compares the experience of a group exposed to some factor with another group not exposed to the factor. If the former group has a higher or lower frequency of an outcome than the unexposed, then an association between exposure and outcome is evident.

The defining characteristic of all cohort studies is that they track people forward in time from exposure to outcome. Researchers doing this kind of study must, therefore, go forward in time from the present or go back in time to choose their cohorts (figure 2). Either way, a cohort study moves in the same direction, although gathering data might not. For example, an investigator who wants to study the epidemic of multiple births stemming from assisted reproductive technologies³ could begin a cohort study now. Women exposed to these technologies and a similar group who conceived naturally

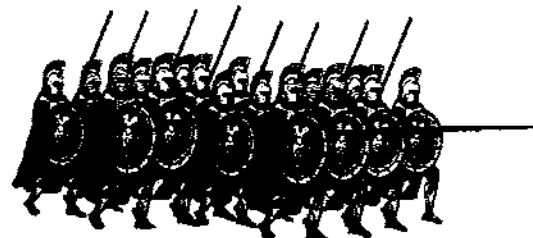


Figure 1: An early cohort in search of favourable outcomes

could be tracked forward through their pregnancies to monitor the frequency of multiple births (a concurrent cohort study). Alternatively, the investigator might use existing medical records and go back in time several years to identify women exposed and not exposed to these technologies. He would then track them forward through records to note the birth outcomes. Again, the study moves from exposure to outcome, though the data collection occurred after the fact.

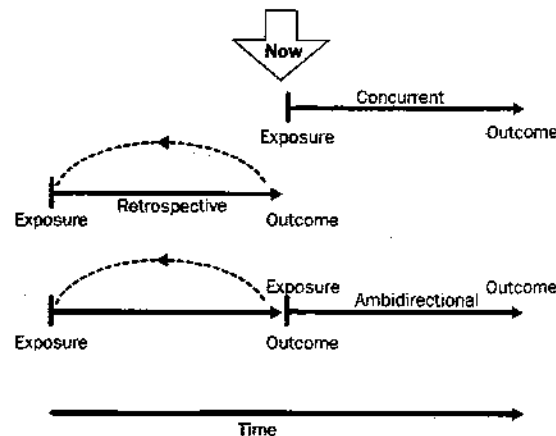


Figure 2: Schematic diagram of concurrent, retrospective, and ambidirectional cohort studies

Lancet 2002; 359: 341–45

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Correspondence to: Dr David A Grimes (e-mail: dgrimes@fhi.org)

Yet a third variation exists: ambidirectional.⁴ As the name implies, data collection goes in both directions. This approach can be useful for exposures that have both short-term and long-term outcomes. In this hypothetical example, assisted reproductive technologies might be associated with multiple births and with ovarian cancer in later life.⁵ The investigator might, therefore, look back through records for multiple births and also start to follow-up these women into the future for ovarian cancer occurrence.

Advantages of cohort studies

Cohort studies have many appealing features. They are the best way to ascertain both the incidence and natural history of a disorder.⁶ The temporal sequence between putative cause and outcome is usually clear: the exposed and unexposed can often be seen to be free of the outcome at the outset. By contrast, this chicken-egg question often frustrates cross-sectional and case-control studies. For example, in a case-control study, patients with chronic widespread pain were more likely to have mental illness than controls.⁷ Do mood and anxiety disorders increase this risk, or do patients with chronic pain develop mood and anxiety disorders as a result of their disorder?

Cohort studies are useful in investigation of multiple outcomes that might arise after a single exposure. A prototype would be cigarette smoking (the exposure) and stroke, emphysema, oral cancer, and heart disease (the outcomes). Although assessment of many outcomes is often cited as a positive attribute of cohort studies, this feature can be abused. For example, testing the associations between exposure and many outcomes, but only reporting the significant ones, represents misleading science. Investigators should preferably have planned primary and secondary associations to examine (sometimes called hypothesis confirmation). Although investigators can look at other outcomes (hypothesis generation), they should report the findings of all examinations, not just significant ones, so that readers can correctly interpret the results.

The cohort design is also useful in the study of rare exposures: a researcher can often recruit people with uncommon exposures—eg, to ionising radiation or chemicals—in the workplace. A hospital or factory might provide a large number of individuals with the exposure of interest, which would be rare in the general population. Since the investigator does not assign exposure, no ethical concerns arise.

Cohort studies also reduce the risk of survivor bias.⁸ Diseases that are rapidly fatal are difficult to study because of this factor. For example, a hospital-based case-control study of the link between snow-shovelling and myocardial infarction would miss all those who died in the driveway. A cohort study would be a less biased (but more cumbersome) approach: compare rates of myocardial infarction among those who shovel and those who do not shovel. Finally, cohort studies allow calculation of incidence rates, relative risks, and confidence intervals.⁹ Other outcome measures in cohort studies include life-table rates, survival curves, and hazard ratios (panel 1).⁸⁻¹⁰ By contrast, case-control studies cannot provide incidence rates; at best, odds ratios approximate relative risks only when the outcome is uncommon.

Disadvantages of cohort studies

Cohort studies have important limitations too. Selection bias is built into cohort studies. For example, in a cohort study investigating effects of jogging on cardiovascular

Panel 1: Reporting time-to-event in cohort studies

Survival analysis

Survival analysis is useful when lengths of follow-up vary substantially or when participants enter a study at different times.⁸ The Kaplan-Meier method provides a more sophisticated expression of the risk of the outcome over time than does a simple dichotomous outcome.⁹ It can determine the probability (P) of the outcome at any point in time; this result is graphed as a step function (which jumps at every event). A complementary, mirror-image graph portrays the likelihood of avoiding the outcome (1-P) as a function of time (Kaplan-Meier survival curve). The log-rank test compares survival curves of different groups.¹⁰

Proportional hazard model

Another approach to different lengths of follow-up is the Cox proportional hazard model. It is a multivariate technique that has time-to-event (such as illness) as the dependent variable. By contrast, multiple logistic regression has "yes-no" as the dependent variable.⁹ Coefficients from this model can be used to calculate the risk ratio (hazard ratio) of the outcome, after controlling for other covariates in the equation. The hazard ratio (with 95% CIs) is interpreted in the same way as a relative risk for dichotomous outcomes.¹⁰

disease, those who choose to jog probably differ in other important ways (such as diet and smoking) from those who do not exercise.¹¹ In theory, both groups should be the same in all important respects, except for the exposure of interest (jogging), but this seldom occurs. The cohort design is not optimum for rare diseases—eg, scleroderma—or those that take a long time to develop—eg, cancer. However, several large (and thus expensive) cohort studies have made landmark contributions to our knowledge of uncommon diseases. Examples include the Royal College of General Practitioners' Oral Contraceptive Study,¹² the Framingham Heart Study,¹³ the Nurses Health Study,¹⁴ and the British Physicians' Study.¹⁵

Loss to follow-up can be a difficulty, even at 1 month, and particularly so with longitudinal studies that continue for decades. Differential losses to follow-up between those exposed and unexposed can bias results. Over time, the exposure status of study participants can change. For example, a proportion of women who use oral contraceptives will switch to an intrauterine device, and vice versa.¹⁶ Partitioning might be needed to avoid a blurring of exposure, sometimes termed contamination.

What to look for in cohort studies

Who is at risk?

All participants (both exposed and unexposed) in a cohort study must be at risk of developing the outcome.⁶ For example, since women who have had a tubal sterilisation operation have almost no risk of salpingitis,¹⁷ they should not be included in cohort studies of pelvic inflammatory disease.

Who is exposed?

Cohort studies need a clear, unambiguous definition of the exposure at the outset. This definition sometimes involves quantifying the exposure by degree, rather than just yes or no. For example, the minimum exposure might have to be 14 cigarettes per day or less,¹⁸ or 3-6 months of oral contraceptives.¹⁶ Definition of exposure levels in this way can result in more than two groups—eg, non-smokers, light smokers, and heavy smokers.¹⁸

Who is an appropriate control?

The key notion is that controls (the unexposed) should be similar to the exposed in all important respects, except for the lack of exposure. If so, the unexposed group will reveal the background rate of the outcome in the community.

The unexposed group can come from either internal (persons from the same time and place, such as a hospital ward) or external sources. Internal comparisons are most desirable. In a particular population, individuals segregate by themselves (or through medical interventions) into exposure status—eg, cigarette smoking, occupation, contraception. For example, in a cohort study, 138 patients with HIV-1-associated Kaposi's sarcoma were divided into two groups: those with oral and those with cutaneous lesions. The presence of oral lesions (the exposure) had a poorer prognosis, with a median survival (the outcome) one-third that of the other group.²⁰

If satisfactory internal controls are not available, researchers look elsewhere (sometimes termed a double-cohort study).⁶ In a trial of an occupational exposure, finding an adequate number of employees in the factory without the exposure might be difficult. Hence, one might choose workers in a similar factory in the same community. This choice assumes that workers in the other factory have the same baseline risk of the outcome in question, which might not be the case. Even less desirable is use of population norms; disease-specific mortality rates are an example. A researcher might compare lung-cancer death rates among workers in the factory with rates of persons of the same age and sex in the population. Bias inevitably creeps into such comparisons because of the healthy worker effect: those who work are healthier, in general, than those who do not (or cannot) work.⁴⁹ Additionally, work reaps economic benefits which might further bias comparisons.

Have outcomes been assessed equally?

Outcomes must be defined in advance; they should be clear, specific, and measurable. Identification of outcomes should be comparable in every way for the exposed and unexposed to avoid information bias. Failure to define objective outcomes leads to uninterpretable results. This challenge relates not only to subjective syndromes such as Gulf War,²¹ chronic fatigue,^{22,23} and premenstrual,²⁴ but also to more mundane health problems such as endometritis. Just how tender must a uterus be? Keeping those who judge outcomes unaware of the exposure status of participants (blinding) in a cohort study is important for subjective outcomes, such as tenderness or erythema. By contrast, with objective outcome measures, such as fever or death, blinding the exposure status is less important.

Outcome information can come from many sources. For mortality studies, the death certificate is often used. Although convenient, the validity of the clinical information is highly variable. For non-fatal outcomes, sources include hospital charts, insurance records, laboratory records, disease registries, hospital discharge logs, and physical examination and measurement of participants. Optimally, the person who judges outcomes should be unaware of the exposure. When diagnoses vary in their confidence, assignment of levels of assurance might be helpful, such as definite, probable, and suspect.⁷

Tracking participants over time

Have losses been minimised?

Although loss of participants damages the power and precision of a study, differential loss to follow-up is more sinister. Bail-outs are not random events. If the likelihood

of bailing out is related both to exposure and outcome, then bias can result.²⁵ For example, some participants given a new antibiotic might have such poor outcomes that they are unable to complete questionnaires or to return for examination.²⁶ Their disappearance from the cohort would make the new antibiotic look better than it is.

The best way of dealing with loss to follow-up is to avoid it. For example, restrict participation to only those judged likely to complete the study. Additionally, several safeguards are customary. Obtaining the names of several family members or friends who do not live with the respondent is often helpful at the start of such studies. The participant's family doctor might also be helpful. Should the respondent move, these contacts would probably know their new address. Motor vehicle registration records can be useful too. Furthermore, national vital statistics registries, such as the National Death Index in the USA, facilitate follow-up. Participants can be offered financial compensation for their time lost from work as a result of the study. Diligent tracking of participants is hard work, and might require hiring personnel for this task alone.

Reporting cohort studies

Many researchers who do cohort studies report their findings in an unsatisfactory way (panel 2).²⁷ An investigator's first challenge is to convince the editor (then readers) that the exposed and unexposed groups were indeed similar in all important respects, except for the exposure. The first table in reports of cohort studies customarily provides demographic and other prognostic factors for both groups with hypothesis testing (p values) to show the likelihood that observed differences could be due to chance.

For dichotomous outcome measures, such as sick or well, the investigator should provide raw data sufficient for the reader to confirm the results. For cumulative incidence, the investigator should calculate the proportion who developed the outcome during the specified study interval. For incidence rates, the value is expressed per unit of time.⁴ Then, relative risks and confidence intervals should be provided. Use of p values should not replace interval estimation (relative risks with confidence

Panel 2: Features to look for in a cohort study

How much selection bias was present?

- 1 Were only people at risk of the outcome included?
- 1 Was the exposure clear, specific, and measurable?
- 1 Were the exposed and unexposed groups similar in all important respects except for the exposure?

What steps were taken to minimise information bias?

- 1 Was the outcome clear, specific, and measurable?
- 1 Was the outcome identified in the same way for both groups?
- 1 Was determination of outcome made by an observer blinded as to treatment?

How complete was the follow-up of both groups?

- 1 What efforts were made to limit loss to follow-up?
- 1 Was loss to follow-up similar in both groups?

Were potential confounding factors sought and controlled for in the analysis?

- 1 Did the investigators anticipate and gather information on potential confounding factors?
- 1 What method(s) were used to assess and control for confounding?

intervals)²⁸ and should only be used as supplemental information.²⁹

Like other observational studies, cohort studies have built-in bias. Investigators should identify potential biases in their data and show how these might have affected results. Whenever possible, confounding should be controlled for in the analysis. These techniques are discussed in an earlier essay in this series.²⁹

Variations on the cohort theme

Before-after studies

Before-after studies (time series) have important limitations. Here, an investigator takes a measurement, exposes participants to an intervention (often a drug), repeats the measurements, then compares them. First, regression to the mean is often ignored. If admission to the cohort includes extreme measurements,³⁰ such as high laboratory values, then lower mean values will arise at follow-up, irrespective of treatment.³¹ Second, secular trends, such as seasonal changes in the frequency of pneumonia, can affect results. Third, washout periods are often needed to avoid a carryover effect of drugs given during the initial observation period.⁶

Nested case-control studies

Cohort studies sometimes spawn other studies. One of the most frequent is the nested case-control study.^{6,25} Why would an investigator carve out a case-control study in the midst of a cohort study? The answer often involves body fluids and a freezer. Some exposure or predictor variables are simply too expensive to determine on everyone in a study. A sophisticated blood test is the prototype. A clever way to skirt this financial obstacle is to do a cohort study that will yield a sufficient number of cases. All participants entering the cohort study have a tube of blood drawn at enrolment; serum is frozen until the study's conclusion. All those in the cohort study who develop the outcome of interest now become the cases for the nested study. The investigator then chooses a random sample of all participants who did not develop the outcome (controls). Next, the blood test is done on serum from only the cases and controls, not the whole group of exposed and unexposed. In this way, the laboratory cost is minimised while assuring that the exposure—eg, a positive laboratory test—was present before development of the outcome. Controls are generally matched to cases by important characteristics, such as age and sex.⁶

A nested case-control study, for example, examined the potential relation between body concentrations of organochlorines and non-Hodgkin's lymphoma. The blood samples were obtained on entry to a large cohort study started in Maryland, USA, in 1974. Blood samples were eventually analysed for only 74 individuals with lymphoma and 147 controls.³² Thus, instead of measuring organochlorine concentrations of the entire cohort of 25 802, the investigators incurred this laboratory expense for less than 1% of the cohort. In view of the availability of banked blood specimens around the world, this type of research design is likely to become popular. However, nested case-control studies might be useful for other studies that do not require blood tests but in which determination of the exposure is expensive or difficult³—eg, measurement of nerve conduction³³ or job stressors.³⁴

Conclusion

Cohort studies are common in medical research. Like other research designs, they entail important trade-offs. Readers should make sure that investigators provide clear,

specific, and measurable definitions of exposures and outcomes. The unexposed group should resemble the exposed group in all important respects, and determination of outcomes should be objective and, whenever possible, blinded. Results for dichotomous outcomes should be provided as rates, relative risks, and confidence intervals, which offer more information than do p values. Reports of cohort studies should identify and describe the potential effect of biases. Importantly, investigators should measure and control for potential confounding.

We thank Willard Cates and David L Sackett for their helpful comments on an earlier version of this report. Much of this material stems from our 15 years of teaching the Berlex Foundation Faculty Development Course.

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Uses of error

The error cascade

Nell Gittoes

Having just been appointed consultant physician, I found myself reflecting on my career and realising that I could at last stand alone and that finally the buck stops with me. There was a time that I wished it didn't. I was a medical senior house officer when I saw an elderly man who described a subacute onset of breathlessness and a dry cough. He had trouble speaking and was using his accessory muscles. He had initially received standard nebulised treatment for exacerbated chronic obstructive pulmonary disease, although his chest radiograph showed a small pneumothorax on the left. After conferring with senior colleagues, I inserted a chest drain on the left, and verified its position with a second radiograph. In the middle of the night the house officer saw the patient with worsening shortness of breath and surgical emphysema. He pushed the tube in further, but an hour later the arrest team were called because the patient had developed extreme respiratory distress and had become cyanosed. They thought that he had developed a contralateral

pneumothorax and proceeded to insert a chest drain on the right. Arriving on the ward the following morning, I was horrified to find my patient with bilateral chest drains and surgical emphysema from head to scrotum. However, at least he was alive. Chest radiographs and computed tomography showed bilateral pneumothoraces with both drains embedded deeply within the lung parenchyma, just short of the mediastinum on the right, and abutting the left ventricle on the left. I inserted bilateral anterior drains and cautiously removed the lateral ones. After a few days the right-sided pneumothorax resolved, although the left side needed surgical correction. He was finally discharged, and on reviewing the radiographs it was apparent that I had inserted the original drain where there was a small area of pleural adhesion. The two pleural surfaces remained contiguous, and the drain entered the lung parenchyma. The subsequent errors of management turned the situation rapidly into a life-threatening predicament.

Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2 TH UK (N Gittoes MRCP)

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From: "Barbara Stoll" <Barbara.Stoll@oz.ped.emory.edu>
To: "Lbrion" (b)(6) gmail.com>
CC: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, <" <Luc.Bri...>
Date: 2/5/2010 2:08 PM
Subject: Proposal

Luc

Your proposal was reviewed on the GDB Subcommittee call this morning. There was general enthusiasm for doing a study to look at clinical practices and outcomes pre and post SUPPORT. However, the subcommittee thought the proposal needed revisions before it would be ready for presentation at a Steering Committee Meeting. The Subcommittee suggested that you consider putting off this study so that you could do an analysis of the pre/post SUPPORT eras-- ie look at intubation/outcome in the years before SUPPORT and compare to the period following completion of SUPPORT and the end of the current Network (April 2011).

Specific comments:

Subcommittee thought it likely that the those infants who were eligible but not randomized into SUPPORT would likely be different-- need analysis to understand these differences not simply whether there was a change in DR interventions vs pre SUPPORT

RTI statisticians thought that this would be a more complicated analysis than presented and wanted to work with you to better think through the analysis and write up. Please contact Dr Das re analysis.

Need to evaluate uniform time periods, rather than based on when a center started or stopped SUPPORT

Might have substantial missing data in the non SUPPORT group who don't have as intense tracking after discharge

Suggest adding PDA and Late onset sepsis to the secondary outcomes-- because of their impact on outcome of preterm infants

In addition to intubation in the DR suggest looking at chest compressions and code drugs

This would be a paper from the full steering committee-- with all PIs (or designees) included as authors because of the enormous amount of work that went into completing SUPPORT and GDB

No need for additional IRB approval-- have approval for both GDB and SUPPORT

Best regards

BJS

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics

Chief Academic Officer, Children's Healthcare of Atlanta
President and CEO, Emory-Children's Center
2015 Uppergate Dr
Atlanta GA 30022
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barbara_stoll@oz.ped.emory.edu

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From: Das, Abhik
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Nolen, Tracy; Wallace, Dennis
Subject: RE: The New England Journal of Medicine, October 4, 2012
Date: Wednesday, October 10, 2012 10:30:28 AM

Thanks. We can certainly do that, but the FDA tends to march to its own tune!

Abhik

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Wednesday, October 10, 2012 10:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: FW: The New England Journal of Medicine, October 4, 2012

Interesting article on missing data. Wonder if we should cite it in the Inositol protocol for how we propose to handle the missing outcomes?

SPECIAL REPORT

The Prevention and Treatment of Missing Data in Clinical Trials

R. J. Little and Others | N Engl J Med 2012;367:1355-1360

From: NEJM [mailto:nejmtoc@nejm.org]
Sent: Wednesday, October 03, 2012 5:19 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: The New England Journal of Medicine, October 4, 2012

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S. Girirajan and Others | N Engl J Med 2012;367:1321-1331 | Published Online September 12, 2012

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J. de Ligt and Others | October 3, 2012 | DOI: 10.1056/NEJMoa1206524

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The Prevention and Treatment of Missing Data in Clinical Trials

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From: Finer, Neil
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) (E); Pablo Sanchez; (b)(6)@gmail.com; "Wally Carlo, M.D."; Wrage, Lisa Ann; "Barbara Stoll"; Das, Abhik
Subject: Re: Revised abstract
Date: Monday, October 08, 2012 1:31:19 PM

Looks Good Luc
The manuscript will deal all the other issues
Great work and thanks
Neil

From: "Luc.Brion@UTSouthwestern.edu<mailto:Luc.Brion@UTSouthwestern.edu>"
<Luc.Brion@UTSouthwestern.edu<mailto:Luc.Brion@UTSouthwestern.edu>>
Date: Monday, October 8, 2012 8:25 AM
To: Rosemary Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, Pablo Sanchez
<Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>>, (b)(6)@gmail.com<mailto:(b)(6)@gmail.com>,"
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<nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>, Abhik Das <adas@rti.org<mailto:adas@rti.org>>
Subject: Revised abstract

Rose et al;
Here is Jackie LeVan's updated abstract after trimming the number of authors as you suggested.
I added back information that had been removed to fit all names.
Please let me know if you have any additional suggestions.
Should this be sent to additional people at the NRN to approval before submitting?
If you wish to look at the website here are the codes; (b)(6)
Thanks and best regards,
Luc

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From: Luc Brion
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez; (b)(6)@gmail.com; Wally Carlo, M.D.;
Wrage, Lisa Ann; Barbara Stoll; Finer, Neil
Subject: RE: Revised abstract
Date: Monday, October 08, 2012 12:52:31 PM

PS:

For the study at Parkland we also did exactly what you propose: comparison of serial data; this showed a sharp decrease in DR intubation during SUPPORT recruitment. I will also include this as a method to analyze the NRN data for the current study comparing before SUPPORT/after dissemination of SUPPORT results.

Luc

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, October 08, 2012 11:40 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez; (b)(6)@gmail.com; Wally Carlo, M.D.; Wrage, Lisa Ann; Barbara Stoll; Finer, Neil
Subject: RE: Revised abstract

Luc:

I think this looks ok. The problem with any before/after analysis is of course in the attribution of cause. We don't know if the decline in 2010-11 vs 2003-04 is entirely attributable to SUPPORT, or if there are broader trends over time that may be responsible. For the paper, perhaps we can look in more detail year by year and see if there is a sharp decline after SUPPORT publication, or if the long term time trend is more monotonic, which may help with the attribution.

Thanks

Abhik

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, October 08, 2012 11:26 AM

From: Luc Brion
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez; (b)(6)@gmail.com; Wally Carlo, M.D.; Wraga, Lisa Ann; Barbara Stoll; Finer, Neil
Subject: RE: Revised abstract
Date: Monday, October 08, 2012 12:49:17 PM

Abhik et al:

Thanks for your email.

I agree with you. I am also concerned about secular trends with this before/after study design. For the related study at Parkland (which describes changes during SUPPORT; this was the first version of what we had submitted to the NRN) we have obtained an agreement from Roger Soll at VON; he has agreed to share the data on contemporaneous GA-matched patients from VON. This will allow us to compare data at Parkland with those at VON using an interaction test.

I spoke with Rose about this at the latest Steering Committee Meeting. Rose told me that I should also consider another alternative: comparing our data to those of the Canadian Network; and that I should submit an application to the Steering Committee.

Before going forward with this, could you all please let me know your thoughts about working with VON or with the Canadian Network.

Best regards,

Luc

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, October 08, 2012 11:40 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez; (b)(6)@gmail.com; Wally Carlo, M.D.; Wraga, Lisa Ann; Barbara Stoll; Finer, Neil
Subject: RE: Revised abstract

Luc:

I think this looks ok. The problem with any before/after analysis is of course in the attribution of cause. We don't know if the decline in 2010-11 vs 2003-04 is entirely attributable to SUPPORT, or if there are broader trends over time that may be responsible. For the paper, perhaps we can look in

more detail year by year and see if there is a sharp decline after SUPPORT publication, or if the long term time trend is more monotonic, which may help with the attribution.

Thanks

Abhik

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Monday, October 08, 2012 11:26 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez; (b)(6)@gmail.com; 'Wally Carlo, M.D.'; Wrage, Lisa Ann; 'Barbara Stoll'; Finer, Neil; Das, Abhik
Subject: Revised abstract

Rose et al;

Here is Jackie LeVan's updated abstract after trimming the number of authors as you suggested.

I added back information that had been removed to fit all names.

Please let me know if you have any additional suggestions.

Should this be sent to additional people at the NRN to approval before submitting?

If you wish to look at the website here are the codes; (b)(6)

Thanks and best regards,

Luc

Luc P. Brion, MD
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From: Wally Carlo, M.D.
To: Luc Brion; Myra Wyckoff; Pablo Sanchez; Mambarambath Jaleel; Roy Heyne; Barbara Stoll; nfiner@ucsd.edu
Cc: Jackie LeVan; Higgins, Rosemary (NIH/NICHD) IE
Subject: Re: revised abstract
Date: Monday, October 08, 2012 8:23:05 AM

Pablo.

Nor a problem at all.

Wally

-----Original message-----

From: Luc Brion <Luc.Brion@UTSouthwestern.edu>
To: Myra Wyckoff <Myra.Wyckoff@UTSouthwestern.edu>, Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>, Mambarambath Jaleel <Mambarambath.Jaleel@UTSouthwestern.edu>, Roy Heyne <Roy.Heyne@UTSouthwestern.edu>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>
Cc: Jackie LeVan <(b)(6)@gmail.com>, "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
Sent: Mon, Oct 8, 2012 12:02:43 GMT+00:00
Subject: FW: revised abstract

Myra, Roy, Jaleel, Wally, Neil, Barbara:

Thanks for all your comments.

See below,

Rose Higgins recommends to limit NRN abstract to three authors: first, senior and statistician, to allow more data to be included in the abstract. All authors will be in the manuscript of course.

All my apologies.

Luc P. Brion, MD

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From: Pablo Sanchez
Sent: Monday, October 08, 2012 2:08 AM
To: Luc Brion
Subject: RE: revised abstract

Hi Luc--I was not able to make any tracked changes in the version that you sent out--would send it out in a version where changes can be made. I think that it is still early and people may still want changes, but at least so far so good. I would change it as per Rose suggested --no more than 3 (main author, senior investigator, statistician) on behalf of the NICHD NRN --that would be jackie, you and the statistician--I do agree that you will be able to add more results--there were more descriptive information in the last version that I saw. Also, do you think that you should spell out SUPPORT--it may not be obvious to all. --pablo

From: Luc Brion
Sent: Monday, October 08, 2012 1:43 AM
To: Pablo Sanchez
Subject: FW: revised abstract

Pablo:
FYI
I have not received any comment since then.
Since all fits it looks like we are OK with this version.
Please advise.
Luc

Luc P. Brion, MD
Professor of Pediatrics

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: revised abstract
Date: Friday, October 05, 2012 11:10:20 PM

Rose:

If in your or anyone else's assessment I should add anything to the abstract, please let me know. I will then notify the other authors and remove their names as you indicated.

Thanks again for all your advices and support.

Best regards,

Luc

Luc P. Brion, MD
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From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, October 05, 2012 8:20 AM
To: Luc Brion; Wrage, Lisa Ann; Das, Abhik; doctorlevan@gmail.com; 'Wally Carlo, M.D.'
Subject: RE: revised abstract

IN order to save space on PAS abstracts, I suggest no more than 3 (main author, senior investigator, statistician) on behalf of the NICHD NRN>

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

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higginsr@mail.nih.gov

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Thursday, October 04, 2012 2:47 PM
To: Wrage, Lisa Ann; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@gmail.com; 'Wally Carlo, M.D.'
Subject: FW: revised abstract

Hi everyone;

Thanks a lot for your help and suggestions.

Lisa, thanks again.

I entered the multivariate analysis of death: univariate is significant, multivariate is not.

Here is the updated version of the abstract loaded onto the PAS website but not submitted.

This version fits into the prescribed size.

ID: lucbrion; password: nichdrn

If you have any suggestion please let me know.

Rose: please advise regarding list of names.

Best regards

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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www.utsouthwestern.edu (<http://www.utsouthwestern.edu/>)

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Thursday, October 04, 2012 11:12 AM
To: Luc Brion
Cc: Das, Abhik

Subject: RE: revised abstract

Hi Luc,

I've attached the updated information. The adjusted info for death is in the footnote to Table 3 and in the SAS output attached.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, October 04, 2012 10:06 AM
To: Wrage, Lisa Ann
Cc: Wally Carlo (wacarlo@uab.edu); Rosemary (NIH/NICHD) [E Higgins; doctorfevan@gmail.com]
Subject: Re: revised abstract

Tks

I have updated the abstract on the PAS website

Luc

Sent from my iPhone

On Oct 4, 2012, at 8:57 AM, "Wrage, Lisa Ann" <wrage@rti.org> wrote:

Yes, will do.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, October 03, 2012 8:34 PM
To: Wrage, Lisa Ann; Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: revised abstract

Lisa;

Could you please run the multivariate analysis of death to discharge.

Thanks

Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, October 03, 2012 5:13 PM
To: Luc Brion
Subject: RE: revised abstract

Luc:

Can we add death to the table? I thought Abhik supported it, no one objected (at least in the emails I got) and you had the data. I really think it may be very important to add it.

I hope I am being as helpful as possible.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
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Cell: 205 266 4004

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, October 03, 2012 10:46 AM
To: Das, Abhik
Cc: Wrage, Lisa Ann; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHHD) [E]; wcarlo@uab.edu; Jackie LeVan
Subject: Re: revised abstract

Thanks everyone for your feedback.

I made all the changes on the website abstract as discussed.

aps-spr.org

ID: (b)(6)

password: (b)(6)

I entered the results of death into the body of the abstract.
I also made all the corrections in the body of the text that Wally had suggested.

Rose: is any change needed re list of authors and affiliations?

If you have any additional suggestions please let me know.
Best regards,

Luc

Sent from my iPad

On Oct 3, 2012, at 9:26 AM, "Das, Abhik" <adas@rti.org> wrote:

You can perhaps keep things simple by just reporting any hospital deaths.
Thanks

Abhik

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, October 03, 2012 10:13 AM
To: Wraga, Lisa Ann; Wally Carlo, M.D.; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wacarolo@uab.edu; Jackie LeVan
Subject: Re: revised abstract

Abhik, Rose, Wally:
I understand we need to look into partition of death/BPD and death ROP for the manuscript.
However, if we add death to the abstract shouldn't we need to present two additional variables: death at 36 weeks and death at discharge? This results from the planned time of assessment of ROP/death at discharge, and death/BPD at 36 weeks.
In addition, this would add two post hoc analyses to the abstract. I understand that Abhik recommends to leave them out.
Please advise.

Lisa:

Could you please calculate death at 36 weeks and death at discharge to the univariate outcomes, and run multivariate analyses of death until discharge and until 36 weeks, respectively, using the same predictors as ROP/death and BPD/death.
Did you use the entry criterion "syndrome/major malformation" as exclusion criterion?

Thanks,

Luc

Sent from my iPad

On Oct 3, 2012, at 7:18 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

Luc:

Exceptional job putting this together. It is more succinct and the message is clearer.

Big picture things first:

I think you should add death to the table. Even though it was not specified, it is a component of 2 of 3 of your outcome measures. You only have three outcome measures and 2 of them include death so I think it is ok to add it. Adding death may clarify whether in the adjusted model, all the benefit is from decreased ROP (the effect size is in the CI range of SUPPORT) or if there is also a trend for reduction in death, as may be possible.

Also, not for the abstract but some food for thought, is to see if Abhik and Lisa could weigh in on whether it is possible for the model to be over compensating as the adj OR for BPD/death goes in the opposite direction. The certainly can happen without over compensation.

Minor issues:

In Methods, should you say "major malformations" or just "malformations"? It depends on your exclusion criterion.

In Result, change odd ratio's to odd ratios.

Technically, you say "after publication of SUPPORT" in several places, but publication was in May. Did you use all of the 2010 data? If so, you could say "after dissemination of the SUPPORT results".

Add a hyphen after post (post-) in Results.

Again, this is a terrific abstract.

You may want to add to the paper duration of ventilation, CPAP, and oxygen supplementation and other measures of respiratory support such as post natal steroids.

Again, you, Jaclyn, and Lisa have done a superb job developing the idea and pulling it through.

Wally

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Director, Newborn Nurseries
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From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Tuesday, October 02, 2012 11:54 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@uab.edu; Wrage, Lisa Ann
Cc: Jackie LeVan
Subject: RE: revised abstract

Wally and Rose:

Thanks for all the suggestions.

I entered a first version of the abstract on line.

ID: (b)(6)

Keyword: (b)(6)

Wally: you were right, I had to trim a lot. Actually only one table with primary outcomes could be entered.

Please review and let me know how this works.

If I need to trim authors please let me know.

Rose; Please advise re list of authors. Should I list each individual institution in addition to NICHD?

Best regards,

Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Tuesday, October 02, 2012 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Luc Brion
Subject: RE: revised abstract

Hi Rose and Luc:

Excellent idea. I have some comments particularly about the use of exploratory analysis and competing outcomes. See my tracked suggestions.

Thanks for the opportunity to comment. Sorry if I had missed the email earlier.

Wally

From: Higgins, Rosemary (NIH/NICHD) [E]
[mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 02, 2012 1:46 PM
To: Wally Carlo (wacarlo@uab.edu)
Cc: (Luc.Brion@UTSouthwestern.edu)
Subject: FW: revised abstract

Wally –

As we discussed, please look this over and send in your
comments

Rose

Rosemary D. Higgins, MD
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Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, October 02, 2012 1:00 PM
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary
(NIH/NICHD) [E]; Barbara Stoll; nfiner@ucsd.edu; Pablo
Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik;
Jackie LeVan
Subject: revised abstract

Here is a revised abstract with leading zero's (picked by
Myra).

Luc

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UT Southwestern Medical Center
The future of medicine, today.

From: Gantz, Marie
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; Finer, Neil; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, October 05, 2012 3:58:32 PM

I agree with Yvonne that the original question is best answered by comparing to all those who were not enrolled, especially since we think that the time spent in hospital, and the lack of time to be approached for or give consent, was a big contributor to the bias caused the antenatal consent process.

Yvonne, is there anything else you need for the abstract -- additional comparisons by consent/refusal status or anything else? As I mentioned before, I will be at a site visit and Steering Committee next week, so if you need additional analyses before the abstract deadline on the 17th it would be helpful to know as soon as possible.

Thanks,
Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Vaucher, Yvonne [mailto:yyvaucher@ucsd.edu]
Sent: Friday, October 05, 2012 3:34 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

For the question we are asking first (is there a difference in outcome-I don't think it matters why you were not enrolled-all of these reasons will apply in any study using antenatal enrollment. However, the differences would be interesting to look at for the presentation/paper.

Yvonne

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

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, October 05, 2012 12:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; Vaucher, Yvonne; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

What are we wanting to compare? Outcomes of those who refused consent vs. those who are enrolled, or something else?

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, October 05, 2012 2:58 PM
To: 'Wally Carlo, M.D.'; Walsh, Michele; Vaucher, Yvonne; Gantz, Marie; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

I agree with Wally - they were approached and given opportunity.

Rise

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
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301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Friday, October 05, 2012 2:56 PM
To: Walsh, Michele; Vaucher, Yvonne; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

I agree that refused would be a much better comparator.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Newborn Nurseries
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Birmingham, AL 35233-7335
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FAX: 205 934 3100
Cell: 205 266 4004

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

From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]
Sent: Friday, October 05, 2012 9:13 AM
To: Vaucher, Yvonne; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

I agree with the issue raised by others- The imbalance in antenatal steroid and abx administration In those enrolled may be the causative factor rather Than being in a trial, so the adjusted are critical.
Refused is a better comparator than not approached Who may have been ineligible on the basis of time in hospital

prior to delivery. Can this be in the abstract Not just the paper?

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, October 05, 2012 9:42 AM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

That (refused vs. not approached) would be interesting to look at also.
We
can do that for the paper.

Marie, Please run the models for death and death or NDI with severe Grade 3-4 IVH (if possible separated from PVL) since IVH occurs in the first few days after birth and it may be an significant factor in early death for the 24-25 week infants, particularly when care is withdrawn. Different situation for PVL so if there is much more PVL it may dilute the effect of IVH if there is one when the two are combined.

Thanks.

Yvonne

On 10/5/12 6:28 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

>Rose, we have not looked at that. I'm not sure what the numbers would
>look like for refused consent and consent not sought, but I can check
to

>see what they would be.

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org

>828-254-6255

>

>

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

>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
>Sent: Tuesday, October 02, 2012 11:19 AM
>To: 'Wally Carlo, M.D.'; Vaucher, Yvonne; Finer, Neil; Gantz, Marie;
>'Kurt Schibler'; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook,
>Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy
newman';
>Rich, Wade; Das, Abhik

>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled
>
>One item from a steering committee discussion - Have we looked at the
>eligible, but not enrolled and divided them by refused consent and
>consent not sought?? There may be some differences between these two
>groups.
>
>ROse
>
>Rosemary D. Higgins, MD
>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal
Research
>Network Pregnancy and Perinatology Branch CDBPM, NIH
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>301-496-5575
>301-496-3790 (FAX)
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>
>
>-----Original Message-----
>From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
>Sent: Friday, September 28, 2012 7:13 AM
>To: Vaucher, Yvonne; Finer, Neil; Gantz, Marie; 'Kurt Schibler';
>mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook, Abbot';
>Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman'; Rich,
>Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled
>
>Yvonne:
>
>Very good as a descriptive study in which we knew the baselines differ
>were huge.
>
>However, with so many differences in baseline characteristics that are
>associated with outcomes, it would be ideal to adjust for baseline
>differences. With the adjusted model, it would then be important to
>assess how good the model is to assure that at least 50% of the
variance
>in the model is accounted for. This would reassure that the differences
>in outcomes were not due to baseline differences although I understand
>that this was not necessarily your intended analytical approach.
>
>An alternative is to match patients for the expected outcome based on
the
>baseline risk and then assess whether enrollment modified their
outcome,
>but again, this was not necessarily what you intended to do.
>
>In summary, as a descriptive study, I think it is ok although to make

>sure readers are aware of your insight, you could state the conclusions
>in a slightly different way such as: "Compared to children enrolled in
>SUPPORT, those eligible but not enrolled were more likely to die or
have
>NDI, due to substantial baseline differences that favored those
>enrolled."

>
>Hope this helps.

>Wally

>Wally Carlo, M.D.

>Edwin M. Dixon Professor of Pediatrics

>University of Alabama at Birmingham

>Director, Division of Neonatology

>Director, Newborn Nurseries

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>Cell: 205 266 4004

>

>

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

>From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]

>Sent: Thursday, September 27, 2012 8:32 PM

>To: Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler';

>'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot';

>Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; Vaucher, Yvonne;

'nancy

>'newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]

>Cc: Archer, Stephanie (NIH/NICHD) [E]

>Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:

Enrolled

>vs. Eligible/Nonenrolled

>

>SUPPORT subcommittee:

>

>PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs.

>Eligible/Nonenrolled attached. (97% full) Please send comments.

>

>Thanks.

>

>Yvonne

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A.I.Ds-related conditions, alcohol, and/or drug dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gillet, Ronnie"
Subject: RE: question for you
Date: Friday, October 05, 2012 12:01:00 PM

Ronnie

There was a SUPPORT consent secondary study – here are the publications thus far:

Enrollment of extremely low birth weight infants in a clinical research study may not be representative.

Rich W, Finer NN, Gantz MG, Newman NS, Hensman AM, Hale EC, Auten KJ, Schibler K, Faix RG, Lupton AR, Yoder BA, Das A, Shankaran S; SUPPORT and Generic Database Subcommittees of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.

Pediatrics. 2012 Mar;129(3):480-4. Epub 2012 Feb 27.

Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment.

Rich WD, Auten KJ, Gantz MG, Hale EC, Hensman AM, Newman NS, Finer NN; National Institute of Child Health and Human Development Neonatal Research Network.

Pediatrics. 2010 Jul;126(1):e215-21. Epub 2010 Jun 29.

As far as a survey study – if it is a survey, we need a 9 month lead time to go through OMB. If it is research and approved by the IRB's, we would not need to go through OMB. If you want to propose a study, we have the concept presentations at steering committee meetings.

The PROPHENO experience needs to be published.

Rose

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Guillet, Ronnie [mailto:Ronnie_Guillet@URMC.Rochester.edu]
Sent: Friday, October 05, 2012 11:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: question for you

Rose,

I have been "threatening" to write up my experience with PROPHENO for quite awhile, but had been procrastinating.....didn't really know how to start that kind of a paper. A couple of weeks ago, one of my colleagues, Rita Dadiz, showed me an article in JAMA that was a call for papers on child health research. The solicitation included Viewpoint articles. I've started working on the paper (and have attached a draft). When thinking about what "new" I have to highlight regarding the barriers to clinical trials in children, I thought about the role of bedside nurses when inpatient studies are proposed. In my literature search, I found articles on barriers related to physicians and patients, but no mention of nursing staff. (I have to look again at the literature, specifically nursing journals, but if there is something, it's not much.)

The reason for this email is twofold:

- Carl seems to remember that someone in the NRN fairly recently did a survey or project on consenting subjects – but couldn't remember who did it or what the main focus was. Do you know?
- Secondly, what do you think of my proposing a survey related to bedside nursing attitudes towards research within the NRN centers? I'm thinking of a couple of approaches.
 - A survey would include general attitudes overall and also attitudes given specific "scenarios" (along the lines of the national survey of practice I did prior to starting PROPHENO).
 - I'm also considering approaching Dale and Hareh and asking them if we could develop a survey of nursing attitudes that would be distributed near the initiation of each of their trials (one an interventional drug study involving an untested drug and several blood draws and the other a comparison of two "standards of care" not involving additional interventions or blood draws, etc.) and then again near the end of enrollment. The results of the surveys could ultimately be correlated with the consent rates for the two studies.

Given the interest in the consent process – within the NRN and nationally – I think this might provide very interesting data and new insights into how best to improve the consent rates for pediatric (inpatient) studies. The cost would be relatively modest.

I'd appreciate your thoughts (comments about both my proposal for the NRN survey and the Viewpoint article if you have the time).

Thanks,
Ronnie

Ronnie Guillet, MD, PhD
Professor of Pediatrics (Neonatology)
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University of Rochester Medical Center
Chief, Department of Pediatrics, Highland Hospital
phone: (585) 275-6209
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email: ronnie_guillet@urmc.rochester.edu
<http://www.urmc.rochester.edu/childrens-hospital/>

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann; Das, Abhik; (b)(6) @gmail.com; "Wally Carlo, M.D."
Subject: RE: revised abstract
Date: Friday, October 05, 2012 11:16:27 AM

Rose;

Should we list the current institution each is in currently: San Antonio, RTI, UTSW Dallas.

This would be Jaclyn LeVan (San Antonio), Lisa Ann Wrage (RTI) and Luc P Brion (UTSW Dallas).

Luc

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www.utsouthwestern.edu (<http://www.utsouthwestern.edu/>)

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, October 05, 2012 8:20 AM
To: Luc Brion; Wrage, Lisa Ann; Das, Abhik; (b)(6) @gmail.com; 'Wally Carlo, M.D.'
Subject: RE: revised abstract

IN order to save space on PAS abstracts, I suggest no more than 3 (main author, senior investigator, statistician) on behalf of the NICHD NRN>

Rose

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, October 04, 2012 2:47 PM
To: Wrage, Lisa Ann; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@gmail.com; 'Wally Carlo, M.D.'
Subject: FW: revised abstract

Hi everyone;

Thanks a lot for your help and suggestions.

Lisa, thanks again.

I entered the multivariate analysis of death: univariate is significant, multivariate is not.

Here is the updated version of the abstract loaded onto the PAS website but not submitted.

This version fits into the prescribed size.

ID (b)(6) password: (b)(6)

If you have any suggestion please let me know.

Rose: please advise regarding list of names.

Best regards

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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www.utsouthwestern.edu (<http://www.utsouthwestern.edu/>)

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Thursday, October 04, 2012 11:12 AM
To: Luc Brion
Cc: Das, Abhik
Subject: RE: revised abstract

Hi Luc,

I've attached the updated information. The adjusted info for death is in the footnote to Table 3 and in the SAS output attached.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, October 04, 2012 10:06 AM
To: Wrage, Lisa Ann

Cc: Wally Carlo (wacarlo@uab.edu); Rosemary (NIH/NICHD) [E Higgins; (b)(6) @gmail.com]
Subject: Re: revised abstract

Tks

I have updated the abstract on the PAS website

Luc

Sent from my iPhone

On Oct 4, 2012, at 8:57 AM, "Wrage, Lisa Ann" <wrage@rti.org> wrote:

Yes, will do.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, October 03, 2012 8:34 PM
To: Wrage, Lisa Ann; Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: revised abstract

Lisa;

Could you please run the multivariate analysis of death to discharge.

Thanks

Luc

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, October 03, 2012 5:13 PM
To: Luc Brion
Subject: RE: revised abstract

Luc:

Can we add death to the table? I thought Abhik supported it, no one objected (at least in the emails I got) and you had the data. I really think it may be very important to add it.

I hope I am being as helpful as possible.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Newborn Nurseries
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Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, October 03, 2012 10:46 AM
To: Das, Abhik
Cc: Wrage, Lisa Ann; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@uab.edu; Jackie LeVan
Subject: Re: revised abstract

Thanks everyone for your feedback.

I made all the changes on the website abstract as discussed.

aps-spr.org

ID: (b)(6)

password: (b)(6)

I entered the results of death into the body of the abstract.

I also made all the corrections in the body of the text that Wally had suggested.

Rose: is any change needed re list of authors and affiliations?

If you have any additional suggestions please let me know.

Best regards,

Luc

Sent from my iPad

On Oct 3, 2012, at 9:26 AM, "Das, Abhik" <adas@rti.org> wrote:

You can perhaps keep things simple by just reporting any hospital deaths.
Thanks

Abhik

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, October 03, 2012 10:13 AM
To: Wrage, Lisa Ann; Wally Carlo, M.D.; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Jackie LeVan
Subject: Re: revised abstract

Abhik, Rose, Wally:

I understand we need to look into partition of death/BPD and death ROP for the manuscript.

However, if we add death to the abstract shouldn't we need to present two additional variables: death at 36 weeks and death at discharge? This results from the planned time of assessment of ROP/death at discharge, and death/BPD at 36 weeks.

In addition, this would add two post hoc analyses to the abstract. I understand that Abhik recommends to leave them out.

Please advise.

Lisa:

Could you please calculate death at 36 weeks and death at discharge to the univariate outcomes, and run multivariate analyses of death until discharge and until 36 weeks, respectively, using the same predictors as ROP/death and BPD/death.

Did you use the entry criterion "syndrome/major malformation" as exclusion criterion?

Thanks,

Luc

Sent from my iPad

On Oct 3, 2012, at 7:18 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

Luc:

Exceptional job putting this together. It is more succinct and the message is clearer.

Big picture things first:

I think you should add death to the table. Even though it was not specified, it is a component of 2 of 3 of your outcome measures. You only have three outcome measures and 2 of them include death so I think it is ok to add it. Adding death may clarify whether in the adjusted model, all the benefit is from decreased ROP (the effect size is in the CI range of SUPPORT) or if there is also a trend for reduction in death, as may be possible.

Also, not for the abstract but some food for thought, is to see if Abhik and Lisa could weigh in on whether it is possible for the model to be over compensating as the adj OR for BPD/death goes in the opposite direction. This certainly can happen without over compensation.

Minor issues:

In Methods, should you say "major malformations" or just "malformations"? It depends on your exclusion criterion.

In Result, change odd ratio's to odd ratios.

Technically, you say "after publication of SUPPORT" in several places, but publication was in May. Did you use all of the 2010 data? If so, you could say "after dissemination of the SUPPORT results".

Add a hyphen after post (post-) in Results.

Again, this is a terrific abstract.

You may want to add to the paper duration of ventilation, CPAP, and oxygen supplementation and other measures of respiratory support such as post natal steroids.

Again, you, Jaclyn, and Lisa have done a superb job developing the idea and pulling it through.

Wally

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Cell: 205 (b)(6)

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, October 02, 2012 11:54 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E];
wacarlo@uab.edu; Wrage, Lisa Ann
Cc: Jackie LeVan
Subject: RE: revised abstract

Wally and Rose:

Thanks for all the suggestions.

I entered a first version of the abstract on line.

ID: (b)(6)

Keyword: (b)(6)

Wally: you were right, I had to trim a lot. Actually only one table with primary outcomes could be entered.

Please review and let me know how this works.

If I need to trim authors please let me know.

Rose; Please advise re list of authors. Should I list each individual institution in addition to NICHD?

Best regards,

Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Tuesday, October 02, 2012 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@uab.edu
Cc: Luc Brion
Subject: RE: revised abstract

Hi Rose and Luc:

Excellent idea. I have some comments particularly about the use of exploratory analysis and competing outcomes. See my tracked suggestions.

Thanks for the opportunity to comment. Sorry if I had missed the email earlier.

Wally

From: Higgins, Rosemary (NIH/NICHD) [E]
[<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, October 02, 2012 1:46 PM
To: Wally Carlo (wcarlo@uab.edu)
Cc: (Luc.Brion@UTSouthwestern.edu)
Subject: FW: revised abstract

Wally --

As we discussed, please look this over and send in your comments

Rose

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Tuesday, October 02, 2012 1:00 PM
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary
(NIH/NICHD) [E]; Barbara Stoll; nfiner@ucsd.edu; Pablo
Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik;
Jackie LeVan
Subject: revised abstract

Here is a revised abstract with leading zero's (picked by
Myra).
Luc

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TX 75390 www.utsouthwestern.edu (
<http://www.utsouthwestern.edu/>)

UT Southwestern Medical Center
The future of medicine, today.

From: Gantz, Marie
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, October 05, 2012 10:49:24 AM

Yvonne, we really cannot include grade 3-4 IVH as a predictor for outcomes that include death, because over 25% of deaths have a missing value for IVH 3-4. In addition, the fact that infants who die earlier have less time to develop or be diagnosed with IVH may bias the estimate of the effect of IVH on death.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, October 05, 2012 9:42 AM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Rich, Wade; Das, Abhik
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

That (refused vs. not approached) would be interesting to look at also. We can do that for the paper.

Marie, Please run the models for death and death or NDI with severe Grade 3-4 IVH (if possible separated from PVL) since IVH occurs in the first few days after birth and it may be an significant factor in early death for the 24-25 week infants, particularly when care is withdrawn. Different situation for PVL so if there is much more PVL it may dilute the effect of IVH if there is one when the two are combined.

Thanks.

Yvonne

On 10/5/12 6:28 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

>Rose, we have not looked at that. I'm not sure what the numbers would
>look like for refused consent and consent not sought, but I can check
>to see what they would be.

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org

>828-254-6255

>

>

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

>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
>Sent: Tuesday, October 02, 2012 11:19 AM
>To: 'Wally Carlo, M.D.'; Vaucher, Yvonne; Finer, Neil; Gantz, Marie;
>'Kurt Schibler'; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook,
>Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy
>newman'; Rich, Wade; Das, Abhik
>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled

>
>One item from a steering committee discussion - Have we looked at the
>eligible, but not enrolled and divided them by refused consent and
>consent not sought?? There may be some differences between these two
>groups.

>
>ROse

>
>Rosemary D. Higgins, MD
>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal
>Research Network Pregnancy and Perinatology Branch CDBPM, NIH
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>MSC 7510
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>301-435-7909
>301-496-5575
>301-496-3790 (FAX)
>higginsr@mail.nih.gov

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

>From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
>Sent: Friday, September 28, 2012 7:13 AM
>To: Vaucher, Yvonne; Finer, Neil; Gantz, Marie; 'Kurt Schibler';
>mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook, Abbot';
>Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman'; Rich,
>Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled

>
>Yvonne:
>
>Very good as a descriptive study in which we knew the baselines differ
>were huge.

>
>However, with so many differences in baseline characteristics that are
>associated with outcomes, it would be ideal to adjust for baseline
>differences. With the adjusted model, it would then be important to
>assess how good the model is to assure that at least 50% of the
>variance in the model is accounted for. This would reassure that the
>differences in outcomes were not due to baseline differences although I
>understand that this was not necessarily your intended analytical approach.

>
>An alternative is to match patients for the expected outcome based on
>the baseline risk and then assess whether enrollment modified their

>outcome, but again, this was not necessarily what you intended to do.

>

>In summary, as a descriptive study, I think it is ok although to make
>sure readers are aware of your insight, you could state the conclusions
>in a slightly different way such as: "Compared to children enrolled in
>SUPPORT, those eligible but not enrolled were more likely to die or
>have NDI, due to substantial baseline differences that favored those
>enrolled."

>

>Hope this helps.

>

>Wally

>

>Wally Carlo, M.D.

>Edwin M. Dixon Professor of Pediatrics

>University of Alabama at Birmingham

>Director, Division of Neonatology

>Director, Newborn Nurseries

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>176F Suite 9380R

>Birmingham, AL 35233-7335

>Phone: 205 934 4680

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>Cell: 205 266 4004

>

>

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

>From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]

>Sent: Thursday, September 27, 2012 8:32 PM

>To: Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler';

>'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot';

>Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; Vaucher, Yvonne;

>'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD)

>[E]

>Cc: Archer, Stephanie (NIH/NICHD) [E]

>Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:

>Enrolled vs. Eligible/Nonenrolled

>

>SUPPORT subcommittee:

>

>PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs.

>Eligible/Nonenrolled attached. (97% full) Please send comments.

>

>Thanks.

>

>Yvonne

From: Wally Carlo, M.D.
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Barbara.Stoll@oz.ped.emory.edu
Subject: RE: revised abstract and possible GDB paper
Date: Friday, October 05, 2012 7:56:22 AM

Luc, Rose, and Barbara:

I think the observation by Luc of decreased mortality over this short period is an important one as the NRN and VON have published lack of decrease in mortality over the last two decades. I think in part this may have been due to inclusion of smaller babies as resuscitation became more effective and less stillbirths occur.

Maybe we could incorporate in the paper (not the abstract) the issue of trends in mort over time in the NRN. If not, we could propose a new GDB protocol that looks as mortality trends over time.

Wally

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FAX: 205 934 3100
Cell: 205 (b)(6)

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, October 04, 2012 1:47 PM
To: Wrage, Lisa Ann; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@gmail.com; Wally Carlo, M.D.
Subject: FW: revised abstract

Hi everyone;

Thanks a lot for your help and suggestions.

Lisa, thanks again.

I entered the multivariate analysis of death: univariate is significant, multivariate is not.

Here is the updated version of the abstract loaded onto the PAS website but not submitted.

This version fits into the prescribed size.

ID: (b)(6) password: (b)(6)

If you have any suggestion please let me know.

Rose: please advise regarding list of names.

Best regards

Luc

Luc P. Brion, MD
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Cc: Das, Abhik
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Subject: RE: revised abstract
Date: Friday, October 05, 2012 7:09:44 AM

Luc:

Excellent. In the BPD or death row and the Pre-SUPPORT column, there is an extra space that can be deleted between the denominator and the %.

The significant reduction in death may be due to the increased use of ANS as well as patient population characteristics as the significance is lost in the adjusted models. Nonetheless, this is important as there have been a lack of reduction in mortality in the NRN's previous reports comparing various time periods. This is something we could study in a separate study.

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Subject: FW: revised abstract
Date: Thursday, October 04, 2012 2:48:27 PM
Attachments: [Report_04Oct12.doc](#)
[PAS 2013 - Abstract Draft LeVan_100412.pdf](#)

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From: [Wrage, Lisa Ann \[mailto:Wrage.LisaAnn@rti.org\]](mailto:Wrage.LisaAnn@rti.org)
Sent: Thursday, October 04, 2012 11:12 AM
To: Luc Brion
Cc: Das, Abhik
Subject: RE: revised abstract

Hi Luc,

I've attached the updated information. The adjusted info for death is in the footnote to Table 3 and in the SAS output attached.

Lisa

From: [Luc Brion \[mailto:Luc.Brion@UTSouthwestern.edu\]](mailto:Luc.Brion@UTSouthwestern.edu)
Sent: Thursday, October 04, 2012 10:06 AM

To: Wrage, Lisa Ann
Cc: Wally Carlo (wcarlo@uab.edu); Rosemary (NIH/NICHD) [E Higgins; doctorlevan@gmail.com]
Subject: Re: revised abstract

Tks
I have updated the abstract on the PAS website
Luc

Sent from my iPhone

On Oct 4, 2012, at 8:57 AM, "Wrage, Lisa Ann" <wrage@rti.org> wrote:

Yes, will do.
Lisa

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, October 03, 2012 8:34 PM
To: Wrage, Lisa Ann; Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: revised abstract

Lisa;
Could you please run the multivariate analysis of death to discharge.
Thanks
Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, October 03, 2012 5:13 PM
To: Luc Brion
Subject: RE: revised abstract

Luc:

Can we add death to the table? I thought Abhik supported it, no one objected (at least in the emails I got) and you had the data. I really think it may be very important to add it.

I hope I am being as helpful as possible.

Wally

Wally Carlo, M.D.
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From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, October 03, 2012 10:46 AM
To: Das, Abhik
Cc: Wrage, Lisa Ann; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@uab.edu; Jackie LeVan
Subject: Re: revised abstract

Thanks everyone for your feedback.

I made all the changes on the website abstract as discussed.

aqs-spr.org

ID: (b)(6)

password: (b)(6)

I entered the results of death into the body of the abstract.

I also made all the corrections in the body of the text that Wally had suggested.

Rose: is any change needed re list of authors and affiliations?

If you have any additional suggestions please let me know.

Best regards,

Luc

Sent from my iPad

On Oct 3, 2012, at 9:26 AM, "Das, Abhik" <adas@rti.org> wrote:

You can perhaps keep things simple by just reporting any hospital deaths.

Thanks

Abhik

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, October 03, 2012 10:13 AM
To: Wrage, Lisa Ann; Wally Carlo, M.D.; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Jackie LeVan
Subject: Re: revised abstract

Abhik, Rose, Wally:

I understand we need to look into partition of death/BPD and death ROP for the manuscript.

However, if we add death to the abstract shouldn't we need to present two additional variables: death at 36 weeks and death at discharge? This results from the planned time of assessment of ROP/death at discharge, and death/BPD at 36 weeks.

In addition, this would add two post hoc analyses to the abstract. I understand that Abhik recommends to leave them out.

Please advise.

Lisa:

Could you please calculate death at 36 weeks and death at discharge to the univariate outcomes, and run multivariate analyses of death until discharge and until 36 weeks, respectively, using the same predictors as ROP/death and BPD/death.

Did you use the entry criterion "syndrome/major malformation" as exclusion criterion?

Thanks,

Luc

Sent from my iPad

On Oct 3, 2012, at 7:18 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>

wrote:

Luc:

Exceptional job putting this together. It is more succinct and the message is clearer.

Big picture things first:

I think you should add death to the table. Even though it was not specified, it is a component of 2 of 3 of your outcome measures. You only have three outcome measures and 2 of them include death so I think it is ok to add it. Adding death may clarify whether in the adjusted model, all the benefit is from decreased ROP (the effect size is in the CI range of SUPPORT) or if there is also a trend for reduction in death, as may be possible.

Also, not for the abstract but some food for thought, is to see if Abhik and Lisa could weigh in on whether it is possible for the model to be over compensating as the adj OR for BPD/death goes in the opposite direction. The certainly can happen without over compensation.

Minor issues:

In Methods, should you say "major malformations" or just "malformations"? It depends on your exclusion criterion.

In Result, change odd ratio's to odd ratios.

Technically, you say "after publication of SUPPORT" in several places, but publication was in May. Did you use all of the 2010 data? If so, you could say "after dissemination of the SUPPORT results".

Add a hyphen after post (post-) in Results.

Again, this is a terrific abstract.

You may want to add to the paper duration of ventilation, CPAP, and oxygen supplementation and other measures of respiratory support such as post natal steroids.

Again, you, Jaclyn, and Lisa have done a superb job

developing the idea and pulling it through.

Wally

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Director, Newborn Nurseries
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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, October 02, 2012 11:54 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E];
wacarlo@uab.edu; Wrage, Lisa Ann
Cc: Jackie LeVan
Subject: RE: revised abstract

Wally and Rose:

Thanks for all the suggestions.

I entered a first version of the abstract on line.

ID: (b)(6)

Keyword: (b)(6)

Wally: you were right, I had to trim a lot. Actually only one table with primary outcomes could be entered.

Please review and let me know how this works.

If I need to trim authors please let me know.

Rose; Please advise re list of authors. Should I list each individual institution in addition to NICHD?

Best regards,

Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Tuesday, October 02, 2012 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Luc Brion
Subject: RE: revised abstract

Hi Rose and Luc:

Excellent idea. I have some comments particularly about the use of exploratory analysis and competing outcomes. See my tracked suggestions.

Thanks for the opportunity to comment. Sorry if I had missed the email earlier.

Wally

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, October 02, 2012 1:46 PM
To: Wally Carlo (wacarlo@uab.edu)
Cc: (Luc.Brion@UTSouthwestern.edu)
Subject: FW: revised abstract

Wally –

As we discussed, please look this over and send in your comments

Rose

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From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Tuesday, October 02, 2012 1:00 PM
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; nfiner@ucsd.edu; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: revised abstract

Here is a revised abstract with leading zero's (picked by Myra).

Luc

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October 4, 2012

Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Updated from October 1 – Including adjusted results for death before discharge.

Neonatal Network Investigator: J. LeVan, Luc Brion

RTI Statistician: Lisa Wrage

Population

Infants of 24-27 weeks gestational age at birth, born during years 2003-2004 or 2010-2011 at one of 11 centers participating in the SUPPORT trial and in the NRN from 2003-2011, excluding infants with known malformations or who had respiratory or other medical support withheld prior to death < 12 hours.

Methods

Primary outcome variables

The primary outcome variables of interest include intubation in the delivery room, BPD or death at 36 weeks, and severe ROP or death before discharge. Intubation in delivery room is recorded in the GDB. BPD is defined as oxygen use at 36 weeks. Severe ROP is defined using ophthalmology information from the GDB, NG03 section H (see appendix for details)

Secondary outcome variables

Other outcomes of interest include BPD, severe ROP, death before discharge, surfactant use, pneumothorax, pulmonary hemorrhage, postnatal steroid use, severe IVH, proven NEC, days of mechanical ventilation (survivors), days on supplemental oxygen (survivors), and length of hospital stay.

Other variables

Maternal and neonatal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Study groups

Infants from the study population were classified as 'pre-SUPPORT' if they were born during 2003-2004 and as 'post-SUPPORT' if they were born during 2010-2011.

Statistical Analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and ttests or Wilcoxon tests, as appropriate, for continuous variables. Logistic regression models were used to obtain adjusted results for each of the primary outcomes. These models included pre-specified covariates (based on the literature) as well as additional covariates that were significantly different by study group in the unadjusted tests, and that occurred prior to outcome. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation rate during the first epoch.

Results

There were a total of n=5323 infants born at 24-27 weeks gestational age during 2003-2004 (n=2998) or 2010-2011 (n=2322) and included in the GDB. Of these n=1581 infants were born in NRN centers not included in this study and an additional n=352 were outborn, these infants were excluded. Of the remaining infants, n=134 infants with known malformations, n=100 infants who had respiratory or medical support withdrawn prior to death < 12 hours were excluded, and 5 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of n=3151 infants. Of these n=1617 infants are in the pre-SUPPORT group and n=1534 infants are in the post-SUPPORT group.

Power Calculations

Power calculations for each of the primary outcomes, based on chi square tests, an alpha of .05, and the sample sizes noted above give these results: a power of 1.0 to detect a change of delivery room intubation from 80% to 68%; a

power of 0.8 to detect a change in outcome 'BPD or death' from 50% to 45%, and a power of 0.94 to detect a change in outcome severe ROP or death from 67% to 61%.

Statistical analysis

Unadjusted comparisons of variables of interest by study group are shown in **Tables 1-3**. Logistic regression models for each of the primary outcomes were also run to obtain adjusted results. The resulting adjusted odds ratios, 95% confidence intervals, and p-values are shown in **Table 2**. Adjusted results for death prior to discharge are shown in a footnote to **Table 3**. Additionally, within center, the percent of infants who were intubated in the delivery room was calculated for each study group and the difference between the post-SUPPORT group and the pre-SUPPORT group was also calculated. Using the results for the 11 centers in this study, the correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.38, $p=0.25$). (see appendix for SAS output for the logistic regression models and for the Spearman correlation).

Table 1. Maternal and Neonatal Characteristics¹

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
Birth weight (g)	824 (191)	816 (190)	0.23
Gestational Age (weeks)	25.7 (1.1)	25.6 (1.1)	0.64
% Male	858 (53.1)	767 (50.0)	0.09
Race:			
NH Black	727 (45.0)	654 (43.5)	0.02
NH White	603 (37.3)	566 (37.6)	
Hispanic	241 (14.9)	210 (14.0)	
Other	46 (2.8)	74 (4.9)	
Antenatal Steroids: any type	1338/1616 (82.8)	1358/1532 (88.6)	<.0001
Antenatal Steroids: betamethasone	953(59.1)	1344/1532 (87.7)	<.0001
Multiple birth	370 (22.9)	360/1532 (23.5)	0.68
Mode of delivery: c-section	1004 (62.1)	1009 (65.9)	0.03
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	360/1482 (24.3)	0.043
Maternal hypertension	322 (19.9)	409/1532 (24.7)	<.0001
Maternal diabetes	42 (2.6)	84 (5.5)	<.0001
Antibiotics	1198/1615 (74.2)	1114/1530 (72.8)	0.38

Table 2. Primary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²	adjusted OR ³ (95% CI)	adjusted p-value ³
Intubated in delivery room	1313 (81.2)	1082 (70.5)	<.0001	0.55 (0.46-0.67)	<.0001
BPD or death at 36 weeks	970 (60.0)	824/1523 (54.1)	.0009	1.1 (0.91-1.3)	0.37
Severe ROP or death	515/1581 (32.6)	408/1501(27.2)	.0011	0.73 (0.60-0.87)	0.0007

Table 3. Secondary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
BPD (O2 at 36 weeks)	664/1311 (50.7)	581/1279 (45.4)	.008
Death at 36 weeks	306 (18.9)	243/1529 (15.9)	.026
Severe ROP	174 (13.5)	138 (10.8)	.036
Death before discharge***	358/1614 (22.2)	285/1519 (18.8)	.017
Surfactant	1427 (88.3)	1266/1528 (82.9)	<.0001
Pneumothorax	135/1604 (8.4)	86/1511 (5.7)	.0030
Pulmonary Hemorrhage	181/1603 (11.3)	106/1512 (7.0)	<.0001
Postnatal Steroids	195/1599 (12.2)	182/1496 (12.2)	0.97
Days on ventilator (survivors)	22.3 (24.4), 13	18.5 (21.2), 10	<.0001
Days on supp. O2 (survivors)	59.2 (36)	56.8 (37.8)	0.10
Severe IVH	288 (18.5)	204 (13.8)	.0004
Proven NEC	177 (11.0)	160 (10.6)	0.71
Length of hospital stay (days)	84.4 (57.5), 83	90.9 (52.9), 90	.0006

¹ presented as mean (SD), median for days on ventilator and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.

² unadjusted p-values from Chi Square tests, t-tests, or Wilcoxon tests, as appropriate.

³ OR reflects odds of the outcome for post_SUPPORT vs. pre_SUPPORT.

***adjusted OR (post vs. pre-SUPPORT) 0.85 (0.69-1.04), p=0.11.

Appendix – Definition of severe ROP:

Severe ROP is defined as “retinal detachment (partial or complete), surgery, or Avastin/Anti-VEGf drug” using questions from NG03 section H ‘Ophthalmology’. Specifically, an infant is defined as having severe ROP if:

Using NG03 2002 – for the pre-SUPPORT group born 2003-2004:

- H.1.a.1.i. Highest Stage of ROP in right or left eye=4 or 5 (retinal detachment) ***or***
- H.3.a.i. retinal ablation performed prior to a threshold diagnosis in Right eye='Y' ***or***
- H.3.a.ii. retinal ablation performed prior to a threshold diagnosis in Left eye='Y' ***or***
- H.3.b.i. any surgery performed in Right eye=1,2,3,4 ***or***
- H.3.b.ii. any surgery performed in Left eye=1,2,3,4.

Using NG03 2008, 2011 – for the post-SUPPORT group born 2010-2011:

- H.1.b.1. retinal ablation performed in either eye='Y' ***or***
- H.1.b.2. scleral buckle or vitrectomy performed in either eye='Y' ***or***
- 2008 H.1.b.3.

Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***

2011 H.1.b.3. Avastin or other anti-VEGF drug='Y' ***or***

2011 H.1.b.4.

Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***

H.2. =2 - Determined severe ROP (ROP surgery, retinal detachment, Avastin or anti-VEGf) in either eye at status.

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08:54 Monday, June 30, 2014 5

LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	intubated_dr	intubated in the delivery room, 1=Yes
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	intubated_dr	Total Frequency
1	1	2306
2	0	733

Probability modeled is intubated_dr=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	1.4009	0.2782	25.3504	<.0001
post_SUPPORT		1	-0.5913	0.0994	35.4106	<.0001
ga2425		1	0.7731	0.1304	35.1311	<.0001
brwtgtp	1= <=600g	1	1.6268	0.2268	51.4630	<.0001
brwtgtp	2=601-700g	1	1.3761	0.1968	48.8930	<.0001
brwtgtp	3=701-800g	1	1.1366	0.1813	39.2928	<.0001
brwtgtp	4=801-900g	1	0.7196	0.1527	22.1974	<.0001
brwtgtp	5=901-1000g	1	0.5737	0.1532	14.0168	0.0002
malex		1	0.1503	0.0992	2.2965	0.1297
MULTBRTH		1	-0.2824	0.1216	5.3910	0.0202
ANTESTER		1	-0.7629	0.1718	19.7140	<.0001
race_bwho	1=Black	1	-0.1800	0.1163	2.3970	0.1216
race_bwho	3=Hispanic	1	-0.2754	0.1772	2.4161	0.1201
race_bwho	4=Other	1	0.0404	0.2932	0.0190	0.8905
CSECT		1	0.3659	0.1084	11.4010	0.0007
ROMGT24		1	-0.1559	0.1164	1.7943	0.1804

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LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.6231	0.1293	23.2044	<.0001
diabetes		1	-0.3508	0.2334	2.2592	0.1328
CENTER	3	1	-0.1911	0.2462	0.6026	0.4376
CENTER	4	1	0.0906	0.2742	0.1092	0.7411
CENTER	5	1	0.7584	0.2688	7.9617	0.0048
CENTER	9	1	-0.0932	0.2440	0.1461	0.7023
CENTER	11	1	-0.7889	0.1902	17.2024	<.0001
CENTER	12	1	0.8173	0.2520	10.5193	0.0012
CENTER	14	1	0.7130	0.2558	7.7714	0.0053
CENTER	15	1	-0.2212	0.2729	0.6571	0.4176
CENTER	16	1	-1.8605	0.1930	92.8898	<.0001
CENTER	18	1	0.6383	0.2327	7.5270	0.0061

Odds Ratio Estimates			
Effect		Point Estimate	95% Wald Confidence Limits
post_SUPPORT		0.554	0.456 0.673
ga2425		2.167	1.678 2.798
brtwtgp	1= <=600g vs 6=>1000g	5.087	3.262 7.935
brtwtgp	2=601-700g vs 6=>1000g	3.960	2.692 5.823
brtwtgp	3=701-800g vs 6=>1000g	3.116	2.184 4.446
brtwtgp	4=801-900g vs 6=>1000g	2.054	1.522 2.770
brtwtgp	5=901-1000g vs 6=>1000g	1.775	1.314 2.397
malex		1.162	0.957 1.412
MULTBRTH		0.754	0.594 0.957
ANTESTER		0.466	0.333 0.653
race_bwho	1=Black vs 2=White	0.835	0.665 1.049
race_bwho	3=Hispanic vs 2=White	0.759	0.536 1.075
race_bwho	4=Other vs 2=White	1.041	0.586 1.850
CSECT		1.442	1.166 1.783
ROMGT24		0.856	0.681 1.075
htn		0.536	0.416 0.691
diabetes		0.704	0.446 1.113

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LOGISTIC MODELS

OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CENTER	3 vs 19	0.826	0.510	1.338
CENTER	4 vs 19	1.095	0.640	1.874
CENTER	5 vs 19	2.135	1.261	3.616
CENTER	9 vs 19	0.911	0.565	1.469
CENTER	11 vs 19	0.454	0.313	0.660
CENTER	12 vs 19	2.264	1.382	3.711
CENTER	14 vs 19	2.040	1.236	3.368
CENTER	15 vs 19	0.802	0.470	1.368
CENTER	16 vs 19	0.156	0.107	0.227
CENTER	18 vs 19	1.893	1.200	2.987

04OCT12 11:16

LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	bpddeath36	BPD or death at 36 weeks
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	bpddeath36	Total Frequency
1	1	1579
2	0	1286

Probability modeled is bpddeath36=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.4745	0.2933	140.3352	<.0001
post_SUPPORT		1	0.0829	0.0922	0.8076	0.3688
intubated_dr		1	0.1272	0.1317	0.9332	0.3340
ga2425		1	0.3410	0.1198	8.1064	0.0044
brwtgtp	1= <=600g	1	2.2816	0.2776	67.5343	<.0001
brwtgtp	2=601-700g	1	1.3640	0.1954	48.7054	<.0001
brwtgtp	3=701-800g	1	1.0284	0.1696	36.7750	<.0001
brwtgtp	4=801-900g	1	0.7031	0.1496	22.1039	<.0001
brwtgtp	5=901-1000g	1	0.5099	0.1517	11.3000	0.0008
sga		1	0.1163	0.2074	0.3142	0.5751
malex		1	0.7688	0.0923	69.3508	<.0001
MULTBRTH		1	-0.1678	0.1111	2.2825	0.1308
ANTESTER		1	0.0335	0.1396	0.0576	0.8103
race_bwho	1=Black	1	-0.2083	0.1072	3.7760	0.0520
race_bwho	3=Hispanic	1	-0.2086	0.1541	1.8328	0.1758
race_bwho	4=Other	1	-0.3767	0.2452	2.3604	0.1245
CSECT		1	-0.0898	0.0987	0.8286	0.3627
ROMGT24		1	-0.0558	0.1079	0.2676	0.6049

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.1063	0.1208	0.7741	0.3790
diabetes		1	0.0517	0.2257	0.0524	0.8189
SURFACT		1	0.7540	0.1609	21.9500	<.0001
fio24ge90		1	1.3394	0.3167	17.8869	<.0001
pda_ligation		1	0.7153	0.1596	20.0960	<.0001
pda_andom		1	0.4663	0.1060	19.3710	<.0001
LOS		1	0.6057	0.0990	37.4165	<.0001
CENTER	3	1	0.8916	0.2247	15.7452	<.0001
CENTER	4	1	1.0962	0.2437	20.2300	<.0001
CENTER	5	1	2.2212	0.2376	87.3674	<.0001
CENTER	9	1	1.2099	0.2286	28.0101	<.0001
CENTER	11	1	1.7521	0.1890	85.9657	<.0001
CENTER	12	1	2.3213	0.2189	112.4709	<.0001
CENTER	14	1	1.2466	0.2072	36.1907	<.0001
CENTER	15	1	1.7989	0.2607	47.6274	<.0001
CENTER	16	1	0.7074	0.1961	13.0095	0.0003
CENTER	18	1	1.2615	0.1979	40.6349	<.0001

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
post SUPPORT	1.086	0.907	1.302
intubated_dr	1.136	0.877	1.470
ga2425	1.406	1.112	1.778
brwtgtp 1= <=600g vs 6=>1000g	9.793	5.683	16.875
brwtgtp 2=601-700g vs 6=>1000g	3.912	2.667	5.738
brwtgtp 3=701-800g vs 6=>1000g	2.797	2.006	3.899
brwtgtp 4=801-900g vs 6=>1000g	2.020	1.507	2.708
brwtgtp 5=901-1000g vs 6=>1000g	1.665	1.237	2.242
sga	1.123	0.748	1.687
malex	2.157	1.800	2.585
MULTBRTH	0.845	0.680	1.051
ANTESTER	1.034	0.787	1.360
race_bwho 1=Black vs 2=White	0.812	0.658	1.002
race_bwho 3=Hispanic vs 2=White	0.812	0.600	1.098
race_bwho 4=Other vs 2=White	0.686	0.424	1.109

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CSECT		0.914	0.753	1.109
ROMGT24		0.946	0.766	1.168
htn		0.899	0.710	1.139
diabetes		1.053	0.677	1.639
SURFACT		2.126	1.551	2.914
fio24ge90		3.817	2.052	7.100
pda_ligation		2.045	1.496	2.796
pda_indom		1.594	1.295	1.962
LOS		1.833	1.509	2.225
CENTER	3 vs 19	2.439	1.570	3.789
CENTER	4 vs 19	2.993	1.856	4.825
CENTER	5 vs 19	9.218	5.786	14.686
CENTER	9 vs 19	3.353	2.142	5.249
CENTER	11 vs 19	5.767	3.982	8.352
CENTER	12 vs 19	10.189	6.635	15.648
CENTER	14 vs 19	3.479	2.317	5.322
CENTER	15 vs 19	6.043	3.626	10.072
CENTER	16 vs 19	2.029	1.381	2.980
CENTER	18 vs 19	3.531	2.396	5.204

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	sevropdeath	severe ROP or death
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	sevropdeath	Total Frequency
1	1	888
2	0	2086

Probability modeled is sevropdeath=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.7451	0.3171	74.9595	<.0001
post_SUPPORT		1	-0.3220	0.0949	11.5044	0.0007
ga2425		1	0.6638	0.1123	34.9175	<.0001
brtwtgp	1= <=600g	1	2.7480	0.2169	160.5657	<.0001
brtwtgp	2=601-700g	1	1.7112	0.2005	72.8247	<.0001
brtwtgp	3=701-800g	1	1.0931	0.1953	31.3110	<.0001
brtwtgp	4=801-900g	1	0.5440	0.1926	7.9772	0.0047
brtwtgp	5=901-1000g	1	0.3030	0.2029	2.2303	0.1353
malex		1	0.5961	0.0951	39.2636	<.0001
MULTBRTH		1	0.2070	0.1134	3.3312	0.0680
ANTESTER		1	-0.2870	0.1366	4.4155	0.0356
race_bwho	1=Black	1	-0.3356	0.1142	8.6379	0.0033
race_bwho	3=Hispanic	1	0.3547	0.1647	4.6368	0.0313
race_bwho	4=Other	1	0.8940	0.2519	12.5895	0.0004
CSECT		1	-0.1137	0.1042	1.1901	0.2753
ROMGT24		1	-0.1885	0.1145	2.7091	0.0998
htn		1	-0.4417	0.1287	11.7883	0.0006
diabetes		1	0.4797	0.2345	4.1852	0.0408

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
SURFACT		1	0.5006	0.1703	8.6465	0.0033
CENTER	3	1	0.4326	0.2373	3.3252	0.0682
CENTER	4	1	0.5324	0.2536	4.4083	0.0358
CENTER	5	1	1.0554	0.2221	22.5791	<.0001
CENTER	9	1	0.3917	0.2422	2.6159	0.1058
CENTER	11	1	0.2798	0.1988	1.9814	0.1592
CENTER	12	1	0.4444	0.2132	4.3446	0.0371
CENTER	14	1	-0.8170	0.2458	11.0468	0.0009
CENTER	15	1	-0.4137	0.2898	2.0374	0.1535
CENTER	16	1	0.1950	0.2065	0.8919	0.3450
CENTER	18	1	0.2956	0.2101	1.9797	0.1594

Odds Ratio Estimates					
Effect			Point Estimate	95% Wald Confidence Limits	
post_SUPPORT			0.725	0.602	0.873
ga2425			1.942	1.558	2.421
brwtgtp	1= <-600g	vs 6=>1000g	15.611	10.205	23.879
brwtgtp	2=601-700g	vs 6=>1000g	5.535	3.737	8.200
brwtgtp	3=701-800g	vs 6=>1000g	2.983	2.034	4.375
brwtgtp	4=801-900g	vs 6=>1000g	1.723	1.181	2.513
brwtgtp	5=901-1000g	vs 6=>1000g	1.354	0.910	2.015
malex			1.815	1.506	2.187
MULTBRTH			1.230	0.985	1.536
ANTESTER			0.751	0.574	0.981
race_bwho	1=Black	vs 2=white	0.715	0.572	0.894
race_bwho	3=Hispanic	vs 2=white	1.426	1.032	1.969
race_bwho	4=Other	vs 2=white	2.445	1.492	4.006
CSECT			0.893	0.728	1.095
ROMGT24			0.828	0.662	1.037
htn			0.643	0.500	0.827
diabetes			1.616	1.020	2.558
SURFACT			1.650	1.182	2.303
CENTER	3	vs 19	1.541	0.968	2.454
CENTER	4	vs 19	1.703	1.036	2.800
CENTER	5	vs 19	2.873	1.859	4.441

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CENTER	9 vs 19	1.480	0.920	2.378
CENTER	11 vs 19	1.323	0.896	1.953
CENTER	12 vs 19	1.560	1.027	2.368
CENTER	14 vs 19	0.442	0.273	0.715
CENTER	15 vs 19	0.661	0.375	1.167
CENTER	16 vs 19	1.215	0.811	1.822
CENTER	18 vs 19	1.344	0.890	2.029

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	DEATH	Died before discharge
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	DEATH	Total Frequency
1	1	621
2	0	2404

Probability modeled is DEATH=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.2428	0.3494	86.1330	<.0001
post_SUPPORT		1	-0.1636	0.1026	2.5397	0.1110
ga2425		1	0.4519	0.1232	13.4654	0.0002
brtwtgp	1= <=600g	1	2.5288	0.2333	117.4619	<.0001
brtwtgp	2=601-700g	1	1.4755	0.2248	43.0952	<.0001
brtwtgp	3=701-800g	1	1.0533	0.2211	22.6898	<.0001
brtwtgp	4=801-900g	1	0.5849	0.2196	7.0947	0.0077
brtwtgp	5=901-1000g	1	0.3920	0.2304	2.8945	0.0889
malex		1	0.6458	0.1030	39.2723	<.0001
MULTBRTH		1	0.00153	0.1228	0.0002	0.9901
ANTESTER		1	-0.6077	0.1403	18.7733	<.0001
race_bwho	1=Black	1	-0.1496	0.1220	1.5036	0.2201
race_bwho	3=Hispanic	1	0.0112	0.1836	0.0037	0.9513
race_bwho	4=Other	1	0.0199	0.2917	0.0047	0.9456
CSECT		1	-0.00895	0.1126	0.0063	0.9366
ROMGT24		1	-0.0497	0.1235	0.1618	0.6875

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LOGISTIC MODELS
OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.3465	0.1378	6.3202	0.0119
diabetes		1	0.1080	0.2629	0.1688	0.6812
SURFACT		1	0.4788	0.1866	6.5836	0.0103
CENTER	3	1	-0.0937	0.2876	0.1061	0.7447
CENTER	4	1	0.6836	0.2844	5.7770	0.0162
CENTER	5	1	1.3456	0.2393	31.6221	<.0001
CENTER	9	1	0.3352	0.2734	1.5039	0.2201
CENTER	11	1	0.8326	0.2209	14.2071	0.0002
CENTER	12	1	0.4678	0.2430	3.7063	0.0542
CENTER	14	1	-0.4162	0.2850	2.1325	0.1442
CENTER	15	1	-0.0197	0.3386	0.0034	0.9537
CENTER	16	1	0.6924	0.2277	9.2467	0.0024
CENTER	18	1	0.5705	0.2367	5.8110	0.0159

Odds Ratio Estimates					
Effect			Point Estimate	95% Wald Confidence Limits	
post_SUPPORT			0.849	0.694	1.038
ga2425			1.571	1.234	2.000
brwtgtp	1= < 600g	vs 6=>1000g	12.538	7.936	19.808
brwtgtp	2=601-700g	vs 6=>1000g	4.373	2.815	6.794
brwtgtp	3=701-800g	vs 6=>1000g	2.867	1.859	4.422
brwtgtp	4=801-900g	vs 6=>1000g	1.795	1.167	2.760
brwtgtp	5=901-1000g	vs 6=>1000g	1.480	0.942	2.325
malex			1.907	1.559	2.334
MULTBRTH			1.002	0.787	1.274
ANTESTER			0.545	0.414	0.717
race_bwho	1=Black	vs 2=White	0.861	0.678	1.094
race_bwho	3=Hispanic	vs 2=White	1.011	0.706	1.449
race_bwho	4=Other	vs 2=White	1.020	0.576	1.807
CSECT			0.991	0.795	1.236
ROMGT24			0.952	0.747	1.212
htn			0.707	0.540	0.926

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
diabetes	1.114	0.665	1.865
SURFACT	1.614	1.120	2.327
CENTER 3 vs 19	0.911	0.518	1.600
CENTER 4 vs 19	1.981	1.134	3.459
CENTER 5 vs 19	3.841	2.403	6.139
CENTER 9 vs 19	1.398	0.818	2.389
CENTER 11 vs 19	2.299	1.491	3.545
CENTER 12 vs 19	1.596	0.992	2.570
CENTER 14 vs 19	0.660	0.377	1.153
CENTER 15 vs 19	0.981	0.505	1.904
CENTER 16 vs 19	1.999	1.079	3.123
CENTER 18 vs 19	1.769	1.113	2.813

27SEP12 17:25

LOGISTIC MODELS
OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

First Author: Jaclyn LeVan, DO
Presenting Author: Jaclyn LeVan DO
Contact Author: Luc P Brion, MD **Email:** luc.brion@utsouthwestern.edu

Filename: 750229

2013 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Disease-Oriented Research

Presenting Author: Jaclyn LeVan DO
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Is Presenting Author a Trainee? No, Not a Trainee

The presenting author is member of these Alliance Societies:

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Presenting Author Sponsor Declaration: As the presenting author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Study Group associated with your submission (if applicable):

Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR

Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, August 1-4, 2013

Research Type: Clinical

Presentation Sabbath Conflict on: N/A

APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS abstract:

Sponsor Name: Luc P Brion

Email: luc.brion@utsouthwestern.edu

Is the Sponsor an Author? Yes

Sponsoring Societies:

American Academy of Pediatrics

American Society of Pediatric Nephrology

Society for Pediatric Research

Title: CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn LeVan, DO¹, Luc P Brion, MD¹, Lisa A Wrage¹, Barbara Stoff, MD¹, Neil Finer, MD¹, Rosemary Higgins, MD¹, Pablo J Sanchez, MD¹, Mambarambath Jaliel, MD¹, Myra Wyckoff, MD¹, Roy Heyne, MD¹ and Wally Carlo, MD¹. ¹Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD, United States

Background: In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates 24-27^{6/7} weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) and subsequent limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85 to 89% or 91 to 95%. The primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks), and death or severe retinopathy of prematurity (ROP) were not affected by the interventions. We hypothesize that the odds of DR intubation would decrease after dissemination of the SUPPORT results, without affecting BPD/death and ROP/death.

Objective: To compare DR intubation, BPD/death at 36 weeks, and severe ROP/death by discharge in time periods before SUPPORT and after its publication.

Design/Methods: This was a retrospective cohort study using the prospective NRN genetic database. We included infants 24-27^{6/7} weeks GA born before (2003-04) and after SUPPORT (2010-11) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes/major malformations and those receiving comfort care.

Results: The % of DR intubation, ROP/death, BPD/death, and death by discharge significantly decreased after SUPPORT (Table). After adjustment for baseline variables, the odds ratios (OR) (post- vs. pre-SUPPORT) of DR intubation and ROP/death, but not those of BPD/death and death, were significantly lower than 1.

Conclusions: The adjusted odds of DR intubation and that of death/ROP, but not those of death/BPD and death by discharge, significantly decreased after dissemination of SUPPORT results in NRN centers involved in the trial.

Parameters	Pre-SUPPORT	Post-SUPPORT	p-value	Adjusted OR (95% CI)	Adjusted p-value
DR Intubation	1313/1617 (81%)	1092/1534 (71%)	<0.0001	0.55 (0.46-0.67)	<0.0001
BPD or death	970/1617 (60%)	824/1522 (54%)	0.0009	1.09 (0.91-1.30)	0.37
Severe ROP or death	515/1581 (33%)	408/1501(27%)	0.0011	0.73 (0.60-0.87)	0.0007
Death by discharge	358/1614 (22%)	285/1519 (19%)	0.017	0.85 (0.69-1.04)	0.11

From: Luc Brion
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; Das, Abhik; Wraga, Lisa Ann
Subject: RE: revised abstract
Date: Wednesday, October 03, 2012 9:29:48 PM
Attachments: Changes in Therapy and Outcomes Associated with the SUPPORT Trial 100312.doc

I attach the revised trimmed abstract with 4 variables in the table (multivariate analysis pending to be entered in table, results and conclusions).

Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Wednesday, October 03, 2012 7:58 PM
To: Luc Brion
Subject: RE: revised abstract

Luc:

Great. Yes, I read the emails but got concerned when I did not see it in the abstract. I agree that death by discharge is the most imp as that is the latest contact we have.

Wally

Wally Carlo, M.D.
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From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Wednesday, October 03, 2012 7:40 PM
To: Wally Carlo, M.D.
Subject: RE: revised abstract

Wally:

Thanks for your email.

Sorry if you did not receive my previous email about this.

My concerns with entering death in the abstract are (1) that we analyzed death/BPD at 36 wk and death/ROP at discharge; therefore to be complete we should analyze death at 36 wk and discharge and this may be too much for the abstract; (2) this is a posthoc analysis.

Abhik agreed with using death at discharge in the abstract.

We do not have the multivariate analysis of death yet; I asked Lisa to run it.

Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]

Sent: Wednesday, October 03, 2012 5:13 PM
To: Luc Brion
Subject: RE: revised abstract

Luc:

Can we add death to the table? I thought Abhik supported it, no one objected (at least in the emails I got) and you had the data. I really think it may be very important to add it.

I hope I am being as helpful as possible.

Wally

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University of Alabama at Birmingham
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To: Das, Abhik
Cc: Wrage, Lisa Ann; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Jackie LeVan
Subject: Re: revised abstract

Thanks everyone for your feedback.
I made all the changes on the website abstract as discussed.

aps-spr.org

ID: (b)(6)

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I entered the results of death into the body of the abstract.
I also made all the corrections in the body of the text that Wally had suggested.

Rose: is any change needed re list of authors and affiliations?

If you have any additional suggestions please let me know.
Best regards,

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UT Southwestern Medical Center
The future of medicine, today.

Title: CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn LeVan, DO¹, Luc P Brion, MD¹, Lisa A Wrage¹, Barbara Stoll, MD¹, Neil Finer, MD¹, Rosemary Higgins, MD¹, Pablo J Sanchez, MD¹, Mambarambath Jaleef, MD¹, Myra Wyckoff, MD¹, Roy Heyne, MD¹ and Wally Carlo, MD¹. ¹Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD, United States.

Background: In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates 24-27^{6/7} weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) and subsequent limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85 to 89% or 91 to 95%. The primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks), and death or severe retinopathy of prematurity (ROP) were not affected by the interventions. We hypothesized that the odds of DR intubation would decrease after dissemination of the SUPPORT results, without affecting BPD or death and ROP or death.

Objective: To compare DR intubation, BPD or death at 36 weeks, and severe ROP or death before discharge in time periods before SUPPORT and after its publication.

Design/Methods: This was a retrospective cohort study using the prospective NRN generic database. We included infants 24-27^{6/7} weeks GA born before (2003-04) and after SUPPORT (2010-11) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes/major malformations and those receiving comfort care.

Results: The % of DR intubation, ROP or death and BPD or death, but not death by discharge significantly decreased after SUPPORT (Table). After adjustment for baseline variables, the odds ratios (OR) (post- vs. pre-SUPPORT) of DR intubation and ROP or death, but not BPD or death were significantly lower than 1 (Table).

Conclusions: The adjusted odds of DR intubation and that of death or ROP, but not that of death or BPD, significantly decreased after dissemination of SUPPORT results in NRN centers involved in the trial.

Parameters of Assessment	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value	Adjusted OR (95% CI)	Adjusted p-value
Intubated in DR	1313 (81%)	1082 (71%)	<0.0001	0.55 (0.46-0.67)	<0.0001
BPD or death	970 (60%)	824/1522 (54%)	0.0009	1.09 (0.91-1.30)	0.37
Severe ROP or death	515/1581 (33%)	408/1501(27%)	0.0011	0.73 (0.60-0.87)	0.0007
Death by discharge	358/1614 (22%)	285/1519 (19%)	0.017		

Characters 2518

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To: [Wrage, Lisa Ann](#)
Cc: [Wally Carlo, M.D.](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); wacarlo@uab.edu; [Jackie LeVan](#)
Subject: Re: revised abstract
Date: Wednesday, October 03, 2012 10:41:50 AM

Lisa:

Thanks a lot

I just checked: We already have univariate analysis of death at 36 weeks and at discharge in the report you have sent me.

Luc

Sent from my iPad

On Oct 3, 2012, at 9:34 AM, "Wrage, Lisa Ann" <wrage@rti.org> wrote:

Hi Luc,

Infants were not included if they were indicated as having 'Syndrome and/or major malformation', NGG03 question I.1='Y' (I.1='Y' on 2011 form) *or* if contributory cause of death was indicated as 'congenital malformation'.

I'll work on the death information.

Lisa

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The future of medicine, today.

From: Luc Brion
To: Wrage, Lisa Ann; Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Jackie LeVan
Subject: FW: revised abstract
Date: Tuesday, October 02, 2012 10:55:44 PM
Attachments: Changes in Therapy and Outcomes Associated with the SUPPORT Trial 100212_rev2wc.doc
drintubchisq_28SEP12.rtf
Report_27Sept12.doc
Revised Jackie LeVan Protocol 12-22-11 rev.docx

Wally and Abhik;

Thanks for all your comments.

The only post-hoc analysis is the chi-square analysis done with all the patients, in contrast with the non-parametric regression, which was done using an n of 11 (centers).

The second table includes the three primary outcome parameters that were agreed upon.

FYI I attach the protocol as it was accepted by the GDB in December, and all the results of the tests done so far by Lisa.

Abhik, Rose, Lisa, Wally: please advise regarding posthoc analyses: chi-square before/after SUPPORT and multivariate analysis of death.

I will start entering the information on the PAS website to check size.

Thanks for all the help and comments.

Best regards,

Luc

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From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]

Sent: Tuesday, October 02, 2012 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Luc Brion
Subject: RE: revised abstract

Hi Rose and Luc:

Excellent idea. I have some comments particularly about the use of exploratory analysis and competing outcomes. See my tracked suggestions.

Thanks for the opportunity to comment. Sorry if I had missed the email earlier.

Wally

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 02, 2012 1:46 PM
To: Wally Carlo (wacarlo@uab.edu)
Cc: (Luc.Brion@UTSouthwestern.edu)
Subject: FW: revised abstract

Wally—

As we discussed, please look this over and send in your comments

Rose

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Sent: Tuesday, October 02, 2012 1:00 PM
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; nfiner@ucsd.edu; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: revised abstract

Here is a revised abstract with leading zero's (picked by Myra).

Luc

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UT Southwestern Medical Center
The future of medicine, today.

CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL. *Jaelyn M LeVan, Luc P Brion, Lisa Wrage, Myra H Wyckoff, Pablo J Sánchez, Roy Heyne, Mambarambath Jaleel, Neil Finer, Abhik Das, Barbara Stoll, Rose Higgins, Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.*

BACKGROUND

The NICHD Neonatal Research Network (NRN) SUPPORT trial was a 2 X 2 factorial trial, in which preterm neonates 24-27^{6/7} weeks' gestational age (GA) were randomized at birth to two interventions: (1) continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85 to 89% or 91 to 95%. The primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks), and death or severe retinopathy of prematurity (ROP) were not affected by the interventions. However, death was more frequent and severe ROP less frequent among infants randomized to low O₂ saturation targets. We hypothesized that (1) the percentage (%) of DR intubation would decrease after publication of SUPPORT, without affecting BPD or death and ROP or death; and (2) the decrease in DR intubation in each center would depend on the % of pre-SUPPORT DR intubation.

OBJECTIVE

To compare DR intubation, BPD or death at 36 weeks, and severe ROP or death before discharge in time periods before SUPPORT and after its publication.

DESIGN/METHODS

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24-27^{6/7} weeks GA born before (2003-04) and after SUPPORT (2010-11) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with known malformations and those receiving comfort care.

RESULTS

This study included 3151 infants (1617 pre-SUPPORT and 1534 post-SUPPORT).

Baseline Characteristics	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value
Birth weight (g) (mean ±SD)	824±191	816±190	0.23
Gestational Age (weeks)	26±1	26±1	0.64
Antenatal corticosteroids	1338/1616* (83%)	1358/1532 (89%)	<0.0001
Race/ethnicity: Black Not Hispanic (NH); White NH, Hispanic; Other (%)	45:37:15:3	44:38:14:5	0.02
Cesarean section	1004 (62%)	1009 (66%)	0.03
Rupture of membranes > 24 hours	436/1586 (27%)	360/1482 (24%)	0.043
Maternal hypertension	322 (20%)	409/1532 (25%)	<0.0001
Maternal diabetes	42 (3%)	84 (5%)	<0.0001

*Denominator indicates missing data

Comment [WC1]: Because of space limitations, you could address baseline differences in text format to allow more space for results. You already appear to be over the word limit.

Comment [WC2]: You may want to be more consistent in the formatting of the table including specifying n/N, %, M±SD and units of measure as appropriate and include the denominator every time rather than on the top of the columns.

Formatted: Indent: Left: 0.5"

Parameters of Assessment	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value	Adjusted OR (95% CI)	Adjusted p-value
Intubated in DR	1313 (81%)	1082 (71%)	<0.0001	0.55 (0.46-0.67)	<0.0001
BPD or death	970 (60%)	824/1522 (54%)	0.0009	1.1 (0.91-1.3)	0.37
Severe ROP or death	515/1581 (33%)	408/1501(27%)	0.0011	0.73 (0.60-0.87)	0.0007

The %proportion of patients intubated in the DR was significantly lower in the post-SUPPORT group than in the pre-SUPPORT group (Table). The odds ratio (OR) of DR intubation (post vs. pre-SUPPORT) remained significant (Table) after adjusting for GA group (24-25^{6/7} vs. 26-27^{6/7} weeks), 100-grams birth weight groups, gender, race/ethnicity, multiple birth, antenatal steroids, prolonged rupture of membranes, cesarean section, maternal hypertension, maternal diabetes and center. The OR of ROP or death (adjusted for these variables and for surfactant), but not that of BPD or death, was significantly different from 1. The correlation between pre-SUPPORT center-specific % of DR intubation and the change after SUPPORT was not significant (Spearman $r = -0.38$; $p = 0.25$). Centers with $\geq 80\%$ DR intubation pre-SUPPORT were likely to have a significant reduction post-SUPPORT ($p < 0.0001$) whereas centers with $< 80\%$ DR intubation pre-SUPPORT were not ($p = 0.54$).

CONCLUSIONS

The adjusted odds of DR intubation, and that of death or ROP, but not that of death or BPD, significantly decreased after publication of SUPPORT in NRN centers involved in the trial. DR intubation was more likely to decrease after SUPPORT in centers with $\geq 80\%$ pre-SUPPORT DR intubation.

39924000 characters

Comment [WC3]: I would add death as a row as it is an outcome with more long term relevance and is the competing outcome of the outcomes of interest. This may also clarify the adjustment in BPD OR. You could also have BPD and ROP reported separately.

Comment [WC4]: It is interesting that the adjustment causes the OR to be above 1 even though there is a lower BPD/death rate post-SUPPORT in the unadjusted analysis.

Comment [WC5]: I think you are over the word limit but this sentence APPEARS to contradict the following sentence but it is probably due to the small number of centers and the large variability in changes. Did you compare absolute or relative change? There can be arguments in support of either. I think absolute difference analysis would bias in favor of your hypothesis. I would ask Abhik for help discerning the association and the best statistical approach to study it.

Comment [WC6]: These are arbitrary cut-offs which may have to be justified. It may be best to keep this out of the abstract and Conclusions.

Comment [WC7]: This analysis is from exploratory analysis. It should not be emphasized.

Neonatal Research Network

28SEP12 08:45

Tables of intubation in DR by pre/post SUPPORT epoch
grouped by: Centers with pre SUPPORT % dr intubations < 80, and >= 80

The FREQ Procedure

Table 1 of post_SUPPORT by intubated_dr			
Controlling for prepctl80=No			
post_SUPPORT	intubated_dr(intubated in the delivery room, 1=Yes)		
Frequency Row Pct	No	Yes	Total
No	116 9.80	1068 90.20	1184
Yes	252 23.03	842 76.97	1094
Total	368	1910	2278

Statistics for Table 1 of post_SUPPORT by intubated_dr
Controlling for prepctl80=No

Statistic	DF	Value	Prob
Chi-Square	1	73.5613	<.0001
Likelihood Ratio Chi-Square	1	74.7199	<.0001
Continuity Adj. Chi-Square	1	72.5872	<.0001
Mantel-Haenszel Chi-Square	1	73.5290	<.0001
Phi Coefficient		-0.1797	
Contingency Coefficient		0.1769	
Cramer's V		-0.1797	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	116
Left-sided Pr <= F	4.560E-18
Right-sided Pr >= F	1.0000
Table Probability (P)	2.926E-18
Two-sided Pr <= P	8.532E-18

Sample Size = 2278

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28SEP12 08:45

Tables of intubation in DR by pre/post SUPPORT epoch
 grouped by: Centers with pre SUPPORT % dr intubations < 80, and >= 80

The FREQ Procedure

Table 2 of post_SUPPORT by intubated_dr			
Controlling for prepctl80=Yes			
post_SUPPORT	intubated_dr(intubated in the delivery room, 1=Yes)		
Frequency Row Pct	No	Yes	Total
No	188 43.42	245 56.58	433
Yes	200 45.45	240 54.55	440
Total	388	485	873

Statistics for Table 2 of post_SUPPORT by intubated_dr
 Controlling for prepctl80=Yes

Statistic	DF	Value	Prob
Chi-Square	1	0.3666	0.5449
Likelihood Ratio Chi-Square	1	0.3666	0.5449
Continuity Adj. Chi-Square	1	0.2887	0.5910
Mantel-Haenszel Chi-Square	1	0.3662	0.5451
Phi Coefficient		-0.0205	
Contingency Coefficient		0.0205	
Cramer's V		-0.0205	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	188
Left-sided Pr <= F	0.2955
Right-sided Pr >= F	0.7497
Table Probability (P)	0.0452
Two-sided Pr <= P	0.5859

Sample Size = 873

Neonatal Research Network

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Tables of intubation in DR by pre/post SUPPORT epoch
 grouped by: Centers with pre SUPPORT % dr intubations < 80, and >= 80

The FREQ Procedure

Summary Statistics for post_SUPPORT by intubated_dr
 Controlling for prepctl80

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)				
Statistic	Alternative Hypothesis	DF	Value	Prob
1	Nonzero Correlation	1	48.5068	<.0001
2	Row Mean Scores Differ	1	48.5068	<.0001
3	General Association	1	48.5068	<.0001

Estimates of the Common Relative Risk (Row1/Row2)				
Type of Study	Method	Value	95% Confidence Limits	
Case-Control (Odds Ratio)	Mantel-Haenszel	0.5426	0.4558	0.6460
	Logit	0.5477	0.4586	0.6542
Cohort (Col1 Risk)	Mantel-Haenszel	0.6537	0.5789	0.7381
	Logit	0.7218	0.6402	0.8139
Cohort (Col2 Risk)	Mantel-Haenszel	1.1432	1.1001	1.1879
	Logit	1.1591	1.1184	1.2013

Breslow-Day Test for Homogeneity of the Odds Ratios	
Chi-Square	26.2474
DF	1
Pr > ChiSq	<.0001

Total Sample Size = 3151

September 27, 2012

Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Updated from September 25 – additional variables added to models

Neonatal Network Investigator: J. LeVan, Luc Brion

RTI Statistician: Lisa Wrage

Population

Infants of 24-27 weeks gestational age at birth, born during years 2003-2004 or 2010-2011 at one of 11 centers participating in the SUPPORT trial and in the NRN from 2003-2011, excluding infants with known malformations or who had respiratory or other medical support withheld prior to death < 12 hours.

Methods

Primary outcome variables

The primary outcome variables of interest include intubation in the delivery room, BPD or death at 36 weeks, and severe ROP or death before discharge. Intubation in delivery room is recorded in the GDB. BPD is defined as oxygen use at 36 weeks. Severe ROP is defined using ophthalmology information from the GDB, NG03 section H (see appendix for details)

Secondary outcome variables

Other outcomes of interest include BPD, severe ROP, death before discharge, surfactant use, pneumothorax, pulmonary hemorrhage, postnatal steroid use, severe IVH, proven NEC, days of mechanical ventilation (survivors), days on supplemental oxygen (survivors), and length of hospital stay.

Other variables

Maternal and neonatal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Study groups

Infants from the study population were classified as 'pre-SUPPORT' if they were born during 2003-2004 and as 'post-SUPPORT' if they were born during 2010-2011.

Statistical Analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and ttests or Wilcoxon tests, as appropriate, for continuous variables. Logistic regression models were used to obtain adjusted results for each of the primary outcomes. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation rate during the first epoch.

Results

There were a total of n=5323 infants born at 24-27 weeks gestational age during 2003-2004 (n=2998) or 2010-2011 (n=2322) and included in the GDB. Of these n=1581 infants were born in NRN centers not included in this study and an additional n=352 were outborn, these infants were excluded. Of the remaining infants, n=134 infants with known malformations, n=100 infants who had respiratory or medical support withdrawn prior to death < 12 hours were excluded, and 5 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of n=3151 infants. Of these n=1617 infants are in the pre-SUPPORT group and n=1534 infants are in the post-SUPPORT group.

Power Calculations

Power calculations for each of the primary outcomes, based on chi square tests, an alpha of .05, and the sample sizes noted above give these results: a power of 1.0 to detect a change of delivery room intubation from 80% to 68%; a power of 0.8 to detect a change in outcome 'BPD or death' from 50% to 45%, and a power of 0.94 to detect a change in outcome severe ROP or death from 67% to 61%.

Statistical analysis

Unadjusted comparisons of variables of interest by study group are shown in **Tables 1-3**. Logistic regression models for each of the primary outcomes were also run to obtain adjusted results. The resulting adjusted odds ratios, 95% confidence intervals, and p-values are shown in **Table 2**. Additionally, within center, the percent of infants who were intubated in the delivery room was calculated for each study group and the difference between the post-SUPPORT group and the pre-SUPPORT group was also calculated. Using the results for the 11 centers in this study, the correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.38, $p=0.25$). (see appendix for SAS output for the logistic regression models and for the Spearman correlation).

Table 1. Maternal and Neonatal Characteristics¹

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
Birth weight (g)	824 (191)	816 (190)	0.23
Gestational Age (weeks)	25.7 (1.1)	25.6 (1.1)	0.64
% Male	858 (53.1)	767 (50.0)	0.09
Race:			
NH Black	727 (45.0)	654 (43.5)	0.02
NH White	603 (37.3)	566 (37.6)	
Hispanic	241 (14.9)	210 (14.0)	
Other	46 (2.8)	74 (4.9)	
Antenatal Steroids: betamethasone	953(59.1)	1344/1532 (87.7)	<.0001
Multiple birth	370 (22.9)	360/1532 (23.5)	0.68
Mode of delivery: c-section	1004 (62.1)	1009 (65.9)	0.03
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	360/1482 (24.3)	0.043
Maternal hypertension	322 (19.9)	409/1532 (24.7)	<.0001
Maternal diabetes	42 (2.6)	84 (5.5)	<.0001
Antibiotics	1198/1615 (74.2)	1114/1530 (72.8)	0.38

Table 2. Primary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²	adjusted OR ³ (95% CI)	adjusted p-value ³
Intubated in delivery room	1313 (81.2)	1082 (70.5)	<.0001	0.63 (0.51-0.77)	<.0001
BPD or death at 36 weeks	970 (60.0)	824/1523 (54.1)	.0009	1.06 (0.88-1.3)	0.53
Severe ROP or death	515/1581 (32.6)	408/1501(27.2)	.0011	0.80 (0.64-0.97)	0.024

Table 3. Secondary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
BPD (O2 at 36 weeks)	664/1311 (50.7)	581/1279 (45.4)	.008
Death at 36 weeks	306 (18.9)	243/1529 (15.9)	.026
Severe ROP	174 (13.5)	138 (10.8)	.036
Death before discharge	358/1614 (22.2)	285/1519 (18.8)	.017
Surfactant	1427 (88.3)	1266/1528 (82.9)	<.0001
Pneumothorax	135/1604 (8.4)	86/1511 (5.7)	.0030
Pulmonary Hemorrhage	181/1603 (11.3)	106/1512 (7.0)	<.0001
Postnatal Steroids	195/1599 (12.2)	182/1496 (12.2)	0.97
Days on ventilator (survivors)	22.3 (24.4), 13	18.5 (21.2), 10	<.0001
Days on supp. O2 (survivors)	59.2 (36)	56.8 (37.8)	0.10
Severe IVH	288 (18.5)	204 (13.8)	.0004
Proven NEC	177 (11.0)	160 (10.6)	0.71
Length of hospital stay (days)	84.4 (57.5), 83	90.9 (52.9), 90	.0006

¹ presented as mean (SD), median for days on ventilator and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.

² unadjusted p-values from Chi Square tests, ttests, or Wilcoxon tests, as appropriate.

³ OR reflects odds of the outcome for post_SUPPORT vs. pre_SUPPORT.

Appendix – Definition of severe ROP:

Severe ROP is defined as “retinal detachment (partial or complete), surgery, or Avastin/Anti-VEGf drug” using questions from NG03 section H ‘Ophthalmology’. Specifically, an infant is defined as having severe ROP if:

Using NG03 2002 – for the pre-SUPPORT group born 2003-2004:

- H.1.a.1.i. Highest Stage of ROP in right or left eye=4 or 5 (retinal detachment) ***or***
- H.3.a.i. retinal ablation performed prior to a threshold diagnosis in Right eye='Y' ***or***
- H.3.a.ii. retinal ablation performed prior to a threshold diagnosis in Left eye='Y' ***or***
- H.3.b.i. any surgery performed in Right eye=1,2,3,4 ***or***
- H.3.b.ii. any surgery performed in Left eye=1,2,3,4.

Using NG03 2008, 2011 – for the post-SUPPORT group born 2010-2011:

- H.1.b.1. retinal ablation performed in either eye='Y' ***or***
- H.1.b.2. scleral buckle or vitrectomy performed in either eye='Y' ***or***
- 2008 H.1.b.3.

Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***

2011 H.1.b.3. Avastin or other anti-VEGF drug='Y' ***or***

2011 H.1.b.4.

Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***

H.2. =2 - Determined severe ROP (ROP surgery, retinal detachment, Avastin or anti-VEGf) in either eye at status.

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LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	intubated_dr	intubated in the delivery room, 1=Yes
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	intubated_dr	Total Frequency
1	1	2304
2	0	733

Probability modeled is intubated_dr=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	1.2113	0.2543	22.6952	<.0001
post_SUPPORT		1	-0.4687	0.1034	20.5546	<.0001
ga2425		1	0.7892	0.1302	36.7255	<.0001
brwtgtp	1= <=600g	1	1.5891	0.2253	49.7592	<.0001
brwtgtp	2=601-700g	1	1.3445	0.1961	46.9995	<.0001
brwtgtp	3=701-800g	1	1.1025	0.1806	37.2791	<.0001
brwtgtp	4=801-900g	1	0.6913	0.1525	20.5414	<.0001
brwtgtp	5=901-1000g	1	0.5428	0.1532	12.5470	0.0004
malex		1	0.1522	0.0992	2.3560	0.1248
MULTBRTH		1	-0.3070	0.1213	6.4021	0.0114
antester_beta		1	-0.6588	0.1431	21.1928	<.0001
race_bwho	1=Black	1	-0.1722	0.1162	2.1960	0.1384
race_bwho	3=Hispanic	1	-0.2508	0.1772	2.0034	0.1569
race_bwho	4=Other	1	0.0626	0.2924	0.0458	0.8305
CSECT		1	0.3867	0.1084	12.7273	0.0004
ROMGT24		1	-0.1757	0.1161	2.2899	0.1302

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09:04 Monday, June 30, 2014 6

LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.6205	0.1290	23.1306	<.0001
diabetes		1	-0.3525	0.2335	2.2787	0.1312
CENTER	3	1	-0.3715	0.2519	2.1751	0.1403
CENTER	4	1	-0.0247	0.2817	0.0077	0.9301
CENTER	5	1	0.7656	0.2684	8.1382	0.0043
CENTER	9	1	-0.1973	0.2464	0.6413	0.4232
CENTER	11	1	-0.7581	0.1895	16.0115	<.0001
CENTER	12	1	0.7980	0.2518	10.0425	0.0015
CENTER	14	1	0.6604	0.2560	6.6519	0.0099
CENTER	15	1	-0.2131	0.2720	0.6137	0.4334
CENTER	16	1	-1.8287	0.1923	90.4280	<.0001
CENTER	18	1	0.5458	0.2343	5.4257	0.0198

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
post_SUPPORT		0.626	0.511	0.766
ga2425		2.202	1.706	2.842
brwtgtp	1= <=600g vs 6=>1000g	4.899	3.150	7.619
brwtgtp	2=601-700g vs 6=>1000g	3.836	2.612	5.634
brwtgtp	3=701-800g vs 6=>1000g	3.012	2.114	4.290
brwtgtp	4=801-900g vs 6=>1000g	1.996	1.480	2.692
brwtgtp	5=901-1000g vs 6=>1000g	1.721	1.274	2.324
malex		1.164	0.959	1.414
MULTBRTH		0.736	0.580	0.933
antester_beta		0.517	0.391	0.685
race_bwho	1=Black vs 2=White	0.842	0.670	1.057
race_bwho	3=Hispanic vs 2=White	0.778	0.550	1.101
race_bwho	4=Other vs 2=White	1.065	0.600	1.888
CSECT		1.472	1.190	1.821
ROMGT24		0.839	0.668	1.053
htn		0.538	0.418	0.692
diabetes		0.703	0.445	1.111

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09:04 Monday, June 30, 2014 7

LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect			Point Estimate	95% Wald Confidence Limits
CENTER	3	vs 19	0.690	0.421 1.130
CENTER	4	vs 19	0.976	0.562 1.694
CENTER	5	vs 19	2.150	1.271 3.638
CENTER	9	vs 19	0.821	0.506 1.331
CENTER	11	vs 19	0.469	0.323 0.679
CENTER	12	vs 19	2.221	1.356 3.638
CENTER	14	vs 19	1.936	1.172 3.197
CENTER	15	vs 19	0.808	0.474 1.377
CENTER	16	vs 19	0.161	0.110 0.234
CENTER	18	vs 19	1.726	1.090 2.732

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LOGISTIC MODELS
OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	bpddeath36	BPD or death at 36 weeks
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	bpddeath36	Total Frequency
1	1	1578
2	0	1286

Probability modeled is bpddeath36=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.5159	0.2783	159.6514	<.0001
post_SUPPORT		1	0.0606	0.0975	0.3864	0.5342
intubated_dr		1	0.1302	0.1317	0.9772	0.3229
ga2425		1	0.3412	0.1197	8.1263	0.0044
brwtgtp	1= <=600g	1	2.2784	0.2774	67.4438	<.0001
brwtgtp	2=601-700g	1	1.3606	0.1952	48.5834	<.0001
brwtgtp	3=701-800g	1	1.0281	0.1694	36.8283	<.0001
brwtgtp	4=801-900g	1	0.7018	0.1493	22.0935	<.0001
brwtgtp	5=901-1000g	1	0.5082	0.1518	11.2067	0.0008
sga		1	0.1167	0.2074	0.3166	0.5736
malex		1	0.7661	0.0924	68.8146	<.0001
MULTBRTH		1	-0.1677	0.1109	2.2862	0.1305
antester_beta		1	0.0925	0.1192	0.6023	0.4377
race_bwho	1=Black	1	-0.2062	0.1071	3.7097	0.0541
race_bwho	3=Hispanic	1	-0.2096	0.1539	1.8553	0.1732
race_bwho	4=Other	1	-0.3795	0.2452	2.3962	0.1216
CSECT		1	-0.0901	0.0987	0.8338	0.3612
ROMGT24		1	-0.0638	0.1071	0.3540	0.5518

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LOGISTIC MODELS
OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.1063	0.1208	0.7753	0.3786
diabetes		1	0.0635	0.2259	0.0789	0.7787
SURFACT		1	0.7564	0.1609	22.1057	<.0001
fio24ge90		1	1.3426	0.3165	17.9897	<.0001
pda_ligation		1	0.7154	0.1595	20.1311	<.0001
pda_indom		1	0.4671	0.1059	19.4420	<.0001
LOS		1	0.6069	0.0990	37.5517	<.0001
CENTER	3	1	0.9273	0.2296	16.3156	<.0001
CENTER	4	1	1.1417	0.2496	20.9259	<.0001
CENTER	5	1	2.2141	0.2377	86.7587	<.0001
CENTER	9	1	1.2351	0.2310	28.5861	<.0001
CENTER	11	1	1.7539	0.1889	86.2447	<.0001
CENTER	12	1	2.3285	0.2191	112.9164	<.0001
CENTER	14	1	1.2571	0.2077	36.6489	<.0001
CENTER	15	1	1.8008	0.2607	47.7070	<.0001
CENTER	16	1	0.7062	0.1962	12.9599	0.0003
CENTER	18	1	1.2842	0.2002	41.1427	<.0001

Odds Ratio Estimates			
Effect		Point Estimate	95% Wald Confidence Limits
post_SUPPORT		1.062	0.878 1.286
intubated_dr		1.139	0.880 1.475
ga2425		1.407	1.113 1.779
brwtgtp	1= <=600g vs 6=>1000g	9.761	5.667 16.813
brwtgtp	2=601-700g vs 6=>1000g	3.899	2.659 5.716
brwtgtp	3=701-800g vs 6=>1000g	2.796	2.006 3.897
brwtgtp	4=801-900g vs 6=>1000g	2.017	1.506 2.703
brwtgtp	5=901-1000g vs 6=>1000g	1.662	1.234 2.238
sga		1.124	0.748 1.687
malex		2.151	1.795 2.578
MULTBRTH		0.846	0.680 1.051
antester_beta		1.097	0.868 1.386
race_bwho	1=Black vs 2=White	0.814	0.660 1.004
race_bwho	3=Hispanic vs 2=White	0.811	0.600 1.096
race_bwho	4=Other vs 2=White	0.684	0.423 1.106

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
CSECT	0.914	0.753	1.109
ROMGT24	0.938	0.761	1.157
htn	0.899	0.710	1.139
diabetes	1.066	0.684	1.659
SURFACT	2.131	1.554	2.920
fio24ge90	3.829	2.059	7.120
pda_ligation	2.045	1.496	2.795
pda_indom	1.595	1.296	1.963
LOS	1.835	1.511	2.228
CENTER 3 vs 19	2.528	1.612	3.964
CENTER 4 vs 19	3.132	1.920	5.109
CENTER 5 vs 19	9.153	5.744	14.584
CENTER 9 vs 19	3.439	2.187	5.408
CENTER 11 vs 19	5.777	3.990	8.365
CENTER 12 vs 19	10.263	6.679	15.768
CENTER 14 vs 19	3.515	2.340	5.281
CENTER 15 vs 19	6.054	3.632	10.092
CENTER 16 vs 19	2.026	1.380	2.976
CENTER 18 vs 19	3.612	2.440	5.347

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	sevropdeath	severe ROP or death
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	sevropdeath	Total Frequency
1	1	887
2	0	2085

Probability modeled is sevropdeath=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.7160	0.3056	78.9797	<.0001
post_SUPPORT		1	-0.2275	0.1009	5.0875	0.0241
ga2425		1	0.6591	0.1126	34.2712	<.0001
brwtgtp	1= <=600g	1	2.7580	0.2171	161.4150	<.0001
brwtgtp	2=601-700g	1	1.7164	0.2008	73.0686	<.0001
brwtgtp	3=701-800g	1	1.0975	0.1955	31.5278	<.0001
brwtgtp	4=801-900g	1	0.5279	0.1929	7.4867	0.0062
brwtgtp	5=901-1000g	1	0.2972	0.2031	2.1405	0.1435
malex		1	0.6057	0.0954	40.3424	<.0001
MULTBRTH		1	0.2068	0.1135	3.3219	0.0684
antester_beta		1	-0.3822	0.1214	9.9194	0.0016
race_bwho	1=Black	1	-0.3434	0.1143	9.0340	0.0027
race_bwho	3=Hispanic	1	0.3656	0.1648	4.9191	0.0266
race_bwho	4=Other	1	0.9008	0.2527	12.7124	0.0004
CSECT		1	-0.1123	0.1044	1.1581	0.2819
ROMGT24		1	-0.1955	0.1138	2.9493	0.0859
htn		1	-0.4465	0.1289	11.9932	0.0005
diabetes		1	0.4642	0.2343	3.9249	0.0476

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
SURFACT		1	0.4952	0.1705	8.4313	0.0037
CENTER	3	1	0.2831	0.2427	1.3606	0.2434
CENTER	4	1	0.3981	0.2596	2.3506	0.1252
CENTER	5	1	1.0627	0.2224	22.8359	<.0001
CENTER	9	1	0.3015	0.2452	1.5118	0.2189
CENTER	11	1	0.2869	0.1987	2.0850	0.1487
CENTER	12	1	0.4161	0.2137	3.7913	0.0515
CENTER	14	1	-0.8750	0.2469	12.5578	0.0004
CENTER	15	1	-0.4073	0.2902	1.9688	0.1606
CENTER	16	1	0.2082	0.2068	1.0138	0.3140
CENTER	18	1	0.1953	0.2132	0.8394	0.3596

Odds Ratio Estimates					
Effect			Point Estimate	95% Wald Confidence Limits	
post_SUPPORT			0.797	0.654	0.971
ga2425			1.933	1.550	2.410
brwtgtp	1= <=600g	vs 6=>1000g	15.769	10.304	24.132
brwtgtp	2=601-700g	vs 6=>1000g	5.564	3.754	8.248
brwtgtp	3=701-800g	vs 6=>1000g	2.997	2.043	4.395
brwtgtp	4=801-900g	vs 6=>1000g	1.695	1.162	2.475
brwtgtp	5=901-1000g	vs 6=>1000g	1.346	0.904	2.004
malex			1.833	1.520	2.209
MULTBRTH			1.230	0.985	1.536
antester_beta			0.682	0.538	0.866
race_bwho	1=Black	vs 2=White	0.709	0.567	0.887
race_bwho	3=Hispanic	vs 2=White	1.441	1.043	1.991
race_bwho	4=Other	vs 2=White	2.462	1.500	4.039
CSECT			0.894	0.728	1.097
ROMGT24			0.822	0.658	1.028
htn			0.640	0.497	0.824
diabetes			1.591	1.005	2.518
SURFACT			1.641	1.175	2.292
CENTER	3	vs 19	1.327	0.825	2.136
CENTER	4	vs 19	1.489	0.895	2.477
CENTER	5	vs 19	2.894	1.872	4.475

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LOGISTIC MODELS
OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CENTER	9 vs 19	1.352	0.836	2.186
CENTER	11 vs 19	1.332	0.903	1.967
CENTER	12 vs 19	1.516	0.997	2.305
CENTER	14 vs 19	0.417	0.257	0.676
CENTER	15 vs 19	0.665	0.377	1.175
CENTER	16 vs 19	1.231	0.821	1.847
CENTER	18 vs 19	1.216	0.800	1.846

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publications | Stevens, SUPPORT Breathing Outcomes
Date: Tuesday, October 02, 2012 2:48:00 PM

Leave her for now and I will send Brenda an email

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From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, October 02, 2012 2:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Publications | Stevens, SUPPORT Breathing Outcomes

What about Anna Dusick?

Stephanie Wilson Archer
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 02, 2012 2:45 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publications | Stevens, SUPPORT Breathing Outcomes

Don't strike anyone out – all FU PIs are to be included as per the original plan with the study.

You can send to the sites

Rose

Rosemary D. Higgins, MD

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From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, October 02, 2012 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Publications | Stevens, SUPPORT Breathing Outcomes

Working on the author list and boilerplate for Tim Stevens' Breathing Outcomes paper. Can you look this over to see if it looks OK? Those with strikeout are second authors from the same center as someone on the SUPPORT Subcommittee.

Steph

From: Luc Brion
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; nfiner@ucsd.edu; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: revised abstract
Date: Tuesday, October 02, 2012 1:01:56 PM
Attachments: Changes in Therapy and Outcomes Associated with the SUPPORT Trial 100212.rev2.doc

Here is a revised abstract with leading zero's (picked by Myra).

Luc

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Application to the NICHD GDB Committee

**Changes in Therapy and Outcomes Associated
with The SUPPORT Trial**

**Jaclyn LeVan, DO, Myra Wyckoff, MD, Pablo Sánchez, MD, Roy Heyne, MD,
Mambarambath Jaleel, MD, Luc P Brion, MD,
Neil Finer (SUPPORT Subcommittee), Abhik Das,
Barbara Stoll, MD, Rose Higgins, MD**

For the NICHD Neonatal Research Network

Version 4

12/22/11

A. ABSTRACT:

We propose an observational study (before/after study design) of GDB data to examine the changes in clinical practices and outcomes following the results of the SUPPORT Trial.

B. STATEMENT of the PROBLEM

The SUPPORT trial (Finer 2010; Carlo 2010) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in June 2010. The rates of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7. Among infants with gestational age (GA) 24 0/7 weeks to 25 6/7 weeks, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group.

The rates of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups. However, in the lower oxygen saturation target group, death was significantly more frequent while severe retinopathy of prematurity among survivors occurred significantly less often.

In a retrospective study conducted at Parkland Memorial Hospital, we found that the frequency of DR intubation among GA-matched infants (who did not participate in the SUPPORT trial) decreased significantly after initiation of the SUPPORT trial (Brion 2008; LeVan 2012).

C. HYPOTHESES:

1. We hypothesize that release of the results of the SUPPORT Trial would be followed by a decrease in frequency of endotracheal intubation in the DR in preterm infants with GA between 24 0/7 and 27 6/7 weeks, and that the decrease in the frequency of DR intubation in each NRN center would depend on baseline rate before the trial.
2. We hypothesize that the release of the SUPPORT trial results would not affect the rate of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age (BPD, defined by O₂ requirement at 36 weeks of postmenstrual age), or the rate of death or severe ROP (defined as ROP surgery or retinal detachment).

D. SPECIFIC AIMS:

1. To determine the impact of the results of the SUPPORT trial on clinical practice, specifically the incidence of endotracheal intubation in the DR in preterm inborn infants
2. To determine the impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between 24 0/7 and 27 6/7 weeks, including: incidence of death or BPD at 36 weeks' postmenstrual age (defined by O₂ requirement at 36 weeks of postmenstrual age) and incidence of death or severe ROP (defined as ROP surgery or retinal detachment).

E. RATIONALE/JUSTIFICATION:

We submit the current proposal to compare therapy and outcomes in two cohorts of patients: one before the SUPPORT Trial, and one after release of the results of the SUPPORT Trial to all centers at the Steering Committee in November 2009. The study will be limited to the 11 centers that participated in the SUPPORT Trial and were active members of the NICHD NRN during these two periods.

The SUPPORT trial showed no difference in primary outcome between the two respiratory support strategies but advantages of early CPAP on four secondary outcomes: rate of intubation, rate of postnatal steroids for BPD, days of mechanical ventilation among survivors, and rate of being alive and off mechanical ventilation by day 7.

Among infants with gestational age (GA) 24 0/7 weeks to 25 6/7 weeks, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group.

We expect that providers using endotracheal intubation as standard of care in the DR before the SUPPORT trial would change their attitudes towards more CPAP and less intubation after the release of the results of the SUPPORT Trial and several other trials described below. The intubation rate among extremely low birth weight infants was high (80%) in NRN centers in 1993-1997 (Shankaran 2002) and was still high at Parkland Memorial Hospital in 2005 before starting enrollment into the SUPPORT trial (Brion 2008, LeVan 2012). Since there is substantial heterogeneity in therapy and outcomes across NRN centers, we expect that the change in practice after release of the results of the SUPPORT trial would be inversely related to the baseline rate of intubation in each center. We would expect a decrease in the rate of intubation after the SUPPORT trial in centers that predominantly used intubation in the DR before initiating enrollment, but less change in the rate of intubation in centers that were using higher rates of CPAP before initiating enrollment.

The SUPPORT trial showed no difference in primary outcome between the two oxygen saturation targets, but showed significantly higher mortality and lower rate of ROP with low oxygen saturation target. Specifically the trial showed that targeting lower oxygen saturation resulted in one additional death for approximately every 2 cases of severe ROP prevented. Since the SUPPORT trial is the first trial to show that targeting low oxygen saturation significantly increases mortality in extremely preterm infants, some centers or

providers using low oxygen saturation target before the SUPPORT trial might consider increasing their target levels or their alarm limits after releasing the results of the SUPPORT trial. However several centers or providers may choose to wait instead for the release of long-term data results from the SUPPORT trial and for the results of additional trials (e.g., the BOOST-II UK trial (Johnston 2011)).

F. BACKGROUND/PREVIOUS STUDIES:

F.1. CPAP vs. endotracheal intubation and surfactant:

Prophylactic and early natural surfactant administration at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in intubated preterm infants who either are at risk for respiratory distress syndrome (< 30 weeks of GA) or have established respiratory distress syndrome (Soll 1997, Soll 1999, Soll 2001). Several studies have suggested a benefit for early CPAP for preterm infants with respiratory distress syndrome, including a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity (Avery 1987, Van Marter 2000, VanPee 2007, Jonsson 1997, Gitterman 1997) except for an increase in the risk of pneumothorax (summary relative risk 2.36; 95% confidence interval 1.25, 5.54) (Ho 2002). In one observational study, 76% of infants with a birth weight \leq 1250 g who were initially treated with CPAP did not require intubation within 72 hours (Ammari 2005).

The NICHD Feasibility Trial (Finer 2004) was designed to determine the feasibility of randomizing ELBW infants of < 28 weeks' gestation to CPAP/positive end expiratory pressure (PEEP) or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine DR intubation for surfactant administration. Forty-five percent (47 of 104) of infants < 28 weeks' gestation required intubation for resuscitation in the DR. CPAP/ PEEP in the DR did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life.

Several multicenter randomized controlled trials (RCTs) have compared early CPAP with intubation in the DR. The IFDAS trial (Thomson 2001) showed no significant difference between 4 groups (Elective intubation with surfactant administration and extubation within 2 hrs; early nasal CPAP with selective short intubation for surfactant administration; elective intubation with surfactant administration and artificial ventilation; selective intubation with surfactant administration and artificial ventilation based on clinical criteria) in total respiratory support until estimated date of delivery or discharge home (if earlier) and other neonatal complications. However, this study was not powered for any of the outcomes.

COIN Trial:

The COIN trial (Morley 2008) randomized 610 infants from 25 0/7 to 28 6/7 weeks gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress. Infants were randomized, either to intubation and ventilation, or to CPAP at 8 cm H₂O with intubation for those who met failure criteria. The primary outcome of death or BPD at 36 weeks was similar in the CPAP and in the intubation arms 33.9% vs. 38.9%,

(odds ratio=0.58 to 1.12; P=0.19). Infants randomized to CPAP had a higher frequency of pneumothorax (9.1% vs. 3.0%, p=0.001) and a lower frequency of death or need for oxygen at 28 days (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

CURPAP

Sandri et al randomized 208 25-28 weeks GA infants to assess whether prophylactic surfactant followed by CPAP compared with early CPAP with early selective surfactant would reduce the need for mechanical ventilation in the first 5 days of life (Sandri 2008). They found no difference in the rate of mechanical ventilation during the first 5 days of life, nor in the rate of death and type of survival at 28 days of age or 36 weeks of postmenstrual age.

The Columbian Neonatal Research Network randomized 279 preterm 27-31 week GA infants to either very early surfactant, extubation, and nasal continuous positive airway pressure (treatment group) or nasal continuous airway pressure alone (control group) (Rojas 2009). They found that allocation to the treatment group decreased the need for subsequent mechanical ventilation, and decreased the incidence of air-leak syndrome, but did not affect the rate of chronic lung disease defined as oxygen requirement at 36 weeks of postmenstrual age.

SUPPORT Trial (extracted from Finer 2010 and Carlo 2010):

The SUPPORT trial (Finer 2010; Carlo 2010) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the DR and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The study enrolled 1316 infants.

The primary outcome of the CPAP vs. surfactant trial was the rate of composite primary outcome of death or bronchopulmonary dysplasia (BPD) defined by requirement for oxygen or positive pressure support with CPAP or mechanical ventilation at 36 weeks (with an attempt to remove oxygen in neonates receiving less or equal to 30% oxygen).

The rates of the primary outcome (death or BPD at 36 weeks) were not significantly different between the CPAP and surfactant groups (47.8% vs. 51.0%, Relative risk (RR) 0.95 (95% Confidence interval (CI) 0.85, 1.05, adjusting for GA, center and familial clustering). In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

In post hoc stratified analyses of secondary outcomes, among infants who were born between 24 weeks 0 days and 25 weeks 6 days of gestation, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group (rate of death during hospitalization: 23.9% vs. 32.1%; relative risk with CPAP, 0.74; 95% confidence interval [CI], 0.57 to 0.98; P = 0.03; rate of death at 36 weeks: 20.0% vs. 29.3%; relative risk, 0.68; 95% CI, 0.5 to 0.92; P = 0.01.

The Vermont Oxford Network randomized 648 preterm infants to one of 3 approaches to the initial management: prophylactic surfactant followed by a period of mechanical ventilation (prophylactic surfactant [PS]); prophylactic surfactant with rapid extubation to bubble CPAP (intubate-surfactant-extubate [ISX]) or initial management with nasal bubble CPAP and selective surfactant treatment (nCPAP) (Dunn 2011). When compared with the PS group, the relative risk of BPD or death was 0.78 (95% confidence interval: 0.59-1.03) for the ISX group and 0.83 (95% CI: 0.64-1.09) for the nCPAP group. There were no statistically significant differences in mortality or other complications of prematurity. In the CPAP group, 48% were managed without intubation and ventilation, and 54% without surfactant treatment.

Retrospective study at Parkland Memorial Hospital:

A retrospective study (Brion 2008; LeVan 2012) was conducted at Parkland Memorial Hospital to assess the impact of SUPPORT trial initiation in July 2005 on patient management and short-term outcomes in non-participant preterm infants. We analyzed two prospective databases: the resuscitation registry and the neonatal intensive care unit (NICU) database. We included inborn infants with GA < 35 weeks during 3 epochs: 1st epoch before SUPPORT trial (01/03-06/05), 2nd epoch during SUPPORT trial recruitment at Parkland (07/05-02/09), and 3rd epoch after SUPPORT trial recruitment (3/09-6/10)]. We excluded infants who received comfort care only (infants with lethal congenital anomalies or chromosomal abnormalities and GA less than 23 weeks), and those enrolled in the SUPPORT trial.

Among neonates < 28 weeks of GA, initiation of the SUPPORT trial was associated with a significant decrease in the rate of intubation in the DR, and increase in the rate of early intubation (< 4 hours of age) in the NICU, decrease in the rate of surfactant administration for respiratory distress syndrome, an increase in the rate of DRCPAP, and an increase in the rate of pneumothorax but with no change in the rate of death or BPD (defined as O2 requirement at 28 days; physiologic definition of BPD was not in the database in 2003-05 cohort). Most pneumothoraces occurred in patients who were intubated in the DR. In multivariate analysis pneumothorax was associated with epoch and with administration of surfactant for respiratory distress syndrome (RDS). The rate of death or BPD was significantly associated with need for respiratory support (DR intubation, DR CPAP, surfactant for RDS), with low GA and low weight for GA, but not with epoch.

	1st Epoch N=180	2nd Epoch N=230	3rd Epoch N=78	P
DRintubation	78%	55%	60%	<0.0001
DRCPAP	27%	51%	62%	<0.0001
Early NICU intubation	4%	9%	13%	0.02
Surfactant	69%	56%	64%	0.03
Pneumothorax	7%	10%	18%	0.02
Death or BPD	52%	45%	57%	0.26

F.2. Oxygen administration upon admission to the neonatal intensive care unit:

Trials published in the 1950's comparing restricted ($\leq 50\%$, only for clinical indication or

cyanosis) versus unrestricted (routine for 2-4 weeks or until reaching 1500 g) ambient oxygen in very low birth weight infants upon admission or within the first 48 hours showed a significant reduction in ROP and severe ROP (Duc 1992, Askie 2009) without a significant change in mortality (risk difference 4.9%, 95% CI -5.2, + 14.9; risk ratio 1.23, 95% CI 0.80, 1.90). Observational studies have suggested that targeting low oxygen saturation upon admission in very preterm infants may reduce the risk of ROP (Tin 2007) without increasing mortality (Chow 2003, Deulofeut 2007, Wright 2006). No randomized trials until the SUPPORT trial have assessed the effect of targeting different oxygen saturation levels upon admission on morbidity and mortality in very preterm infants.

SUPPORT Trial:

The primary outcome of the oxygen saturation trial component of the SUPPORT trial was a composite of severe ROP (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) and/or death before discharge from the hospital. The rates of the primary outcome of the oxygen saturation trial (severe ROP or death) were not significantly different between the two oxygen saturation target groups (28.3 vs. 32.1%, respectively; relative risk (RR) 0.90; 95% confidence interval (CI) 0.76, 1.06; $p=0.21$). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs. 16.2%; RR 1.27; CI 1.01, 1.60; $p=0.04$) while severe retinopathy among survivors occurred less often in these infants (8.6 vs. 17.9%; RR 0.52; CI 0.37, 0.73; $p<0.001$). However, in the lower oxygen saturation target group, death was significantly more frequent, while severe retinopathy of prematurity among survivors occurred significantly less often. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

BOOST-II UK trial:

Further analysis of the oxygen saturation algorithm curve used in the SUPPORT Trial showed unexpectedly low frequency of saturation between 87 and 90%, which resulted from merging two separate curves (Johnston 2011). Recruitment into the BOOST-II UK trial (<https://www.npeu.ox.ac.uk/boost>, accessed 12/12/11) has now been completed. Babies in that trial have been randomized to keep the oxygen saturation level as much as possible in the range 85-89% and in the other group in the range 91-95%.

G. METHOD/PROCEDURES:

Study Design:

We propose a retrospective analysis of the GDB using a before/after design with one cohort of patients born before the date of initiation of the SUPPORT trial in each NRN center (1/1/2003-12/31/2004) and a second cohort of patients starting after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2011). We propose to use the 11 centers that participated in the SUPPORT trials and in the NRN during the cycles relevant to the two cohorts.

Study Population:

Cohorts:

We propose to analyze patients in the NRN GDB in two successive cohorts. The first cohort includes patients born during a 2-year period preceding the SUPPORT trial (from

1/1/2003-12/31/2004). The second cohort includes patients born after releasing results of the SUPPORT trial (1/1/2010-12/31/2011).

Eligibility and exclusion criteria:

We will use eligibility and exclusion criteria identical to those in the SUPPORT trial.

Entry criteria: Eligible infants are

- 24 0/7th to 27 6/7th weeks at birth by best obstetrical estimate,
- without known malformations
- inborn
- delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study span (2003-2012)

Exclusion criteria:

- Known malformations
- Respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours; we will include patients who died early, but exclude those whose support was either withheld or withdrawn.

The 11 sites participating in the NRN during the two selected cohorts and participating in the SUPPORT trial are:

Case Western

UTSW

Wayne

Emory

Cincinnati

Indiana

Brown

Stanford

Alabama

Houston

Duke

Gestational age strata:

We will analyze the same strata as in the SUPPORT trial: 24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks.

Study Intervention:

This is a retrospective study of prospectively collected GDB data with before/after study design comparing preterm infants before the date of initiation of the SUPPORT trial and after releasing results the SUPPORT Trial.

Primary/Secondary Outcomes:

We selected variables that are included in several versions of the GDB spanning the 2 cohorts for this study: 1998, 2002, 2008 and 2011.

Primary outcome variables:

The primary outcome variables will be comparisons of data in the 2 cohorts limited to centers participating in the SUPPORT Trial and in the NRN during the entire study span (2003-2012):

- a. The use of intubation in DR (CPAP is not listed in the 1998 and 2002 GDB)
- b. The incidence of composite of death or BPD at 36 weeks (O₂ requirement at 36 weeks of postmenstrual age). We will not use the physiologic definition of the BPD (Walsh 2003, Walsh 2004), which was not available in GDB in 2003-2004.
- c. The incidence of composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital. This outcome is similar but not identical to the primary outcome of the SUPPORT trial

Secondary outcome variables:

- Relationship between baseline intubation rate in each center before initiating enrollment into the SUPPORT trial and the change in intubation rate after releasing results of the SUPPORT trial
- Comparisons of data in the 2 cohorts:
 - BPD (defined by oxygen requirement at 36 weeks)
 - Death or BPD (defined by oxygen requirement at 36 weeks)
 - Mortality rate before discharge
 - ROP stage 3 or worse in either eye;
 - ROP plus disease in either eye;
 - ROP intervention
 - Surfactant administration (number of doses is not listed in 2011)
 - DR O₂,
 - DR bag and mask ventilation,
 - DR chest compressions,
 - DR epinephrine (other drugs are not listed in 2011 GDB Manual)
 - Apgar scores at 1 min and 5 min
 - Temperature within 60 min of birth
 - Pneumothorax
 - Pulmonary hemorrhage
 - Use of postnatal steroids for BPD
 - Duration of ventilation among survivors;
 - Duration of CPAP among survivors
 - FiO₂ at 24 hours
 - Duration of oxygen supplementation among survivors
 - Patent Ductus Arteriosus (PDA),
 - PDA requiring a cox inhibitor (indomethacin during either period or ibuprofen during the second epoch),
 - PDA requiring surgery
 - Severe intraventricular hemorrhage (grade III or IV)
 - Early onset sepsis
 - Late onset sepsis

- First day full feeds (< 20 ml/kg/day IV [2002] or > 120 ml/kg enterally [2008, 2011])
- Weight at 36 weeks
- Necrotizing enterocolitis (stage 2 or greater)
- Length of stay
- Weight at discharge
- Death under 12 hours
- Death or mechanical ventilation at day 7
- 2nd cohort only:
 - DR CPAP

Additional variables available in the GDB will be collected, including

1. Maternal variables: race/ethnicity, gestational age, diabetes, hypertension, singleton vs. multiple pregnancy, prolonged rupture of membranes, antenatal corticosteroids (betamethasone, any/full course), mode of delivery, antibiotics before delivery
2. Neonatal variables: birth weight, gender

Sample Size/Statistical Analysis:

Available sample size:

Data in GDB from January 2002 to December 2004 (DATA AND SAFETY MONITORING PLANS for the SUPPORT Trial) included 4055 infants with a gestational age 24 0/7 – 27 6/7. Assuming 10% exclusions, the first 2-year cohort (1/03-1/05) is estimated to yield approximately 2400 infants for analysis.

The GDB data for 2010 included 1776 inborn infants < 29 weeks gestational age. Therefore we estimate that the second cohort (1/1/10-12/31/11) would include approximately 2800 infants. This number would be reduced to 2400 infants taking into account the number of centers which are not included in the current NRN cycle.

Sample size calculations were based on currently available data:

1. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or survival with BPD (O₂ requirement at 36 weeks of postmenstrual age) of 67%,
2. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or threshold retinopathy of 50%
3. years 1993-1997 intubation rate of rate of 80% among extremely low birth weight infants (Shankaran 2002).
4. 2002-05 mortality rate of 21% in extremely low birth weight infants (Morris 2008)
5. 2002-05 severe ROP frequency of 20% in extremely low birth weight infants (Morris 2008)
6. These calculations will be readjusted to more recent values once we obtain data from the GDB. Specifically we will review data for the period between the

Feasibility Study and the SUPPORT trial, i.e., between February 2003 and January 2005.

For the primary outcome variables, we calculated power using chi-square analysis, a 1.67% level of significance (because we have three primary outcomes) and two-tailed tests. The available sample size ($n = 4800$, 2400 before SUPPORT versus 2400 after SUPPORT) gives a power $> 99\%$ to detect a significant change in DR intubation from 80% to 68% (15% relative risk reduction), a power of 85% to detect a change in death or BPD (by physiologic definition) from 50% to 45% (10% relative risk reduction), an a power of 97% to detect a change in death or severe ROP from 67 to 61% (10% relative risk reduction). For multivariate analyses, the sample size is much larger than 10 patients per covariate.

Bivariate analyses:

We will conduct bivariate analyses comparing the before SUPPORT and after SUPPORT cohorts with respect to variables related to mortality and all the outcomes listed above (antenatal steroids, gender, Apgar scores, etc.). Bivariate analyses will be done using chi-square analysis (Mantel-Haenszel chi-square for analyses by gestational age stratum) for categorical variables and using Student t-test or Mann-Whitney test as appropriate for continuous variables.

To test whether releasing results of the SUPPORT trial impacted mostly centers using infrequent intubation before the trial we will test whether the change in rate of intubation from the first to the second epoch in each center is inversely correlated with intubation rate during the first epoch. For this purpose we will use Spearman rank correlation coefficient or the Pearson correlation coefficient, depending on distribution of the data.

Assuming some centers decided to change their oxygen saturation targets based on the SUPPORT trial results, we will test whether mortality decreased and the rate of ROP increased in centers changing their oxygen saturation target from low (85 to 89% or lower) during the first epoch to high (e.g., 91 to 95%) during the second epoch, but not in the other centers. Because of the small number of centers, we will not be sufficiently powered for this analysis. Furthermore, it is possible that some centers may have changed their target range to different values from those selected for the SUPPORT trial. As an example, it is possible that some centers may have changed their lower saturation limit only.

Multivariate analyses:

We will create logistic regression models to predict primary outcomes based on epoch, center and the prespecified covariates (gestational age, antenatal corticosteroids, gender, singleton vs. multiple, birthweight by 100 g increment) (Tyson 2008). If there are additional variables approaching significance ($p < 0.10$) between the two epochs in

bivariate analysis we will also include them as covariates as long as they precede (in time) the outcome variable.

We will also create models specific for each variable:

- For intubation in the DR: Model using as additional variables mode of delivery, and maternal hypertension
- For mortality: Model using as additional covariates Apgar score at 1 minute (Shankaran 2002), and temperature upon admission (Laptook 2007)
- For death or BPD and for BPD: Model using as additional covariates intubation in the DR, number of doses of surfactant (≤ 1 vs > 1), FiO₂ at 24 hours ($\geq 90\%$ vs $< 90\%$), PDA ligation, indomethacin for PDA, late-onset septicemia/ bacteremia (Schmidt 2006, Schmidt 2007, Tyson 1999, Ambalavanan 2008, Fanaroff 1998, Clyman 2009) and intrauterine growth restriction (Mestan 2011, Bose 2009, Lal 2003, Sharma 2004). For the latter variable, we will assess whether being small for gestational age (birth weight $< 10^{\text{th}}$ percentile) or birth weight z score (Bose 2009) is the better predictor.

We will use survival analysis to predict in-hospital death using a Cox proportional hazards model adjusted for covariates listed above, using the same methods used in the primary SUPPORT analysis. We will assume, as in the SUPPORT, that infants who survived to discharge or transfer continued to survive to one year of life.

Limitations:

Before/after study design is limited by confounding variables that may have occurred in addition to the variable of interest. The two cohorts represent different patient populations separated by five years. Strategies and policies may have changed in the same center between the two epochs, and this process may still be going on at the present time, especially for the oxygen saturation results. For this purpose, we will perform logistic regression analyses as described in the previous section on multivariate analyses.

Prophylactic magnesium administration to women at risk for preterm delivery did not affect the risk of neonatal hypotonia (RR 1.02; 95% CI 0.77 to 1.36; 2444 infants) (Rouse 2008), intubation or resuscitation in the DR (2416 infants) (Rouse 2008), tracheal intubation or epinephrine in the neonatal period (226 infants) (Marrett 2007), or many other neonatal outcomes, but significantly reduced the risk for cerebral palsy (overall RR 0.68; 95% CI 0.54 to 0.87; five trials; 6145 infants) (Doyle 2009). Thus neurodevelopment outcome may be modified by systematic administration of intrapartum magnesium as prophylaxis of neurodevelopment impairment, which may have been started in some NRN centers in response to recent multicenter trials. Since neurodevelopmental impairment (NDI) assessment criteria changed in the NRN between the two cohorts, we will not use NDI as a variable in this study.

One exclusion criterion used for the SUPPORT trial, i.e., decision made not to provide full resuscitation, is not listed in the GDB baseline form.

The primary outcomes of death or physiologic BPD and death or ROP, used in the SUPPORT trial, are not available in GDB. The outcome of physiologic BPD (Walsh 2003, Walsh 2004) is only available in the second cohort in the proposed study. The outcome of ROP as defined in the SUPPORT trial (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) is not available in the GDB. The definitions of ROP changed between 2002 and 2006. We are proposing here to assess the frequency of severe ROP (defined as ROP surgery or retinal detachment).

Some variables cannot be analyzed because they were collected during only one of the two cohorts (e.g., tocolytics, magnesium prophylaxis for neuroprotection).

The small number of centers will limit the power of some analyses as indicated above.

Consenting:

Patients will be selected from GDB using criteria previously explained. We request a waiver for consent form as this research involves minimal risk to patients and collecting data in the GDB has been pre-approved by the IRB in each institution.

Available Population/compatibility with other ongoing protocols

The population available will be those patients in the GDB, corresponding to patients born during the two epochs.

We are not aware of any conflict with other ongoing protocols.

Projected Recruitment Time

Data collection for the proposed study will start in 2012.

H. RISKS/BENEFITS:

The benefit will be mostly for the society in that there is potential quality improvement of patient care in NICU. The risk is minimal and included accidental disclosure of medical information which is unlikely.

I. BUDGET:

Cost for access to GDB and SUPPORT database and statistical analysis

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From: Wally Carlo
 To: Wally Carlo, Archer, Stephanie (NIH/NICHD) [E], alabotok@winn.org, adas@nri.org, Bradley.yoder@hsc.utah.edu, kzarierka@nri.org, kurt.schibler@cchmc.org, mgantz@nri.org, mcw3@cwrn.edu, rxs5@cwrn.edu, rfiner@ucsd.edu, roger.felix@hsc.utah.edu, Higgins, Rosemary (NIH/NICHD) [E], wrich@ucsd.edu, wacario@uab.edu
 Subject: RE: Publications | SUPPORT papers
 Date: Tuesday, October 02, 2012 12:43:49 PM

Agree

Sent with Good (www.good.com)

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

From: Wally Carlo, MD [WCarlo@peds.uab.edu]
 Sent: Tuesday, October 02, 2012 11:11 AM Eastern Standard Time
 To: Archer, Stephanie (NIH/NICHD) [E]; alabotok@winn.org; adas@nri.org; Bradley.yoder@hsc.utah.edu; kzarierka@nri.org; kurt.schibler@cchmc.org; mgantz@nri.org; mcw3@cwrn.edu; rxs5@cwrn.edu; rfiner@ucsd.edu; roger.felix@hsc.utah.edu; Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu; wacario@uab.edu
 Subject: RE: Publications | SUPPORT papers

I agree with Susan's comments in the Comments column, and I think it is probably best to have one combined CUS and MRI manuscript so the two modalities can be combined for example for diagnostic accuracy for NDI and its major components (MDI and CP/PDI).

Regarding the other manuscripts, most are well into completion and I would suggest to pursue publication of each.

Wally

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archer@mail.nih.gov]
 Sent: Tuesday, October 02, 2012 10:02 AM
 To: Abbot Lupton (alupton@winn.org); Abrik Das (adas@nri.org); Brad Yoder (Bradley.yoder@hsc.utah.edu); Kristin Zakerka-Baxter (kzarierka@nri.org); Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@nri.org); Michele Walth (mcw3@cwrn.edu); Nancy Newman (rxs5@cwrn.edu); Neil Finer (rfiner@ucsd.edu); Roger Felix (roger.felix@hsc.utah.edu); Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Wade Rich (wich@ucsd.edu); Wally Carlo (wacario@uab.edu)
 Subject: Publications | SUPPORT papers

SUPPORT Subcommittee,

Following on the discussion at the Steering Committee about whether papers should continue to pursue publication, below is the list of papers for your subcommittee. Please let me know what you want to do with these.

Current Status	Authors	Paper Working Title	Abst Year	Dataset	Submission			Comments/Status	Last Update
					Journal	Submitted	# of Submissions		
1. Pending	Ambalivanan N	Effects of PaCO2 on Outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)		SUPPORT			0	6/2/11 NA: Abstract not accepted at PAS. Manuscript in preparation 1/18/12 NA: Manuscript in preparation - will need additional analyses. 5/7/12 NA: Manuscript in preparation. 7/3/12 NA: Manuscript in preparation.	7/3/12
Published	Di Fiore JM; Wallyh M; Wraga L; Rich W; Finer N; Carlo WA; Martin RJ; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network	Low Oxygen Saturation Target Range is Associated with Increased Incidence of Intermittent Hypoxemia	2011	SUPPORT	J Peds		1	http://www.ncbi.nlm.nih.gov/pubmed/22748367 5/1/11 Presented at PAS 2011 8/2/11 SWA requested update 8/23/11 MCVW draft final revisions back with authors 11/23/11 JMO Received comments from the NIN 1/10/12 approved. Next step: prepare revision to go authors waiting for their responses. 1/22/11 Sent in draft ready to submit to J Peds 4/7/12 JMB Accepted with revisions 7/5/12 SWA requested update 8/24/12 No PMCID yet	8/25/12
1. Pending	(b)(4)								
1. Pending	(b)(4)								
Combined	Hintz SR; Barnes PD; Wraga LA; Bulas D; Slovis TL; Das A; Finer NN; Cheng H; Higgins RD; for the SUPPORT Subcommittee and the NICHD Neonatal Research Network	Brain MRI Findings of Extremely Preterm Infants: The Neuroimaging and Neurodevelopmental Outcomes cohort	2011	SUPPORT			0	5/1/11 Presented at PAS 2011 6/2/11 SH: Manuscript drafts in process 11/23/11 J SH: I am working on the MRI descriptive paper first, then I am re-organizing the CUS paper to include follow up results. 1/17/12 SH: I will have the first paper (MRI descriptive) to authors very soon. 7/6/12 SH: Combining with CUS paper	7/6/12
1. Pending	Hintz SR; Bulas D; Slovis TL; Cheng H; Finer NN; Das A; Higgins RD; for the SUPPORT Subcommittee and NICHD Neonatal Research Network	Early and Late CUS Findings in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes (NEURO) Cohort.	2010	SUPPORT			0	5/1/10 Late Breaker Abstract for PAS 10/15/10 SH: Additional analysis and 3rd central reader adjudication completed; working on paper 12/26/10 SH: requires additional data analysis 3/7/11 SH: Waiting for final tables from Cheng at RTI. Analysis should be complete in next 2 weeks. 3/30/11 SH: Adjudication completed 4/2010; additional analysis completed 3/2011; paper being drafted. 6/2/11 SH: Manuscript drafts in process 11/23/11 SH: Working on MRI descriptive paper first, then reorganizing CUS paper to include FU. 1/17/12 SH: Reworking to include FU because I do not think another CUS descriptive findings paper will be of interest to the readership. 7/6/12 SH: Combining with MRI paper	7/6/12
1. Pending	Hintz SR; Wraga LA; Barnes PD; Bulas D; Slovis T; Das A; Finer NN; Higgins RD; for the SUPPORT Subcommittee	Brain MRI and Outcomes at 18-22 Months: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) Cohort	2012	SUPPORT			0	5/1/12 Presented at PAS 2012 7/6/12 SH: Being written	7/6/12
1. Pending	Hintz SR; Wraga LA; Barnes PD; Bulas D; Slovis T; Das A; Finer NN; Higgins RD; for the SUPPORT	Early and Late Cranial Ultrasound (CUS) to Predict 18-22 Month Outcomes in Extremely Preterm Infants: The Neuroimaging and	2012	SUPPORT			0	5/1/12 Presented at PAS 2012 7/6/12 SH: Being written	7/6/12

	Subcommittee	Neurodevelopmental Outcomes (NEURO) Cohort							
2. Drafted	Kennedy KA; Wraga LA; Higgins RD; Finer NH; Carlo WA; Walsh MC; Lipton AR; Fax RG; Yoder B; Schibler KR; Cantz MG; Das A; Newman NS; Rich W; Phelps DL	Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants	2012	SUPPORT				5/17/12 Presented at PAS 2012 5/25/12 Draft sent to coauthors 7/30/12 Sent to SUPPORT Subcommittee	7/30/12
2. Drafted	Lowe JR; Duncan AF; Watterberg KL; Bann CM; Fuller J; Hintz SR; for the NICHD Neonatal Research Network	Early working memory as a racially and ethnically neutral measure of outcome in extremely preterm children at 18-22 months	2012	SUPPORT			0	5/1/12 Presented at PAS 2012 7/8/12 JL: The manuscript is in preparation and we hope to submit in August. The first draft has been sent to the co-authors. 9/12/12 New version sent to coauthors for review 9/27/12 JL: waiting on Carla Bann to edit the comments specific to statistics.	9/27/12

Thank you,

Stephanie

Stephanie Wilson Archer
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From: Luc Brion
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; nfiner@ucsd.edu; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: Updated Jackie's abstract
Date: Tuesday, October 02, 2012 7:13:18 AM
Attachments: Changes in Therapy and Outcomes Associated with the SUPPORT Trial 100212.doc

Here is an updated version with explanation of denominators (missing data) and clarification of race/ethnicity.

Thanks for all the comments.

Luc

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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL. *Jaclyn M LeVan, Luc P Brion, Lisa Wrage, Myra H Wyckoff, Pablo J Sánchez, Roy Heyne, Mambarambath Jaleel, Neil Finer, Abhik Das, Barbara Stoll, Rose Higgins, Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.*

BACKGROUND

The NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter 2 X 2 factorial trial, in which preterm neonates 24-27^{6/7} weeks' gestational age (GA) were randomized at birth to two interventions: (1) continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O₂) saturation targets of 85 to 89% or 91 to 95%. The primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks), and death or severe retinopathy of prematurity (ROP) were not affected by the interventions. However, death was more frequent and severe ROP less frequent among infants randomized to low O₂ saturation targets. We hypothesized that (1) the percentage (%) of DR intubation would decrease after publication of SUPPORT, without affecting BPD or death and ROP or death; and (2) the decrease in DR intubation in each center would depend on the % of pre-SUPPORT DR intubation.

OBJECTIVE

To compare DR intubation, BPD or death at 36 weeks, and severe ROP or death before discharge in time periods before SUPPORT and after its publication.

DESIGN/METHODS

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24-27^{6/7} weeks GA born before (2003-04) and after SUPPORT (2010-11) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with known malformations and those receiving comfort care.

RESULTS

This study included 3151 infants (1617 pre-SUPPORT and 1534 post-SUPPORT).

Baseline Characteristics	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value
Birth weight (g) (mean ±SD)	824±191	816±190	0.23
Gestational Age (weeks)	26±1	26±1	0.64
Antenatal corticosteroids	1338/1616* (83%)	1358/1532 (89%)	<0.0001
Race/ethnicity: Black Not Hispanic (NH); White NH; Hispanic; Other (%)	45;37;15;3	44;38;14;5	0.02
Cesarean section	1004 (62%)	1009 (66%)	0.03
Rupture of membranes > 24 hours	436/1586 (27%)	360/1482 (24%)	0.043
Maternal hypertension	322 (20%)	409/1532 (25%)	<.0001
Maternal diabetes	42 (3%)	84 (5%)	<.0001

*Denominator indicates missing data

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Parameters of Assessment	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value	Adjusted OR (95% CI)	Adjusted p-value
Intubated in DR	1313 (81%)	1082 (71%)	<0.0001	0.55 (0.46-0.67)	<0.0001
BPD or death	970 (60%)	824/1522 (54%)	0.0009	1.1 (0.91-1.3)	0.37
Severe ROP or death	515/1581 (33%)	408/1501(27%)	0.0011	0.73 (0.60-0.87)	0.0007

The proportion of patients intubated in the DR was significantly lower in the post-SUPPORT group than in the pre-SUPPORT group (Table). The odds ratio (OR) of DR intubation (post vs. pre-SUPPORT) remained significant (Table) after adjusting for GA group (24-25^{6/7} vs. 26-27^{6/7} weeks), 100-grams birth weight groups, gender, race/ethnicity, multiple birth, antenatal steroids, prolonged rupture of membranes, cesarean section, maternal hypertension, maternal diabetes and center. The OR of ROP or death (adjusted for these variables and for surfactant), but not that of BPD or death, was significantly different from 1. The correlation between pre-SUPPORT center-specific % of DR intubation and the change after SUPPORT was not significant (Spearman $r=-0.38$, $p=0.25$). Centers with $\geq 80\%$ DR intubation pre-SUPPORT were likely to have a significant reduction post-SUPPORT ($p<0.0001$) whereas centers with $< 80\%$ DR intubation pre-SUPPORT were not ($p=0.54$).

CONCLUSIONS

The adjusted odds of DR intubation, and that of death or ROP, but not that of death or BPD, significantly decreased after publication of SUPPORT in NRN centers involved in the trial. DR intubation was more likely to decrease after SUPPORT in centers with $\geq 80\%$ pre-SUPPORT DR intubation.

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From: Luc Brion
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary (NIH/NICHD) (E); Barbara Stoll; nfiner@ucsd.edu; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: Revised Jackie's abstract
Date: Monday, October 01, 2012 6:00:51 PM
Attachments: Report_01Oct12.doc
Changes in Therapy and Outcomes Associated with the SUPPORT Trial 10012 rev.doc

Hi everyone:

Thanks a lot for the feedback and thanks Lisa for running the analysis again!

Here is a revised abstract, in which betamethasone was replaced with any antenatal steroids (as originally planned in the protocol) and in which race was clarified.

There is not enough place to discuss betamethasone in the abstract.

Best regards

Luc

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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL. *Jaelyn M LeVan, Luc P Brion, Lisa Wrage, Myra H Wyckoff, Pablo J Sánchez, Roy Heyne, Mambarambath Jaleel, Neil Finer, Abhik Das, Barbara Stoll, Rose Higgins, Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.*

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OBJECTIVE

To compare DR intubation, BPD or death at 36 weeks, and severe ROP or death before discharge in time periods before SUPPORT and after its publication.

DESIGN/METHODS

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24-27^{6/7} weeks GA born before (2003-2004) and after SUPPORT (2010-2011) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-2011. We excluded infants with known malformations and those receiving comfort care.

RESULTS

This study included 3151 infants (1617 pre-SUPPORT and 1534 post-SUPPORT).

Baseline Characteristics	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value
Birth weight (g) (mean ±SD)	824±191	816±190	0.23
Gestational Age (weeks)	26±1	26±1	0.64
Antenatal corticosteroids betamethasone	1338/1616 (83%)953(59%)	1358/1532 (89%)1344/1532 (88%)	<.0001<.0001
Race: Race: Black Not Hispanic (NH); White NH; Hispanic; Other (%)	45;37;15;3	44;38;14;5	0.02
Mode of delivery: Ceesarean section	1004 (62%)	1009 (66%)	0.03
Rupture of membranes > 24 hours	436/1586 (27%)	360/1482 (24%)	0.043
Maternal hypertension	322 (20%)	409/1532 (25%)	<.0001
Maternal diabetes	42 (3%)	84 (5%)	<.0001

Parameters of Assessment	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value	Adjusted OR (95% CI)	Adjusted p-value
Intubated in DR	1313 (81%)	1082 (71%)	<0.0001	0.63 (0.51-0.77) 0.55 (0.46-0.67)	<0.0001
BPD or death	970 (60%)	824/1522 (54%)	0.0009	1.1 (0.91-1.3) 1.06 (0.88-1.3)	0.37 0.53
Severe ROP or death	515/1581 (33%)	408/1501 (27%)	0.0011	0.73 (0.60-0.87) 0.80 (0.64-0.97)	0.0007 0.024

The proportion of patients intubated in the DR was significantly lower in the post-SUPPORT group than in the pre-SUPPORT group (Table). The odds ratio (OR) of DR intubation (post vs. pre-SUPPORT) remained significant (Table) after adjusting for GA group (24-25^{6/7} vs. 26-27^{6/7} weeks), 100-grams birth weight groups, gender, race, multiple birth, anteprenatal steroids, prolonged rupture of membranes, cesarean section, maternal hypertension, maternal diabetes and center. The OR of ROP or death (adjusted for the same variables and for surfactant), but not that of BPD or death, was significantly different from 1. The correlation between pre-SUPPORT center-specific percentage of DR intubation and the change after SUPPORT was not significant (Spearman $r=-0.38$, $p=0.25$). Centers with $\geq 80\%$ DR intubation pre-SUPPORT were likely to have a significant reduction post-SUPPORT ($p<0.0001$) whereas centers with $< 80\%$ intubation pre-SUPPORT were not ($p=0.54$).

CONCLUSIONS

The adjusted odds of DR intubation, and that of death or ROP, but not that of death or BPD, significantly decreased after publication of the results of SUPPORT in NRN centers involved in the trial. DR intubation was more likely to decrease after SUPPORT in centers with $\geq 80\%$ pre-SUPPORT DR intubation.

39844000 characters

October 1, 2012

Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Updated from September 27 – Models re-run to include any antenatal steroids instead of betamethasone.

Neonatal Network Investigator: J. LeVan, Luc Brion

RTI Statistician: Lisa Wrage

Population

Infants of 24-27 weeks gestational age at birth, born during years 2003-2004 or 2010-2011 at one of 11 centers participating in the SUPPORT trial and in the NRN from 2003-2011, excluding infants with known malformations or who had respiratory or other medical support withheld prior to death < 12 hours.

Methods

Primary outcome variables

The primary outcome variables of interest include intubation in the delivery room, BPD or death at 36 weeks, and severe ROP or death before discharge. Intubation in delivery room is recorded in the GDB. BPD is defined as oxygen use at 36 weeks. Severe ROP is defined using ophthalmology information from the GDB, NG03 section H (see appendix for details)

Secondary outcome variables

Other outcomes of interest include BPD, severe ROP, death before discharge, surfactant use, pneumothorax, pulmonary hemorrhage, postnatal steroid use, severe IVH, proven NEC, days of mechanical ventilation (survivors), days on supplemental oxygen (survivors), and length of hospital stay.

Other variables

Maternal and neonatal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Study groups

Infants from the study population were classified as 'pre-SUPPORT' if they were born during 2003-2004 and as 'post-SUPPORT' if they were born during 2010-2011.

Statistical Analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and ttests or Wilcoxon tests, as appropriate, for continuous variables. Logistic regression models were used to obtain adjusted results for each of the primary outcomes. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation rate during the first epoch.

Results

There were a total of n=5323 infants born at 24-27 weeks gestational age during 2003-2004 (n=2998) or 2010-2011 (n=2322) and included in the GDB. Of these n=1581 infants were born in NRN centers not included in this study and an additional n=352 were outborn, these infants were excluded. Of the remaining infants, n=134 infants with known malformations, n=100 infants who had respiratory or medical support withdrawn prior to death < 12 hours were excluded, and 5 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of n=3151 infants. Of these n=1617 infants are in the pre-SUPPORT group and n=1534 infants are in the post-SUPPORT group.

Power Calculations

Power calculations for each of the primary outcomes, based on chi square tests, an alpha of .05, and the sample sizes noted above give these results: a power of 1.0 to detect a change of delivery room intubation from 80% to 68%; a power of 0.8 to detect a change in outcome 'BPD or death' from 50% to 45%, and a power of 0.94 to detect a change in outcome severe ROP or death from 67% to 61%.

Statistical analysis

Unadjusted comparisons of variables of interest by study group are shown in **Tables 1-3**. Logistic regression models for each of the primary outcomes were also run to obtain adjusted results. The resulting adjusted odds ratios, 95% confidence intervals, and p-values are shown in **Table 2**. Additionally, within center, the percent of infants who were intubated in the delivery room was calculated for each study group and the difference between the post-SUPPORT group and the pre-SUPPORT group was also calculated. Using the results for the 11 centers in this study, the correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.38, $p=0.25$). (see appendix for SAS output for the logistic regression models and for the Spearman correlation).

Table 1. Maternal and Neonatal Characteristics¹

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
Birth weight (g)	824 (191)	816 (190)	0.23
Gestational Age (weeks)	25.7 (1.1)	25.6 (1.1)	0.64
% Male	858 (53.1)	767 (50.0)	0.09
Race:			
NH Black	727 (45.0)	654 (43.5)	0.02
NH White	603 (37.3)	566 (37.6)	
Hispanic	241 (14.9)	210 (14.0)	
Other	46 (2.8)	74 (4.9)	
Antenatal Steroids: any type	1338/1616 (82.8)	1358/1532 (88.6)	<.0001
Antenatal Steroids: betamethasone	953(59.1)	1344/1532 (87.7)	<.0001
Multiple birth	370 (22.9)	360/1532 (23.5)	0.68
Mode of delivery: c-section	1004 (62.1)	1009 (65.9)	0.03
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	360/1482 (24.3)	0.043
Maternal hypertension	322 (19.9)	409/1532 (24.7)	<.0001
Maternal diabetes	42 (2.6)	84 (5.5)	<.0001
Antibiotics	1198/1615 (74.2)	1114/1530 (72.8)	0.38

Table 2. Primary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²	adjusted OR ³ (95% CI)	adjusted p-value ³
Intubated in delivery room	1313 (81.2)	1082 (70.5)	<.0001	0.55 (0.46-0.67)	<.0001
BPD or death at 36 weeks	970 (60.0)	824/1523 (54.1)	.0009	1.1 (0.91-1.3)	0.37
Severe ROP or death	515/1581 (32.6)	408/1501(27.2)	.0011	0.73 (0.60-0.87)	0.0007

Table 3. Secondary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
BPD (O2 at 36 weeks)	664/1311 (50.7)	581/1279 (45.4)	.008
Death at 36 weeks	306 (18.9)	243/1529 (15.9)	.026
Severe ROP	174 (13.5)	138 (10.8)	.036
Death before discharge	358/1614 (22.2)	285/1519 (18.8)	.017
Surfactant	1427 (88.3)	1266/1528 (82.9)	<.0001
Pneumothorax	135/1604 (8.4)	86/1511 (5.7)	.0030
Pulmonary Hemorrhage	181/1603 (11.3)	106/1512 (7.0)	<.0001
Postnatal Steroids	195/1599 (12.2)	182/1496 (12.2)	0.97
Days on ventilator (survivors)	22.3 (24.4), 13	18.5 (21.2), 10	<.0001
Days on supp. O2 (survivors)	59.2 (36)	56.8 (37.8)	0.10
Severe IVH	288 (18.5)	204 (13.8)	.0004
Proven NEC	177 (11.0)	160 (10.6)	0.71
Length of hospital stay (days)	84.4 (57.5), 83	90.9 (52.9), 90	.0006

¹ presented as mean (SD), median for days on ventilator and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.

² unadjusted p-values from Chi Square tests, ttests, or Wilcoxon tests, as appropriate.

³ OR reflects odds of the outcome for post_SUPPORT vs. pre_SUPPORT.

Appendix – Definition of severe ROP:

Severe ROP is defined as “retinal detachment (partial or complete), surgery, or Avastin/Anti-VEGF drug” using questions from NG03 section H ‘Ophthalmology’. Specifically, an infant is defined as having severe ROP if:

Using NG03 2002 – for the pre-SUPPORT group born 2003-2004:

- H.1.a.1.i. Highest Stage of ROP in right or left eye=4 or 5 (retinal detachment) ***or***
- H.3.a.i. retinal ablation performed prior to a threshold diagnosis in Right eye='Y' ***or***
- H.3.a.ii. retinal ablation performed prior to a threshold diagnosis in Left eye='Y' ***or***
- H.3.b.i. any surgery performed in Right eye=1,2,3,4 ***or***
- H.3.b.ii. any surgery performed in Left eye=1,2,3,4.

Using NG03 2008, 2011 – for the post-SUPPORT group born 2010-2011:

- H.1.b.1. retinal ablation performed in either eye='Y' ***or***
- H.1.b.2. scleral buckle or vitrectomy performed in either eye='Y' ***or***
- 2008 H.1.b.3.

Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***

2011 H.1.b.3. Avastin or other anti-VEGF drug='Y' ***or***

2011 H.1.b.4.

Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***

H.2. =2 - Determined severe ROP (ROP surgery, retinal detachment, Avastin or anti-VEGF) in either eye at status.

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LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	intubated_dr	intubated in the delivery room, 1=Yes
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	intubated_dr	Total Frequency
1	1	2306
2	0	733

Probability modeled is intubated_dr=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	1.4009	0.2782	25.3504	<.0001
post_SUPPORT		1	-0.5913	0.0994	35.4106	<.0001
ga2425		1	0.7731	0.1304	35.1311	<.0001
brwtgtp	1= <=600g	1	1.6268	0.2268	51.4630	<.0001
brwtgtp	2=601-700g	1	1.3761	0.1968	48.8930	<.0001
brwtgtp	3=701-800g	1	1.1366	0.1813	39.2928	<.0001
brwtgtp	4=801-900g	1	0.7196	0.1527	22.1974	<.0001
brwtgtp	5=901-1000g	1	0.5737	0.1532	14.0168	0.0002
malex		1	0.1503	0.0992	2.2965	0.1297
MULTBRTH		1	-0.2824	0.1216	5.3910	0.0202
ANTESTER		1	-0.7629	0.1718	19.7140	<.0001
race_bwho	1=Black	1	-0.1800	0.1163	2.3970	0.1216
race_bwho	3=Hispanic	1	-0.2754	0.1772	2.4161	0.1201
race_bwho	4=Other	1	0.0404	0.2932	0.0190	0.8905
CSECT		1	0.3659	0.1084	11.4010	0.0007
ROMGT24		1	-0.1559	0.1164	1.7943	0.1804

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LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.6231	0.1293	23.2044	<.0001
diabetes		1	-0.3508	0.2334	2.2592	0.1328
CENTER	3	1	-0.1911	0.2462	0.6026	0.4376
CENTER	4	1	0.0906	0.2742	0.1092	0.7411
CENTER	5	1	0.7584	0.2688	7.9617	0.0048
CENTER	9	1	-0.0932	0.2440	0.1461	0.7023
CENTER	11	1	-0.7889	0.1902	17.2024	<.0001
CENTER	12	1	0.8173	0.2520	10.5193	0.0012
CENTER	14	1	0.7130	0.2558	7.7714	0.0053
CENTER	15	1	-0.2212	0.2729	0.6571	0.4176
CENTER	16	1	-1.8605	0.1930	92.8898	<.0001
CENTER	18	1	0.6383	0.2327	7.5270	0.0061

Odds Ratio Estimates			
Effect		Point Estimate	95% Wald Confidence Limits
post_SUPPORT		0.554	0.456 0.673
ga2425		2.167	1.678 2.798
brwtgtp	1=<-600g vs 6=>1000g	5.087	3.262 7.935
brwtgtp	2=601-700g vs 6=>1000g	3.960	2.692 5.823
brwtgtp	3=701-800g vs 6=>1000g	3.116	2.184 4.446
brwtgtp	4=801-900g vs 6=>1000g	2.054	1.522 2.770
brwtgtp	5=901-1000g vs 6=>1000g	1.775	1.314 2.397
malex		1.162	0.957 1.412
MULTBRTH		0.754	0.594 0.957
ANTESTER		0.466	0.333 0.653
race_bwho	1=Black vs 2=White	0.835	0.665 1.049
race_bwho	3=Hispanic vs 2=White	0.759	.536 1.075
race_bwho	4=Other vs 2=White	1.041	0.586 1.850
CSECT		1.442	1.166 1.783
ROMGT24		0.856	0.681 1.075
htn		0.536	0.416 0.691
diabetes		0.704	0.446 1.113

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LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CENTER	3 vs 19	0.826	0.510	1.338
CENTER	4 vs 19	1.095	0.640	1.874
CENTER	5 vs 19	2.135	1.261	3.616
CENTER	9 vs 19	0.911	0.565	1.469
CENTER	11 vs 19	0.454	0.313	0.660
CENTER	12 vs 19	2.264	1.382	3.711
CENTER	14 vs 19	2.040	1.236	3.368
CENTER	15 vs 19	0.802	0.470	1.368
CENTER	16 vs 19	0.156	0.107	0.227
CENTER	18 vs 19	1.893	1.200	2.987

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	bpdeath36	BPD or death at 36 weeks
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	bpdeath36	Total Frequency
1	1	1579
2	0	1286

Probability modeled is bpdeath36=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.4745	0.2933	140.3352	<.0001
post_SUPPORT		1	0.0829	0.0922	0.8076	0.3688
intubated_dr		1	0.1272	0.1317	0.9332	0.3340
ga2425		1	0.3410	0.1198	8.1064	0.0044
brtwgtp	1= <=600g	1	2.2816	0.2776	67.5343	<.0001
brtwgtp	2=601-700g	1	1.3640	0.1954	48.7054	<.0001
brtwgtp	3=701-800g	1	1.0284	0.1696	36.7750	<.0001
brtwgtp	4=801-900g	1	0.7031	0.1496	22.1039	<.0001
brtwgtp	5=901-1000g	1	0.5099	0.1517	11.3000	0.0008
sga		1	0.1163	0.2074	0.3142	0.5751
malex		1	0.7688	0.0923	69.3508	<.0001
MULTBRTH		1	-0.1678	0.1111	2.2825	0.1308
ANTESTER		1	0.0335	0.1396	0.0576	0.8103
race_bwho	1=Black	1	-0.2083	0.1072	3.7760	0.0520
race_bwho	3=Hispanic	1	-0.2086	0.1541	1.8328	0.1758
race_bwho	4=Other	1	-0.3767	0.2452	2.3604	0.1245
CSECT		1	-0.0898	0.0987	0.8286	0.3627
ROMGT24		1	-0.0558	0.1079	0.2676	0.6049

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.1063	0.1208	0.7741	0.3790
diabetes		1	0.0517	0.2257	0.0524	0.8189
SURFACT		1	0.7540	0.1609	21.9500	<.0001
fio24ge90		1	1.3394	0.3167	17.8869	<.0001
pda_ligation		1	0.7153	0.1596	20.0960	<.0001
pda_indom		1	0.4663	0.1060	19.3710	<.0001
LOS		1	0.6057	0.0990	37.4165	<.0001
CENTER	3	1	0.8916	0.2247	15.7452	<.0001
CENTER	4	1	1.0962	0.2437	20.2300	<.0001
CENTER	5	1	2.2212	0.2376	87.3674	<.0001
CENTER	9	1	1.2099	0.2286	28.0101	<.0001
CENTER	11	1	1.7521	0.1890	85.9657	<.0001
CENTER	12	1	2.3213	0.2189	112.4709	<.0001
CENTER	14	1	1.2466	0.2072	36.1907	<.0001
CENTER	15	1	1.7989	0.2607	47.6274	<.0001
CENTER	16	1	0.7074	0.1961	13.0095	0.0003
CENTER	18	1	1.2615	0.1979	40.6349	<.0001

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
post_SUPPORT		1.086	0.907	1.302
intubated_dr		1.136	0.877	1.470
ga2425		1.406	1.112	1.778
brwtg	1= <=600g vs 6=>1000g	9.793	5.683	16.875
brwtg	2=601-700g vs 6=>1000g	3.912	2.667	5.738
brwtg	3=701-800g vs 6=>1000g	2.797	2.006	3.899
brwtg	4=801-900g vs 6=>1000g	2.020	1.507	2.708
brwtg	5=901-1000g vs 6=>1000g	1.665	1.237	2.242
sga		1.123	0.748	1.687
malex		2.157	1.800	2.585
MULTBRTH		0.845	0.680	1.051
ANTESTER		1.034	0.787	1.360
race_bwho	1=Black vs 2=White	0.812	0.658	1.002
race_bwho	3=Hispanic vs 2=White	0.812	0.600	1.098
race_bwho	4=Other vs 2=White	0.686	0.424	1.109

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CSECT		0.914	0.753	1.109
ROMGT24		0.946	0.766	1.168
htn		0.899	0.710	1.139
diabetes		1.053	0.677	1.639
SURFACT		2.126	1.551	2.914
fic24ge90		3.817	2.052	7.100
pda_ligation		2.045	1.496	2.796
pda_indom		1.594	1.295	1.962
LOS		1.833	1.509	2.225
CENTER	3 vs 19	2.439	1.570	3.789
CENTER	4 vs 19	2.993	1.856	4.825
CENTER	5 vs 19	9.218	5.786	14.686
CENTER	9 vs 19	3.353	2.142	5.249
CENTER	11 vs 19	5.767	3.982	8.352
CENTER	12 vs 19	10.189	6.635	15.648
CENTER	14 vs 19	3.479	2.317	5.222
CENTER	15 vs 19	6.043	3.626	10.072
CENTER	16 vs 19	2.029	1.381	2.980
CENTER	18 vs 19	3.531	2.396	5.204

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LOGISTIC MODELS
OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	sevropdeath	severe ROP or death
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	sevropdeath	Total Frequency
1	1	888
2	0	2086

Probability modeled is sevropdeath=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.7451	0.3171	74.9595	<.0001
post_SUPPORT		1	-0.3220	0.0949	11.5044	0.0007
ga2425		1	0.6638	0.1123	34.9175	<.0001
brwtgtp	1=<=600g	1	2.7480	0.2169	160.5657	<.0001
brwtgtp	2=601-700g	1	1.7112	0.2005	72.8247	<.0001
brwtgtp	3=701-800g	1	1.0931	0.1953	31.3110	<.0001
brwtgtp	4=801-900g	1	0.5440	0.1926	7.9772	0.0047
brwtgtp	5=901-1000g	1	0.3030	0.2029	2.2303	0.1353
malex		1	0.5961	0.0951	39.2636	<.0001
MULTBRTH		1	0.2070	0.1134	3.3312	0.0680
ANTESTER		1	-0.2870	0.1366	4.4155	0.0356
race_bwho	1=Black	1	-0.3356	0.1142	8.6379	0.0033
race_bwho	3=Hispanic	1	0.3547	0.1647	4.6368	0.0313
race_bwho	4=Other	1	0.8940	0.2519	12.5895	0.0004
CSECT		1	-0.1137	0.1042	1.1901	0.2753
ROMGT24		1	-0.1885	0.1145	2.7091	0.0998

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LOGISTIC MODELS
OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.4417	0.1287	11.7883	0.0006
diabetes		1	0.4797	0.2345	4.1852	0.0408
SURFACT		1	0.5006	0.1703	8.6465	0.0033
CENTER	3	1	0.4326	0.2373	3.3252	0.0682
CENTER	4	1	0.5324	0.2536	4.4083	0.0358
CENTER	5	1	1.0554	0.2221	22.5791	<.0001
CENTER	9	1	0.3917	0.2422	2.6159	0.1058
CENTER	11	1	0.2798	0.1988	1.9814	0.1592
CENTER	12	1	0.4444	0.2132	4.3446	0.0371
CENTER	14	1	-0.8170	0.2458	11.0468	0.0009
CENTER	15	1	-0.4137	0.2898	2.0374	0.1535
CENTER	16	1	0.1950	0.2065	0.8919	0.3450
CENTER	18	1	0.2956	0.2101	1.9797	0.1594

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
post_SUPPORT		0.725	0.602	0.873
ga2425		1.942	1.558	2.421
brtwtgp	1=<=600g vs 6=>1000g	15.611	10.205	23.879
brtwtgp	2=601-700g vs 6=>1000g	5.535	3.737	8.200
brtwtgp	3=701-800g vs 6=>1000g	2.983	2.034	4.375
brtwtgp	4=801-900g vs 6=>1000g	1.723	1.181	2.513
brtwtgp	5=901-1000g vs 6=>1000g	1.354	0.910	2.015
malex		1.815	1.506	2.187
MULTBRTH		1.230	0.985	1.536
ANTESTER		0.751	0.574	0.981
race_bwho	1=Black vs 2=White	0.715	0.572	0.894
race_bwho	3=Hispanic vs 2=White	1.426	1.032	1.969
race_bwho	4=Other vs 2=White	2.445	1.492	4.006
CSECT		0.893	0.728	1.095
ROMGT24		0.828	0.662	1.037
htn		0.643	0.500	0.827

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LOGISTIC MODELS
OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
diabetes		1.616	1.020	2.558
SURFACT		1.650	1.182	2.303
CENTER	3 vs 19	1.541	0.968	2.454
CENTER	4 vs 19	1.703	1.036	2.800
CENTER	5 vs 19	2.873	1.859	4.441
CENTER	9 vs 19	1.480	0.920	2.378
CENTER	11 vs 19	1.323	0.896	1.953
CENTER	12 vs 19	1.560	1.027	2.368
CENTER	14 vs 19	0.442	0.273	0.715
CENTER	15 vs 19	0.661	0.375	1.167
CENTER	16 vs 19	1.215	0.811	1.822
CENTER	18 vs 19	1.344	0.890	2.029

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LOGISTIC MODELS
OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

From: Luc Brion
To: Wrage, Lisa Ann; Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; nfiner@ucsd.edu; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract
Date: Monday, October 01, 2012 1:19:16 PM

Thanks a lot.

Luc

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

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Monday, October 01, 2012 12:17 PM
To: Luc Brion; Roy Heyne; Rosemary Higgins; Barbara Stoll; nfiner@ucsd.edu; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract

Ok, I will re-run things using any antenatal steroids.
Lisa

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

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Monday, October 01, 2012 1:13 PM
To: Wrage, Lisa Ann; Roy Heyne; Rosemary Higgins; Barbara Stoll; nfiner@ucsd.edu; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract

Thanks for this response. This clarifies a lot.
The protocol mentioned "antenatal corticosteroids," with betamethasone in parenthesis.
I suggest we should run the analysis using any steroids for the univariate analysis and for the multivariate regression rather than betamethasone, and use this for the abstract.
I would run a study of betamethasone vs. any steroids as an additional analysis.
Luc

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

From: Wrago, Lisa Ann [<mailto:lwrago@rti.org>]
Sent: Monday, October 01, 2012 9:24 AM
To: Luc Brion
Subject: RE: First version of Jackie LeVan's abstract

Hi Luc,

The question is nearly the same on all 3 versions of the form that I used:

(2002)

NG02 c.3. Were steroids given prior to delivery to accelerate maturity?
NG02 c.3.a. if YES Type of antenatal steroid given:
1=Betamethasone, 2=Dexamethasone, 3=Both

(2007)

NG02 c.3. Were steroids given prior to delivery to accelerate maturity?
NG02 c.3.a. if YES Type of antenatal steroid given:
1=Betamethasone, 2=Dexamethasone, 3=Both, 4=UK

(2011)

NG02 c.3. Were steroids given prior to delivery to accelerate lung maturity?
NG02 c.3.a. if YES Type of antenatal steroid given:
1=Betamethasone, 2=Dexamethasone, 3=Both, 4=Unknown

It looked to me that there must have been a switch to using more betamethasone instead of dexamethasone across these time periods. When I look directly at the NG02 data I see that the use of betamethasone has gone up steadily from 2002 to now: (as the proportion of type of antenatal steroid) 2002 57%, 2003 65%, 2004 75%, 2005 87%, 2006 93%, and 97-98% from 2007 to 2012. Typically we use 'any antenatal steroid use' in our analyses. I have not been asked to specify betamethasone use before. If we use 'any antenatal steroid use' then we would have pre-support=82.8%, post-support=88.6%.

Lisa

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

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, October 01, 2012 9:26 AM
To: Wrage, Lisa Ann
Subject: RE: First version of Jackie LeVan's abstract

Thanks a lot
I will get back to you re the multivariate analysis of antenatal steroids.

Luc

Luc P. Brion, MD
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-----Original Message-----

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, October 01, 2012 8:23 AM
To: Luc Brion
Subject: RE: First version of Jackie LeVan's abstract

Hi Luc, I'll check on that and get back to you.
Lisa

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

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Saturday, September 29, 2012 11:00 AM
To: Wrage, Lisa Ann
Subject: FW: First version of Jackie LeVan's abstract

Lisa;
Was there any change in reporting antenatal betamethasone on GDB between before and after SUPPORT?
Luc

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Saturday, September 29, 2012 4:31 AM
To: Luc Brion
Cc: Rosemary Higgins; Barbara Stoll; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: Re: First version of Jackie LeVan's abstract

Thanks Luc

I am struck by the difference in antenatal steroid use and surprised that anything is difference once you adjust for that Why do you think the ANS rate is so much higher post SUPPORT Be well Neil

On Sep 29, 2012, at 3:44 AM, "Luc Brion"
<Luc.Brion@UTSouthwestern.edu<<mailto:Luc.Brion@UTSouthwestern.edu>>> wrote:

Hi everyone:

Here is a first draft of Jackie LeVan's PAS abstract.
Please review and let me know if you have any suggestions, including about the list of authors.
I have included all authors listed in the latest version of the protocol and Lisa Wrage, who did the statistics, and has approved this version.

Best regards and thanks for your collaboration, Luc

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UT Southwestern Medical Center

The future of medicine, today.

<Changes in Therapy and Outcomes Associated with the SUPPORT Trial 092812 rev2.doc>

From: Luc Brion
To: Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; "Barbara Stoll"; nfiner@ucsd.edu; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract
Date: Monday, October 01, 2012 1:02:23 PM
Attachments: Changes in Therapy and Outcomes Associated with the SUPPORT Trial 10012.doc

Thanks, Roy

I edited the abstract accordingly

Luc

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From: Roy Heyne
Sent: Monday, October 01, 2012 9:39 AM
To: Luc Brion; Rosemary Higgins; 'Barbara Stoll'; nfiner@ucsd.edu; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract

This looks good to me, with the exception of the variable "Race". Though it may be possible to include Hispanic ethnicity in this grouping, at a minimum one would need to avoid overlap with

White by qualifying the latter as non-Hispanic white. One would also need to keep in mind that race and ethnicity are captured in two separate questions on NG02 in the GDB, the former of which does not include Hispanic and the latter of which revolves around it (though it also includes "Other").

From: Luc Brion

Sent: Sunday, September 30, 2012 11:27 PM

To: Rosemary Higgins; 'Barbara Stoll'; nfiner@ucsd.edu; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan

Subject: FW: First version of Jackie LeVan's abstract

Here is a version that was revised with Pablo's and Barbara's comments and suggestions.

Luc

Luc P. Brion, MD

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From: Luc Brion

Sent: Sunday, September 30, 2012 4:02 PM

To: 'Barbara Stoll'; Pablo Sanchez

Subject: RE: First version of Jackie LeVan's abstract

Barbara and Pablo:

Thanks for all the comments.

Here is the revised version

Unfortunately, we are at the maximum number of characters (4000) so I needed to trim somewhat to fit it all.

Thanks

Luc

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From: Barbara Stoll [<mailto:Barbara.Stoll@oz.ped.emory.edu>]

Sent: Sunday, September 30, 2012 1:14 PM

To: Luc Brion

Cc: Rosemary Higgins; " <nfiner@ucsd.edu>, " Wrage@ndb-mr2.cc.emory.edu; Lisa Ann " <wrage@rti.org>, " Pablo Sanchez " <Pablo.Sanchez@utsouthwestern.edu>, " Mambarambath.Jaleel " <Mambarambath.Jaleel@utsouthwestern.edu>, " Myra.Wyckoff "

<Myra.Wyckoff@utsouthwestern.edu>, " Roy.Heyne " <Roy.Heyne@utsouthwestern.edu>, " Das@ndb-mr2.; Abhik " <adas@rti.org>, " Jackie.LeVan " <doctorlevan@gmail.com>"@ndb-mr2.cc.emory.edu
Subject: Re: First version of Jackie LeVan's abstract

Luc

Very nice abstract

Attached are some edits

NIH antenatal concensus statement was published ~2000

Increase C/S most likely reflects increased willingness of OBs to aggressively support ELGANS

Increased maternal diabetes is interested in view of national obesity epidemic

Regards

BJSLuc Brion <Luc.Brion@utsouthwestern.edu> writes:
Hi everyone;

Here is a first draft of Jackie LeVan's PAS abstract.

Please review and let me know if you have any suggestions, including about the list of authors.

I have included all authors listed in the latest version of the protocol and Lisa Wrage, who did the statistics, and has approved this version.

Best regards and thanks for your collaboration.

Luc

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George W. Brumley, Jr., Professor and Chair
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President and CEO, Emory-Children's Center
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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL. *Jaelyn M LeVan, Luc P Brion, Lisa Wrage, Myra H Wyckoff, Pablo J Sánchez, Roy Heyne, Mambarambath Jaleel, Neil Finer, Abhik Das, Barbara Stoll, Rose Higgins, Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.*

BACKGROUND

The NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter 2 X 2 factorial trial, in which preterm neonates 24-27^{6/7} weeks' gestational age (GA) were randomized at birth to two interventions: (1) continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy or DR intubation with surfactant administration (within one hour of birth); and (2) oxygen (O₂) saturation targets of 85 to 89% or 91 to 95%. The primary outcomes, death or bronchopulmonary dysplasia (BPD) (O₂ use at 36 weeks), and death or severe retinopathy of prematurity (ROP) were not affected by the interventions. However, death was more frequent and severe ROP less frequent among infants randomized to low O₂ saturation targets. We hypothesized that (1) the percentage of DR intubation would decrease after publication of SUPPORT, without affecting BPD or death and ROP or death; and (2) the decrease in DR intubation in each center would depend on the percentage of pre-SUPPORT DR intubation.

OBJECTIVE

To compare DR intubation, BPD or death at 36 weeks, and severe ROP or death before discharge in time periods before SUPPORT and after its publication.

DESIGN/METHODS

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24-27^{6/7} weeks GA born before (2003-2004) and after SUPPORT (2010-2011) at one of 11 centers which participated in SUPPORT and were part of the NRN in 2003-2011. We excluded infants with known malformations and those receiving comfort care.

RESULTS

This study included 3151 infants (1617 pre-SUPPORT and 1534 post-SUPPORT).

Baseline Characteristics	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value
Birth weight (g) (mean ±SD)	824±191	816±190	0.23
Gestational Age (weeks)	26±1	26±1	0.64
Antenatal betamethasone	953(59%)	1344/1532 (88%)	<.0001
Race: Race : Black Not Hispanic (NH); White NH; Hispanic; Other (%)	45;37;15;3	44;38;14;5	0.02
Mode of delivery : Cesarean section	1004 (62%)	1009 (66%)	0.03
Rupture of membranes > 24 hours	436/1586 (27%)	360/1482 (24%)	0.043
Maternal hypertension	322 (20%)	409/1532 (25%)	<.0001
Maternal diabetes	42 (3%)	84 (5%)	<.0001

Parameters of Assessment	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value	Adjusted OR (95% CI)	Adjusted p-value
Intubated in DR	1313 (81%)	1082 (71%)	<0.0001	0.63 (0.51-0.77)	<0.0001
BPD or death	970 (60%)	824/1522 (54%)	0.0009	1.06 (0.88-1.3)	0.53
Severe ROP or death	515/1581 (33%)	408/1501(27%)	0.0011	0.80 (0.64-0.97)	0.024

The proportion of patients intubated in the DR was significantly lower in the post-SUPPORT group than in the pre-SUPPORT group (Table). The odds ratio (OR) of DR intubation (post vs. pre-SUPPORT) remained significant (Table) after adjusting for GA group (24-25^{6/7} vs. 26-27^{6/7} weeks), 100-grams birth weight groups, gender, race, multiple birth, prenatal steroids, prolonged rupture of membranes, cesarean section, maternal hypertension, maternal diabetes and center. The OR of ROP or death (adjusted for the same variables and for surfactant), but not that of BPD or death, was significantly different from 1. The correlation between pre-SUPPORT center-specific percentage of DR intubation and the change after SUPPORT was not significant (Spearman $r=-0.38$, $p=0.25$). Centers with $\geq 80\%$ DR intubation pre-SUPPORT were likely to have a significant reduction post-SUPPORT ($p<0.0001$) whereas centers with $< 80\%$ intubation pre-SUPPORT were not ($p=0.54$).

CONCLUSIONS

The adjusted odds of DR intubation, and that of death or ROP, but not that of death or BPD, significantly decreased after publication of the results of SUPPORT in NRN centers involved in the trial. DR intubation was more likely to decrease after SUPPORT in centers with $\geq 80\%$ pre-SUPPORT DR intubation.

| 39844000 characters

From: Gantz, Marie
To: Das, Abhik; Vaucher, Yvonne; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam.Peralta, M.D.; nancy.newman
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Monday, October 01, 2012 9:34:30 AM

I agree with Abhik, and we do intend to create adjusted models. Those will be completed prior to the submission of the final abstract to the subcommittee.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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

From: Das, Abhik
Sent: Monday, October 01, 2012 9:30 AM
To: Vaucher, Yvonne; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam.Peralta, M.D.; nancy.newman
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

I think you want to show that the requirement for antenatal consent led to the selection of a sample that was different from the overall trial target population, which led to these babies having different outcomes. Your argument for the latter will be strengthened if you show that the unadjusted outcomes were different, but that difference is completely explained by the different baseline risk factors among the enrolled and non enrolled babies. For that reason alone, I would think that an adjusted analysis is very much worthwhile.

Thanks

Abhik

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, September 28, 2012 3:01 PM
To: Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam.Peralta, M.D.; nancy.newman; Vaucher, Yvonne
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

The point of the abstract is that outcome was different for the enrolled vs. eligible/nonenrolled. Not a surprise but it does have implications for enrollment protocols/generalization. One expects that models will show that some of the differences between the groups (ANS, IVH, BPD, lack of PNC) will predict the worse outcome (primarily death) for the non-enrolled. The most important message is really for our OB colleagues...adequate PNC would identify problems that could be treated or need to be monitored, earlier presentation for delivery would allow time for maternal/fetal stabilization, treatment of infection, ANS, optimal time/route/place of delivery. Much (maybe most) of outcome is really related to what happens before we even enter the picture. We can only work with what we get!

Yvonne

On 9/28/12 7:59 AM, "Das, Abhik" <adas@rti.org> wrote:

>I still think that we need to look at it again at follow up. I don't
>think we can just leave the readers hanging by just presenting
>provocative but unadjusted findings. We can still make the arguments
>that you make in the discussion.

>

>Thanks

>

>Abhik

>

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

>From: Rich, Wade [mailto:wrich@ucsd.edu]

>Sent: Friday, September 28, 2012 10:55 AM

>To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Finer, Neil;

>'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu';

>'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot';

>Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy newman';

>Das, Abhik

>Cc: Archer, Stephanie (NIH/NICHD) [E]

>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:

>Enrolled vs. Eligible/Nonenrolled

>

>Whether there was a positive effect of enrollment in the trial when all

>differences in groups are corrected out is not the question we were

>attempting to answer. The question was, and is, whether the

>substantively different outcomes we found between those infant enrolled

>in the trial and those not enrolled but eligible, would also be

>reflected in their follow-up. I believe the question of a Hawthorne

>effect in this trial was previously looked at by Marie, and found not to exist.

>Wade

>

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

>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

>Sent: Friday, September 28, 2012 5:53 AM

>To: Vaucher, Yvonne; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie;

>'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook,

>Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; 'nancy

>newman'; Rich, Wade; 'Das, Abhik'

>Cc: Archer, Stephanie (NIH/NICHD) [E]

>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:

>Enrolled vs. Eligible/Nonenrolled

>

>This is as expected. Have we done some type of analysis adjusting for

>the baseline differences, especially with respect to ANS?

>

>Thanks

>- we may want to speculate that participation in clinical trials could

>improve outcome!

>

>Rosemary D. Higgins, MD

>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal

>Research Network Pregnancy and Perinatology Branch CDBPM, NIH

>6100 Executive Blvd., Room 4B03

>MSC 7510

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>301-496-5575
>301-496-3790 (FAX)
>higginsr@mail.nih.gov
>
>
>-----Original Message-----
>From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
>Sent: Thursday, September 27, 2012 9:32 PM
>To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler';
>'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot';
>Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; Vaucher, Yvonne;
>'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD)
>[E]
>Cc: Archer, Stephanie (NIH/NICHD) [E]
>Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:
>Enrolled vs. Eligible/Nonenrolled
>
>SUPPORT subcommittee:
>
>PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs.
>Eligible/Nonenrolled attached. (97% full) Please send comments.
>
>Thanks.
>
>Yvonne

From: Luc Brion
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; "Barbara Stoll"; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract
Date: Monday, October 01, 2012 9:15:54 AM

Thanks a lot

Luc

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From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Monday, October 01, 2012 1:51 AM
To: Luc Brion; Rosemary Higgins; 'Barbara Stoll'; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract

Thanks Luc, Pablo and Barbara.

I can't escape the difference in ANS – with or without adjustment – it is such a strong predictor of outcome

This is fine for me

Be well

Neil

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]
Sent: Sunday, September 30, 2012 9:27 PM
To: Rosemary Higgins; 'Barbara Stoll'; Finer, Neil; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: FW: First version of Jackie LeVan's abstract

Here is a version that was revised with Pablo's and Barbara's comments and suggestions.

Luc

Luc P. Brion, MD
Professor of Pediatrics
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From: Luc Brion
Sent: Sunday, September 30, 2012 4:02 PM

To: 'Barbara Stoll'; Pablo Sanchez
Subject: RE: First version of Jackie LeVan's abstract

Barbara and Pablo:
Thanks for all the comments.

Here is the revised version

Unfortunately, we are at the maximum number of characters (4000) so I needed to trim somewhat to fit it all.

Thanks

Luc

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From: Barbara Stoll [<mailto:Barbara.Stoll@oz.ped.emory.edu>]
Sent: Sunday, September 30, 2012 1:14 PM
To: Luc Brion
Cc: Rosemary Higgins; " <nfiner@ucsd.edu>, " Wrage@ndb-mr2.cc.emory.edu; Lisa Ann " <wrage@rti.org>, " Pablo Sanchez " <Pablo.Sanchez@utsouthwestern.edu>, " Mambarambath.Jaleel "

<Mambarambath.Jaleel@utsouthwestern.edu>, " Myra.Wyckoff "
<Myra.Wyckoff@utsouthwestern.edu>, " Roy.Heyne " <Roy.Heyne@utsouthwestern.edu>, " Das@ndb-
mr2.; Abhik " <adas@rti.org>, " Jackie.LeVan " <doctorlevan@gmail.com>"@ndb-mr2.cc.emory.edu
Subject: Re: First version of Jackie LeVan's abstract

Luc
Very nice abstract

Attached are some edits

NIH antenatal concensus statement was published ~2000

Increase C/S most likely reflects increased willingness of OBs to
aggressively support ELGANS

Increased maternal diabetes is interesting in view of national obesity
epidemic

Regards

BJS Luc Brion <Luc.Brion@utsouthwestern.edu> writes:
Hi everyone:

Here is a first draft of Jackie LeVan's PAS abstract.

Please review and let me know if you have any suggestions, including about the list of
authors.

I have included all authors listed in the latest version of the protocol and Lisa Wrage, who did
the statistics and has approved his version.

Best regards and thanks for your collaboration.

Luc

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UT Southwestern Medical Center

The future of medicine, today.

Barbara J. Stoll, MD

George W. Brumley, Jr., Professor and Chair

Department of Pediatrics, Emory University School of Medicine

President and CEO, Emory-Children's Center

SVP and Chief Academic Officer, Children's Healthcare of Atlanta

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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT

TRIAL. *Jaclyn M LeVan, Luc P Brion, Lisa Wrage, Myra H Wyckoff, Pablo J Sánchez, Roy Heyne, Mambarambath Jaleel, Neil Finer, Abhik Das, Barbara Stoll, Rose Higgins, Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.*

BACKGROUND

The NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm neonates of 24-27^{6/7} weeks' gestational age (GA) were randomized at birth to two interventions: (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy or, vs. DR intubation with surfactant administration (within one hour of birth); and (2) either oxygen (O₂) saturation targets of 85 to 89% or vs. 91 to 95%. The primary outcomes, death or bronchopulmonary dysplasia (BPD), (O₂ use at 36 weeks) (BPD), and death or severe retinopathy of prematurity (ROP) were not affected by the interventions. However, death was more frequent and severe ROP less frequent among infants randomized to low O₂ saturation targets. We hypothesized that (1) that the percentage of DR intubation would decrease after publication of SUPPORT, without affecting BPD or death and ROP or death; and (2) that the decrease in DR intubation in each center would depend on the percentage of pre-SUPPORT DR intubation.

OBJECTIVE

To compare DR intubation, BPD or death at 36 weeks, and severe ROP or death before discharge in time periods before SUPPORT and after its publication.

DESIGN/METHODS

This was a retrospective cohort study using the prospective NRN/NICHD generic database. We included infants of 24-27^{6/7} weeks GA born before (2003-2004) and after SUPPORT (2010-2011) at one of 11 centers which participated in SUPPORT and were part of participating in the NRN in 2003-2011, before SUPPORT (2003-2004) and after SUPPORT (2010-2011). We excluded infants with known malformations and those who received comfort care.

RESULTS

This study included 3151 infants (1617 pre-SUPPORT and 1534 post-SUPPORT).

Baseline Characteristics	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value
Birth weight (g) (mean ±SD)	824±191	816±190	0.23
Gestational Age (weeks)	26.5-7±1.1	25.6±1.1	0.64
Antenatal betamethasone	953 (59.4%)	1344/1532 (88.7%)	<.0001
Race: Black; White; Hispanic; Other (%)	45.0; 37.3; 15.4; 9.32-8	44.3; 5.387; 6.140; 54-9	0.02
Mode of delivery: cesarean section	1004 (62.4%)	1009 (66.5.9%)	0.03
Rupture of membranes > 24 hours	436/1586 (27.5%)	360/1482 (24.3%)	0.043
Maternal hypertension	322 (20.19.9%)	409/1532 (254.7%)	<.0001
Maternal diabetes	42 (32.6%)	84 (5.5%)	<.0001

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Parameters of Assessment	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value	Adjusted OR (95% CI)	Adjusted p-value
Intubated in DR	1313 (81.2%)	1082 (710.5%)	<0.0001	0.63 (0.51-0.77)	<0.0001
BPD or death	970 (60.0%)	824/1522 (54.1%)	0.0009	1.06 (0.88-1.3)	0.53
Severe ROP or death	515/1581 (332.6%)	408/1501(27.2%)	0.0011	0.80 (0.64-0.97)	0.024

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The proportion of patients intubated in the DR was significantly lower in the post-SUPPORT group than in the pre-SUPPORT group (Table). The odds ratio (OR) of DR intubation (post vs. pre-SUPPORT) remained significant (Table) after adjusting for GA group (24-25^{6/7} vs. 26-27^{6/7} weeks), 100-grams birth weight groups, gender, race, multiple birth, prenatal steroids, prolonged rupture of membranes, cesarean section, maternal hypertension, maternal diabetes and center. The OR of ROP or death (adjusted for the same variables and for surfactant), but not that of BPD or death, was significantly different from 1. The correlation between pre-SUPPORT center-specific percentage of DR intubation and the change after SUPPORT was not significant (Spearman $r=-0.38$, $p=0.25$). Centers with $\geq 80\%$ DR intubation rate pre-SUPPORT were likely to have a significant reduction post-SUPPORT ($p<0.0001$) whereas centers with $< 80\%$ intubation rate pre-SUPPORT were not ($p=0.54$).

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CONCLUSIONS

The adjusted odds of DR intubation, and that of death or ROP, but not that of death or BPD, significantly decreased after publication of the results of SUPPORT in NRN centers involved in the trial. DR intubation was more likely to decrease after SUPPORT in centers with $\geq 80\%$ pre-SUPPORT DR intubation rate.

40003994 characters

From: Luc Brion
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract
Date: Saturday, September 29, 2012 11:47:12 AM

Neil.

I thought a bit more about this

Here are three possible hypotheses:

1. change in policy in some centers
2. change in ANS reporting (I asked Lisa to check on that)
3. change in patients. For this, we may do a post hoc multivariate analysis with ANS exposure as output variable and factors as independent variables (GA group, maternal hypertension, maternal diabetes, multiple, center etc)

Luc

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Saturday, September 29, 2012 4:31 AM
To: Luc Brion
Cc: Rosemary Higgins; Barbara Stoll; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: Re: First version of Jackie LeVan's abstract

Thanks Luc

I am struck by the difference in antenatal steroid use and surprised that anything is difference once you adjust for that Why do you think the ANS rate is so much higher post SUPPORT Be well Neil

On Sep 29, 2012, at 3:44 AM, "Luc Brion"

<Luc.Brion@UTSouthwestern.edu<<mailto:Luc.Brion@UTSouthwestern.edu>>> wrote:

Hi everyone:

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Please review and let me know if you have any suggestions, including about the list of authors.

I have included all authors listed in the latest version of the protocol and Lisa Wrage, who did the statistics, and has approved this version.

Best regards and thanks for your collaboration, Luc

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<Changes in Therapy and Outcomes Associated with the SUPPORT Trial 092812 rev2.doc>

From: Luc Brion
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: RE: First version of Jackie LeVan's abstract
Date: Saturday, September 29, 2012 10:41:48 AM
Attachments: Report_27Sept12.doc
drintubchisq_28SEP12.rtf

Neil:

Thank you for your email.

I am not sure why ANS increased after correction for all the other variables. nor why severe ROP/death decreased after SUPPORT.

We had hypothesized ROP/death would not change since death increased and ROP decreased with low saturation in SUPPORT.

I attach files with the results we have at this point (those selected for starting to work on the abstract).

Once all planned analyses are completed, we may consider/discuss additional exploratory approaches, such as finding out if there was any change in policy (e.g., ANS or O2 saturation goals) in any of the 11 units.

Luc

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<Changes in Therapy and Outcomes Associated with the SUPPORT Trial 092812 rev2.doc>

September 27, 2012

Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Updated from September 25 – additional variables added to models

Neonatal Network Investigator: J. LeVan, Luc Brion

RTI Statistician: Lisa Wrage

Population

Infants of 24-27 weeks gestational age at birth, born during years 2003-2004 or 2010-2011 at one of 11 centers participating in the SUPPORT trial and in the NRN from 2003-2011, excluding infants with known malformations or who had respiratory or other medical support withheld prior to death < 12 hours.

Methods

Primary outcome variables

The primary outcome variables of interest include intubation in the delivery room, BPD or death at 36 weeks, and severe ROP or death before discharge. Intubation in delivery room is recorded in the GDB. BPD is defined as oxygen use at 36 weeks. Severe ROP is defined using ophthalmology information from the GDB, NG03 section H (see appendix for details)

Secondary outcome variables

Other outcomes of interest include BPD, severe ROP, death before discharge, surfactant use, pneumothorax, pulmonary hemorrhage, postnatal steroid use, severe IVH, proven NEC, days of mechanical ventilation (survivors), days on supplemental oxygen (survivors), and length of hospital stay.

Other variables

Maternal and neonatal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Study groups

Infants from the study population were classified as 'pre-SUPPORT' if they were born during 2003-2004 and as 'post-SUPPORT' if they were born during 2010-2011.

Statistical Analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and ttests or Wilcoxon tests, as appropriate, for continuous variables. Logistic regression models were used to obtain adjusted results for each of the primary outcomes. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation rate during the first epoch.

Results

There were a total of n=5323 infants born at 24-27 weeks gestational age during 2003-2004 (n=2998) or 2010-2011 (n=2322) and included in the GDB. Of these n=1581 infants were born in NRN centers not included in this study and an additional n=352 were outborn, these infants were excluded. Of the remaining infants, n=134 infants with known malformations, n=100 infants who had respiratory or medical support withdrawn prior to death < 12 hours were excluded, and 5 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of n=3151 infants. Of these n=1617 infants are in the pre-SUPPORT group and n=1534 infants are in the post-SUPPORT group.

Power Calculations

Power calculations for each of the primary outcomes, based on chi square tests, an alpha of .05, and the sample sizes noted above give these results: a power of 1.0 to detect a change of delivery room intubation from 80% to 68%; a power of 0.8 to detect a change in outcome 'BPD or death' from 50% to 45%, and a power of 0.94 to detect a change in outcome severe ROP or death from 67% to 61%.

Statistical analysis

Unadjusted comparisons of variables of interest by study group are shown in **Tables 1-3**. Logistic regression models for each of the primary outcomes were also run to obtain adjusted results. The resulting adjusted odds ratios, 95% confidence intervals, and p-values are shown in **Table 2**. Additionally, within center, the percent of infants who were intubated in the delivery room was calculated for each study group and the difference between the post-SUPPORT group and the pre-SUPPORT group was also calculated. Using the results for the 11 centers in this study, the correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.38, $p=0.25$). (see appendix for SAS output for the logistic regression models and for the Spearman correlation).

Table 1. Maternal and Neonatal Characteristics¹

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
Birth weight (g)	824 (191)	816 (190)	0.23
Gestational Age (weeks)	25.7 (1.1)	25.6 (1.1)	0.64
% Male	858 (53.1)	767 (50.0)	0.09
Race:			
NH Black	727 (45.0)	654 (43.5)	0.02
NH White	603 (37.3)	566 (37.6)	
Hispanic	241 (14.9)	210 (14.0)	
Other	46 (2.8)	74 (4.9)	
Antenatal Steroids: betamethasone	953(59.1)	1344/1532 (87.7)	<.0001
Multiple birth	370 (22.9)	360/1532 (23.5)	0.68
Mode of delivery: c-section	1004 (62.1)	1009 (65.9)	0.03
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	360/1482 (24.3)	0.043
Maternal hypertension	322 (19.9)	409/1532 (24.7)	<.0001
Maternal diabetes	42 (2.6)	84 (5.5)	<.0001
Antibiotics	1198/1615 (74.2)	1114/1530 (72.8)	0.38

Table 2. Primary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²	adjusted OR ³ (95% CI)	adjusted p-value ³
Intubated in delivery room	1313 (81.2)	1082 (70.5)	<.0001	0.63 (0.51-0.77)	<.0001
BPD or death at 36 weeks	970 (60.0)	824/1523 (54.1)	.0009	1.06 (0.88-1.3)	0.53
Severe ROP or death	515/1581 (32.6)	408/1501(27.2)	.0011	0.80 (0.64-0.97)	0.024

Table 3. Secondary Outcomes¹

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value ²
BPD (O2 at 36 weeks)	664/1311 (50.7)	581/1279 (45.4)	.008
Death at 36 weeks	306 (18.9)	243/1529 (15.9)	.026
Severe ROP	174 (13.5)	138 (10.8)	.036
Death before discharge	358/1614 (22.2)	285/1519 (18.8)	.017
Surfactant	1427 (88.3)	1266/1528 (82.9)	<.0001
Pneumothorax	135/1604 (8.4)	86/1511 (5.7)	.0030
Pulmonary Hemorrhage	181/1603 (11.3)	106/1512 (7.0)	<.0001
Postnatal Steroids	195/1599 (12.2)	182/1496 (12.2)	0.97
Days on ventilator (survivors)	22.3 (24.4), 13	18.5 (21.2), 10	<.0001
Days on supp. O2 (survivors)	59.2 (36)	56.8 (37.8)	0.10
Severe IVH	288 (18.5)	204 (13.8)	.0004
Proven NEC	177 (11.0)	160 (10.6)	0.71
Length of hospital stay (days)	84.4 (57.5), 83	90.9 (52.9), 90	.0006

¹ presented as mean (SD), median for days on ventilator and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.

² unadjusted p-values from Chi Square tests, ttests, or Wilcoxon tests, as appropriate.

³ OR reflects odds of the outcome for post_SUPPORT vs. pre_SUPPORT.

Appendix – Definition of severe ROP:

Severe ROP is defined as “retinal detachment (partial or complete), surgery, or Avastin/Anti-VEGf drug” using questions from NG03 section H ‘Ophthalmology’. Specifically, an infant is defined as having severe ROP if:

Using NG03 2002 – for the pre-SUPPORT group born 2003-2004:

- H.1.a.1.i. Highest Stage of ROP in right or left eye=4 or 5 (retinal detachment) ***or***
- H.3.a.i. retinal ablation performed prior to a threshold diagnosis in Right eye='Y' ***or***
- H.3.a.ii. retinal ablation performed prior to a threshold diagnosis in Left eye='Y' ***or***
- H.3.b.i. any surgery performed in Right eye=1,2,3,4 ***or***
- H.3.b.ii. any surgery performed in Left eye=1,2,3,4.

Using NG03 2008, 2011 – for the post-SUPPORT group born 2010-2011:

- H.1.b.1. retinal ablation performed in either eye='Y' ***or***
- H.1.b.2. scleral buckle or vitrectomy performed in either eye='Y' ***or***
- 2008 H.1.b.3.
Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***
- 2011 H.1.b.3. Avastin or other anti-VEGF drug='Y' ***or***
- 2011 H.1.b.4.
Other therapies='Y' (? if there are any of these I will look at the specifics and will check with you to see if these fit the definition) ***or***
- H.2. =2 - Determined severe ROP (ROP surgery, retinal detachment, Avastin or anti-VEGf) in either eye at status.

27SEP12 17:25

09:23 Monday, June 30, 2014 5

LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	intubated_dr	intubated in the delivery room, 1=Yes
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	intubated_dr	Total Frequency
1	1	2304
2	0	733

Probability modeled is intubated_dr=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	1.2113	0.2543	22.6952	<.0001
post_SUPPORT		1	-0.4687	0.1034	20.5546	<.0001
ga2425		1	0.7892	0.1302	36.7255	<.0001
brwtgtp	1= <=600g	1	1.5891	0.2253	49.7592	<.0001
brwtgtp	2=601-700g	1	1.3445	0.1961	46.9995	<.0001
brwtgtp	3=701-800g	1	1.1025	0.1806	37.2791	<.0001
brwtgtp	4=801-900g	1	0.6913	0.1525	20.5414	<.0001
brwtgtp	5=901-1000g	1	0.5428	0.1532	12.5470	0.0004
malex		1	0.1522	0.0992	2.3560	0.1248
MULTBRTH		1	-0.3070	0.1213	6.4021	0.0114
antester_beta		1	-0.6588	0.1431	21.1928	<.0001
race_bwho	1=Black	1	-0.1722	0.1162	2.1960	0.1384
race_bwho	3=Hispanic	1	-0.2508	0.1772	2.0034	0.1569
race_bwho	4=Other	1	0.0626	0.2924	0.0458	0.8305
CSECT		1	0.3867	0.1084	12.7273	0.0004
ROMGT24		1	-0.1757	0.1161	2.2899	0.1302

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LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.6205	0.1290	23.1306	<.0001
diabetes		1	-0.3525	0.2335	2.2787	0.1312
CENTER	3	1	-0.3715	0.2519	2.1751	0.1403
CENTER	4	1	-0.0247	0.2817	0.0077	0.9301
CENTER	5	1	0.7656	0.2684	8.1382	0.0043
CENTER	9	1	-0.1973	0.2464	0.6413	0.4232
CENTER	11	1	-0.7581	0.1895	16.0115	<.0001
CENTER	12	1	0.7980	0.2518	10.0425	0.0015
CENTER	14	1	0.6604	0.2560	6.6519	0.0099
CENTER	15	1	-0.2131	0.2720	0.6137	0.4334
CENTER	16	1	-1.8287	0.1923	90.4280	<.0001
CENTER	18	1	0.5458	0.2343	5.4257	0.0198

Odds Ratio Estimates					
Effect			Point Estimate	95% Wald Confidence Limits	
post_SUPPORT			0.626	0.511	0.766
ga2425			2.202	1.706	2.842
brwtgtp	1= <=600g	vs 6=>1000g	4.899	3.150	7.619
brwtgtp	2=601-700g	vs 6=>1000g	3.836	2.612	5.634
brwtgtp	3=701-800g	vs 6=>1000g	3.012	2.114	4.290
brwtgtp	4=801-900g	vs 6=>1000g	1.996	1.480	2.692
brwtgtp	5=901-1000g	vs 6=>1000g	1.721	1.274	2.324
malex			1.164	0.959	1.414
MULTBRTH			0.736	0.580	0.933
antester_beta			0.517	0.391	0.685
race_bwho	1=Black	vs 2=White	0.842	0.670	1.057
race_bwho	3=Hispanic	vs 2=White	0.778	0.550	1.101
race_bwho	4=Other	vs 2=White	1.065	0.600	1.888
CSECT			1.472	1.190	1.821
ROMGT24			0.839	0.668	1.053
htn			0.538	0.418	0.692
diabetes			0.703	0.445	1.111

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LOGISTIC MODELS
OUTCOME: INTUBATED IN DELIVERY ROOM

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CENTER	3 vs 19	0.690	0.421	1.130
CENTER	4 vs 19	0.976	0.562	1.694
CENTER	5 vs 19	2.150	1.271	3.638
CENTER	9 vs 19	0.821	0.506	1.331
CENTER	11 vs 19	0.469	0.323	0.679
CENTER	12 vs 19	2.221	1.356	3.638
CENTER	14 vs 19	1.936	1.172	3.197
CENTER	15 vs 19	0.808	0.474	1.377
CENTER	16 vs 19	0.161	0.110	0.234
CENTER	18 vs 19	1.726	1.090	2.732

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	bpddeath36	BPD or death at 36 weeks
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	bpddeath36	Total Frequency
1	1	1578
2	0	1286

Probability modeled is bpddeath36=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.5159	0.2783	159.6514	<.0001
post_SUPPORT		1	0.0606	0.0975	0.3864	0.5342
intubated_dr		1	0.1302	0.1317	0.9772	0.3229
ga2425		1	0.3412	0.1197	8.1263	0.0044
brwtgtp	1=<=600g	1	2.2784	0.2774	67.4438	<.0001
brwtgtp	2=601-700g	1	1.3606	0.1952	48.5834	<.0001
brwtgtp	3=701-800g	1	1.0281	0.1694	36.8283	<.0001
brwtgtp	4=801-900g	1	0.7018	0.1493	22.0935	<.0001
brwtgtp	5=901-1000g	1	0.5082	0.1518	11.2067	0.0008
sga		1	0.1167	0.2074	0.3166	0.5736
malex		1	0.7661	0.0924	68.8146	<.0001
MULTBRTH		1	-0.1677	0.1109	2.2862	0.1305
antester_beta		1	0.0925	0.1192	0.6023	0.4377
race_bwho	1=Black	1	-0.2062	0.1071	3.7097	0.0541
race_bwho	3=Hispanic	1	-0.2096	0.1539	1.8553	0.1732
race_bwho	4=Other	1	-0.3795	0.2452	2.3962	0.1216
CSECT		1	-0.0901	0.0987	0.8338	0.3612
ROMGT24		1	-0.0638	0.1071	0.3540	0.5518

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
htn		1	-0.1063	0.1208	0.7753	0.3786
diabetes		1	0.0635	0.2259	0.0789	0.7787
SURFACT		1	0.7564	0.1609	22.1057	<.0001
fio24ge90		1	1.3426	0.3165	17.9897	<.0001
pda_ligation		1	0.7154	0.1595	20.1311	<.0001
pda_indom		1	0.4671	0.1059	19.4420	<.0001
LOS		1	0.6069	0.0990	37.5517	<.0001
CENTER	3	1	0.9273	0.2296	16.3156	<.0001
CENTER	4	1	1.1417	0.2496	20.9259	<.0001
CENTER	5	1	2.2141	0.2377	86.7587	<.0001
CENTER	9	1	1.2351	0.2310	28.5861	<.0001
CENTER	11	1	1.7539	0.1889	86.2447	<.0001
CENTER	12	1	2.3285	0.2191	112.9164	<.0001
CENTER	14	1	1.2571	0.2077	36.6489	<.0001
CENTER	15	1	1.8008	0.2607	47.7070	<.0001
CENTER	16	1	0.7062	0.1962	12.9599	0.0003
CENTER	18	1	1.2842	0.2002	41.1427	<.0001

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
post_SUPPORT		1.062	0.878	1.286
intubated_dr		1.139	0.880	1.475
ga2425		1.407	1.113	1.779
brwtgtp	1= <=600g vs 6=>1000g	9.761	5.667	16.813
brwtgtp	2=601-700g vs 6=>1000g	3.899	2.659	5.716
brwtgtp	3=701-800g vs 6=>1000g	2.796	2.006	3.897
brwtgtp	4=801-900g vs 6=>1000g	2.017	1.506	2.703
brwtgtp	5=901-1000g vs 6=>1000g	1.662	1.234	2.238
sga		1.124	0.748	1.687
malex		2.151	1.795	2.578
MULTBRTH		0.846	0.680	1.051
antester_beta		1.097	0.868	1.386
race_bwho	1=Black vs 2=White	0.814	0.660	1.004
race_bwho	3=Hispanic vs 2=White	0.811	0.600	1.096
race_bwho	4=Other vs 2=White	0.684	0.423	1.106

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LOGISTIC MODELS
 OUTCOME: BPD OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
CSECT	0.914	0.753	1.109
ROMGT24	0.938	0.761	1.157
htn	0.899	0.710	1.139
diabetes	1.066	0.684	1.659
SURFACT	2.131	1.554	2.920
fio24ge90	3.829	2.059	7.120
pda_ligation	2.045	1.496	2.795
pda_indom	1.595	1.296	1.963
LOS	1.835	1.511	2.228
CENTER 3 vs 19	2.528	1.612	3.964
CENTER 4 vs 19	3.132	1.920	5.109
CENTER 5 vs 19	9.153	5.744	14.584
CENTER 9 vs 19	3.439	2.187	5.408
CENTER 11 vs 19	5.777	3.990	8.365
CENTER 12 vs 19	10.263	6.679	15.768
CENTER 14 vs 19	3.515	2.340	5.281
CENTER 15 vs 19	6.054	3.632	10.092
CENTER 16 vs 19	2.026	1.380	2.976
CENTER 18 vs 19	3.612	2.440	5.347

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LOGISTIC MODELS
OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Model Information		
Data Set	DAT.ANALYSIS	
Response Variable	sevropdeath	severe ROP or death
Number of Response Levels	2	
Model	binary logit	
Optimization Technique	Fisher's scoring	

Response Profile		
Ordered Value	sevropdeath	Total Frequency
1	1	887
2	0	2085

Probability modeled is sevropdeath=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.7160	0.3056	78.9797	<.0001
post_SUPPORT		1	-0.2275	0.1009	5.0875	0.0241
ga2425		1	0.6591	0.1126	34.2712	<.0001
brwtgtp	1= <=600g	1	2.7580	0.2171	161.4150	<.0001
brwtgtp	2=601-700g	1	1.7164	0.2008	73.0686	<.0001
brwtgtp	3=701-800g	1	1.0975	0.1955	31.5278	<.0001
brwtgtp	4=801-900g	1	0.5279	0.1929	7.4867	0.0062
brwtgtp	5=901-1000g	1	0.2972	0.2031	2.1405	0.1435
malex		1	0.6057	0.0954	40.3424	<.0001
MULTBRTH		1	0.2068	0.1135	3.3219	0.0684
antester_beta		1	-0.3822	0.1214	9.9194	0.0016
race_bwho	1=Black	1	-0.3434	0.1143	9.0340	0.0027
race_bwho	3=Hispanic	1	0.3656	0.1648	4.9191	0.0266
race_bwho	4=Other	1	0.9008	0.2527	12.7124	0.0004
CSECT		1	-0.1123	0.1044	1.1581	0.2819
ROMGT24		1	-0.1955	0.1138	2.9493	0.0859
htn		1	-0.4465	0.1289	11.9932	0.0005
diabetes		1	0.4642	0.2343	3.9249	0.0476

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LOGISTIC MODELS
 OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
SURFACT		1	0.4952	0.1705	8.4313	0.0037
CENTER	3	1	0.2831	0.2427	1.3606	0.2434
CENTER	4	1	0.3981	0.2596	2.3506	0.1252
CENTER	5	1	1.0627	0.2224	22.8359	<.0001
CENTER	9	1	0.3015	0.2452	1.5118	0.2189
CENTER	11	1	0.2869	0.1987	2.0850	0.1487
CENTER	12	1	0.4161	0.2137	3.7913	0.0515
CENTER	14	1	-0.8750	0.2469	12.5578	0.0004
CENTER	15	1	-0.4073	0.2902	1.9688	0.1606
CENTER	16	1	0.2082	0.2068	1.0138	0.3140
CENTER	18	1	0.1953	0.2132	0.8394	0.3596

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
post_SUPPORT		0.797	0.654	0.971
ga2425		1.933	1.550	2.410
brwtgtp	1=<=600g vs 6=>1000g	15.769	10.304	24.132
brwtgtp	2=601-700g vs 6=>1000g	5.564	3.754	8.248
brwtgtp	3=701-800g vs 6=>1000g	2.997	2.043	4.395
brwtgtp	4=801-900g vs 6=>1000g	1.695	1.162	2.475
brwtgtp	5=901-1000g vs 6=>1000g	1.346	0.904	2.004
malex		1.833	1.520	2.209
MULTBRTH		1.230	0.985	1.536
antester_beta		0.682	0.538	0.866
race_bwho	1=Black vs 2=White	0.709	0.567	0.887
race_bwho	3=Hispanic vs 2=White	1.441	1.043	1.991
race_bwho	4=Other vs 2=White	2.462	1.500	4.039
CSECT		0.894	0.728	1.097
ROMGT24		0.822	0.658	1.028
htn		0.640	0.497	0.824
diabetes		1.591	1.005	2.518
SURFACT		1.641	1.175	2.292
CENTER	3 vs 19	1.327	0.825	2.136
CENTER	4 vs 19	1.489	0.895	2.477
CENTER	5 vs 19	2.894	1.872	4.475

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LOGISTIC MODELS
OUTCOME: SEVERE ROP OR DEATH

The LOGISTIC Procedure

Odds Ratio Estimates				
Effect		Point Estimate	95% Wald Confidence Limits	
CENTER	9 vs 19	1.352	0.836	2.186
CENTER	11 vs 19	1.332	0.903	1.967
CENTER	12 vs 19	1.516	0.997	2.305
CENTER	14 vs 19	0.417	0.257	0.676
CENTER	15 vs 19	0.665	0.377	1.175
CENTER	16 vs 19	1.231	0.821	1.847
CENTER	18 vs 19	1.216	0.800	1.846

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Tables of intubation in DR by pre/post SUPPORT epoch
 grouped by: Centers with pre SUPPORT % dr intubations < 80, and >= 80

The FREQ Procedure

Table 1 of post_SUPPORT by intubated_dr			
Controlling for prepctl80=No			
post_SUPPORT	intubated_dr(intubated in the delivery room, 1=Yes)		
Frequency Row Pct	No	Yes	Total
No	116 9.80	1068 90.20	1184
Yes	252 23.03	842 76.97	1094
Total	368	1910	2278

Statistics for Table 1 of post_SUPPORT by intubated_dr
 Controlling for prepctl80=No

Statistic	DF	Value	Prob
Chi-Square	1	73.5613	<.0001
Likelihood Ratio Chi-Square	1	74.7199	<.0001
Continuity Adj. Chi-Square	1	72.5872	<.0001
Mantel-Haenszel Chi-Square	1	73.5290	<.0001
Phi Coefficient		-0.1797	
Contingency Coefficient		0.1769	
Cramer's V		-0.1797	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	116
Left-sided Pr <= F	4.560E-18
Right-sided Pr >= F	1.0000
Table Probability (P)	2.926E-18
Two-sided Pr <= P	8.532E-18

Sample Size = 2278

Neonatal Research Network

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Tables of intubation in DR by pre/post SUPPORT epoch
 grouped by: Centers with pre SUPPORT % dr intubations < 80, and >= 80

The FREQ Procedure

Table 2 of post_SUPPORT by intubated_dr			
Controlling for prepctl80=Yes			
post_SUPPORT	intubated_dr(intubated in the delivery room, 1=Yes)		
Frequency Row Pct	No	Yes	Total
No	188 43.42	245 56.58	433
Yes	200 45.45	240 54.55	440
Total	388	485	873

Statistics for Table 2 of post_SUPPORT by intubated_dr
 Controlling for prepctl80=Yes

Statistic	DF	Value	Prob
Chi-Square	1	0.3666	0.5449
Likelihood Ratio Chi-Square	1	0.3666	0.5449
Continuity Adj. Chi-Square	1	0.2887	0.5910
Mantel-Haenszel Chi-Square	1	0.3662	0.5451
Phi Coefficient		-0.0205	
Contingency Coefficient		0.0205	
Cramer's V		-0.0205	

Fisher's Exact Test	
Cell (1,1) Frequency (F)	188
Left-sided Pr <= F	0.2955
Right-sided Pr >= F	0.7497
Table Probability (P)	0.0452
Two-sided Pr <= P	0.5859

Sample Size = 873

Neonatal Research Network

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Tables of intubation in DR by pre/post SUPPORT epoch
grouped by: Centers with pre SUPPORT % dr intubations < 80, and >= 80

The FREQ Procedure

Summary Statistics for post_SUPPORT by intubated_dr
Controlling for prepctl80

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)				
Statistic	Alternative Hypothesis	DF	Value	Prob
1	Nonzero Correlation	1	48.5068	<.0001
2	Row Mean Scores Differ	1	48.5068	<.0001
3	General Association	1	48.5068	<.0001

Estimates of the Common Relative Risk (Row1/Row2)				
Type of Study	Method	Value	95% Confidence Limits	
Case-Control (Odds Ratio)	Mantel-Haenszel	0.5426	0.4558	0.6460
	Logit	0.5477	0.4586	0.6542
Cohort (Col1 Risk)	Mantel-Haenszel	0.6537	0.5789	0.7381
	Logit	0.7218	0.6402	0.8139
Cohort (Col2 Risk)	Mantel-Haenszel	1.1432	1.1001	1.1879
	Logit	1.1591	1.1184	1.2013

Breslow-Day Test for Homogeneity of the Odds Ratios	
Chi-Square	26.2474
DF	1
Pr > ChiSq	<.0001

Total Sample Size = 3151

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; "Barbara Stoll"; nfiner@ucsd.edu; Wrage, Lisa Ann; Pablo Sanchez; Mambarambath Jaleel; Myra Wyckoff; Roy Heyne; Das, Abhik; Jackie LeVan
Subject: First version of Jackie LeVan's abstract
Date: Friday, September 28, 2012 9:43:56 PM
Attachments: Changes in Therapy and Outcomes Associated with the SUPPORT Trial 092812 rev2.doc

Hi everyone:

Here is a first draft of Jackie LeVan's PAS abstract.

Please review and let me know if you have any suggestions, including about the list of authors.

I have included all authors listed in the latest version of the protocol and Lisa Wrage, who did the statistics, and has approved this version.

Best regards and thanks for your collaboration,
Luc

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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL. *Jaclyn M LeVan, Luc P Brion, Lisa Wrage, Myra H Wyckoff, Pablo Sánchez, Roy Heyne, Mambarambath Jaleel, Neil Finer, Abhik Das, Barbara Stoll, Rose Higgins, Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.*

BACKGROUND

The NICHD Neonatal Research Network (NRN) SUPPORT was a multicenter randomized 2 X 2 factorial trial, in which preterm neonates of 24-27^{6/7} weeks' gestational age (GA) were randomized at birth to two interventions: (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, vs. DR intubation with surfactant administration (within one hour of birth); and (2) either oxygen (O₂) saturation targets of 85 to 89% vs. 91 to 95%. The primary outcomes, death or bronchopulmonary dysplasia (O₂ use at 36 weeks) (BPD), and death or severe retinopathy of prematurity (ROP) were not affected by the interventions. However, death was more frequent and severe ROP less frequent among infants randomized to low O₂ saturation targets. We hypothesized (1) that the percentage of DR intubation would decrease after publication of SUPPORT, without affecting BPD or death and ROP or death; and (2) that the decrease in DR intubation in each center would depend on pre-SUPPORT DR intubation.

OBJECTIVE

To compare DR intubation, BPD or death at 36 weeks, and severe ROP or death before discharge before and after SUPPORT.

DESIGN/METHODS

This was a retrospective cohort using the prospective NICHD generic database. We included infants of 24-27^{6/7} weeks GA born at one of 11 centers involved in SUPPORT and participating in NRN before SUPPORT (2003-2004) and after SUPPORT (2010-2011). We excluded infants with known malformations and those who received comfort care.

RESULTS

This study included 3151 infants (1617 pre-SUPPORT and 1534 post-SUPPORT).

Baseline Characteristics	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value
Birth weight (g) (mean ±SD)	824±191	816±190	0.23
Gestational Age (weeks)	25.7±1.1	25.6±1.1	0.64
Antenatal betamethasone	953(59.1%)	1344/1532 (87.7%)	<.0001
Race: Black; White; Hispanic; Other (%)	45.0;37.3;14.9;2.8	43.5;37.6;14.0;4.9	0.02
Mode of delivery: cesarean section	1004 (62.1%)	1009 (65.9%)	0.03
Rupture of membranes > 24 hours	436/1586 (27.5%)	360/1482 (24.3%)	0.043
Maternal hypertension	322 (19.9%)	409/1532 (24.7%)	<.0001
Maternal diabetes	42 (2.6%)	84 (5.5%)	<.0001

Parameters of Assessment	Pre-SUPPORT N=1617	Post-SUPPORT N=1534	p-value	Adjusted OR (95% CI)	Adjusted p-value
Intubated in DR	1313 (81.2%)	1082 (70.5%)	<.0001	0.63 (0.51-0.77)	<.0001
BPD or death	970 (60.0%)	824/1522 (54.1%)	.0009	1.06 (0.88-1.3)	0.53
Severe ROP or death	515/1581 (32.6%)	408/1501(27.2%)	.0011	0.80 (0.64-0.97)	0.024

The proportion of patients intubated in the DR was significantly lower in the post-SUPPORT group than in the pre-SUPPORT group.(Table). The odds ratio (OR) of DR intubation (post vs. pre-SUPPORT) remained significant (Table) after adjusting for GA group (24-25^{6/7} vs. 26-27^{6/7} weeks), 100-grams birth weight groups, gender, race, multiple birth, prenatal steroids, prolonged rupture of membranes, cesarean section, maternal hypertension, maternal diabetes and center. The OR of ROP or death (adjusted for the same variables and for surfactant), but not that of BPD or death, was significantly different from 1. The correlation between pre-SUPPORT center-specific percentage of DR intubation and the change after SUPPORT was not significant (Spearman $r=-0.38$, $p=0.25$). Centers with $\geq 80\%$ DR intubation rate pre-SUPPORT were likely to have a significant reduction post-SUPPORT whereas centers with $< 80\%$ intubation rate pre-SUPPORT were not.

CONCLUSIONS

The adjusted odds of DR intubation, and that of death or ROP, but not that of death or BPD, significantly decreased after publication of the results of SUPPORT in NRN centers involved in the trial. DR intubation was more likely to decrease after SUPPORT in centers with $\geq 80\%$ pre-SUPPORT DR intubation rate.

3994 characters

From: Vaucher, Yvonne
To: Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman; Vaucher, Yvonne
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, September 28, 2012 3:00:52 PM

The point of the abstract is that outcome was different for the enrolled vs. eligible/nonenrolled. Not a surprise but it does have implications for enrollment protocols/generalization. One expects that models will show that some of the differences between the groups (ANS, IVH, BPD, lack of PNC) will predict the worse outcome (primarily death) for the non-enrolled. The most important message is really for our OB colleagues...adequate PNC would identify problems that could be treated or need to be monitored, earlier presentation for delivery would allow time for maternal/fetal stabilization, treatment of infection, ANS, optimal time/route/place of delivery. Much (maybe most) of outcome is really related to what happens before we even enter the picture. We can only work with what we get!

Yvonne

On 9/28/12 7:59 AM, "Das, Abhik" <adas@rti.org> wrote:

>I still think that we need to look at it again at follow up. I don't
>think we can just leave the readers hanging by just presenting
>provocative but unadjusted findings. We can still make the arguments that
>you make in the discussion.

>

>Thanks

>

>Abhik

>

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

>From: Rich, Wade [mailto:wrich@ucsd.edu]

>Sent: Friday, September 28, 2012 10:55 AM

>To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Finer, Neil;

>'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu';

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>'Myriam Peralta, M.D.'; 'nancy newman'; Das, Abhik

>Cc: Archer, Stephanie (NIH/NICHD) [E]

>Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome:

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>attempting to answer. The question was, and is, whether the

>substantively different outcomes we found between those infant enrolled

>in the trial and those not enrolled but eligible, would also be reflected

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>trial was previously looked at by Marie, and found not to exist.

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>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

>Sent: Friday, September 28, 2012 5:53 AM
>To: Vaucher, Yvonne; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie;
>'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook,
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>
>
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>From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
>Sent: Thursday, September 27, 2012 9:32 PM
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>[E]
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>SUPPORT subcommittee:
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>PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs.
>Eligible/Nonenrolled attached. (97% full) Please send comments.
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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, September 28, 2012 1:11:31 PM

Not sure why he doesn't say it to the whole group!

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

From: Wally Carlo, M.D. [mailto:WCarlo@pediatrics.uab.edu]
Sent: Friday, September 28, 2012 12:59 PM
To: Das, Abhik
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

Agree 100%!

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 266 4004

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Sent: Friday, September 28, 2012 10:00 AM
To: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; Kurt Schibler; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; Laptook, Abbot; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; nancy newman
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Thanks

Abhik

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Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled

SUPPORT subcommittee:

PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs. Eligible/Nonenrolled attached. (97% full) Please send comments.

Thanks.

Yvonne

From: Vaucher, Yvonne
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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, September 28, 2012 10:19:39 AM

Marie is doing adjustments.

On 9/28/12 5:52 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, September 28, 2012 9:32:44 AM

I agree that we need to report adjusted associations if we were to draw any definitive conclusions from this analysis.

Thanks

Abhik

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 28, 2012 8:53 AM
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Thanks.

Yvonne

From: [Wally Carlo, M.D.](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, September 28, 2012 8:58:24 AM

Rose:

YES. I would love to speculate that enrollment in the trial may have improved outcomes but that would require an adjusted analysis. That would be fantastic. That is what I think we should do. Otherwise, it is a "statement of the obvious" or "as expected" as you well stated because baseline differences were so large and the groups were not comparable from the beginning.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Friday, September 28, 2012 7:53 AM
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Thanks.

Yvonne

From: [Finer, Neil](#)
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Cc: [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)
Subject: RE: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Friday, September 28, 2012 6:52:51 AM

Yvonne
Looks good and appropriate wording to me
Neil

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]
Sent: Thursday, September 27, 2012 6:32 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.'; Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS Abstract draft: SUPPORT Neurodevelopmental Outcome: Enrolled vs. Eligible/Nonenrolled
Date: Thursday, September 27, 2012 9:33:19 PM
Attachments: SUPPORTNDOOutcomeEnrolledvsEligibleNonenrolledDraft_092712.docx

SUPPORT subcommittee:

PAS Abstract draft SUPPORT Neurodevelopmental Outcome-Enrolled vs. Eligible/Nonenrolled attached. (97% full)

Please send comments.

Thanks.

Yvonne

Title: ANTENATAL ENROLLMENT IN CLINICAL TRIALS: IS NEURODEVELOPMENTAL OUTCOME REPRESENTATIVE?

Yvonne E Vaucher, MD, MPH¹, Susan R Hintz, MD, MS², Wade Rich, BSMS, RRT¹, Marie G Gantz, PhD³ and Neil N Finer, MD¹. ¹Dept. of Pediatrics, University of California, San Diego, CA, United States; ²Dept. of Pediatrics, Stanford University, Palo Alto, CA, United States and ³Statistics and Epidemiology, RTI International, Rockville, MD, United States.

Background: Antenatal enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) was associated with differences in demographic, perinatal and neonatal characteristics between the enrolled vs. non-enrolled extremely preterm infants. Mothers of eligible but non-enrolled infants were less likely to be White/non-Hispanic, insured, have prenatal care, or receive antenatal steroids. Eligible/non-enrolled infants were more likely to have lower Apgar Scores, require resuscitation in the delivery room, to develop BPD and severe IVH and to die before discharge.

Objective: To determine whether antenatal enrollment in SUPPORT was associated with differences in death or neurodevelopmental outcome in enrolled vs. eligible/non-enrolled children.

Design/Methods: We identified all 24-26 week gestation infants at 18 Neonatal Research Network (NRN) sites with BW > 500 g, born from 1/2006 to 2/2009, who were eligible for inclusion in SUPPORT. A comprehensive neurodevelopmental evaluation was performed at 18-22 mo corrected age (CA) using a standardized neuromotor assessment and the cognitive scale of the BSID-III. In this study we compare the neurodevelopmental outcome for enrolled vs. eligible/non-enrolled children including Death or neurodevelopmental impairment (NDI), individual components of NDI [cognitive BSID-III score < 70, Gross Motor Function Classification System Score (GMFCS) \geq 2, moderate-severe cerebral palsy, blind, deaf] and levels of cognitive delay.

Results: The primary composite SUPPORT outcome (Death or NDI) was determined for 95% (695/729) of children enrolled in SUPPORT vs. 90.9% (1471/1618) of children eligible/non-enrolled ($p < .001$). Compared to enrolled children, eligible/non-enrolled children were more likely to have Death or NDI (41.4% vs. 33.4%, $p < .001$), more likely to die before 18-22 mo CA (31.7% vs. 24.8%, $p < .001$), and more likely to have a cognitive score < 80 (19.9% vs. 15.5%, $P = .038$). There were no differences between groups in NDI or the individual components of NDI. For all children, the risks of Death or NDI, NDI, and CP doubled; the risks of death, cognitive score < 70, and GMFCS \geq 2 tripled between 26 and 24 wks gestation.

Conclusions: Compared to children enrolled in SUPPORT, those eligible but not enrolled were more likely to die or have NDI. However, in survivors the risk of severe cognitive delay, neuromotor or neurosensory impairment were similar.

From: Ricki Goldstein, M.D.
To: yvaucher@ucsd.edu; Myriam Peralta, M.D.; Shankaran, Seetha; editorial@nejm.org; yvaucher@ucsd.edu; nfiner@ucsd.edu; Wally Carlo, M.D.; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com); Patricia.W.Evans@uth.tmc.edu; michael.acarregui@providence.org; iadamsc@emory.edu; Pappas, Athina; shintz@stanford.edu; bpointex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com); cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com)
Subject: RE: New England Journal of Medicine 12-08506.R2
Date: Saturday, September 22, 2012 2:10:51 PM

Congratulations! This is really great news.
Ricki

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

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Subject: New England Journal of Medicine 12-08506.R2

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To: Myriam Peralta, M.D.; Shankaran, Seetha; editorial@nejm.org; yvaucher@ucsd.edu; nfiner@ucsd.edu; Wally Carlo, M.D.; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley Yoder; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; Pappas, Athina; srhinz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
Subject: RE: New England Journal of Medicine 12-08506.R2
Date: Friday, September 21, 2012 2:19:31 PM

World-class work by world-class people and curious, compliant and receptive babies and families!

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Sent: Friday, September 21, 2012 12:11 PM
To: Shankaran, Seetha; editorial@nejm.org; yvaucher@ucsd.edu; nfiner@ucsd.edu; Wally Carlo, M.D.; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley Yoder; Roger Faix; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; Pappas, Athina; srhinz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
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Yeah!! Thank you to everyone!!!

From: Shankaran, Seetha [sshankar@med.wayne.edu]
Sent: Friday, September 21, 2012 1:05 PM
To: editorial@nejm.org; yvaucher@ucsd.edu; Myriam Peralta, M.D.; nfiner@ucsd.edu; Wally Carlo, M.D.; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; Pappas, Athina; srhinz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
Subject: RE: New England Journal of Medicine 12-08506.R2

Congrats team!
Seetha

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Cc: (b)(6)@hol.com; (b)(6)@aol.com; kimberly.volton@cchmc.org; kurt.schibler@cchmc.org; michele.walsh@cwru.edu; nxs5@cwru.edu; iadamsc@emory.edu; (b)(6)@gmail.com; Bradley.voder@hsc.utah.edu; roger.faix@hsc.utah.edu; bpindex@iupui.edu; Higgins, Rosemary (NTH/NICHD) [E]; golds005@mc.duke.edu; apappas@med.wayne.edu; adusick@pediatrics.wisc.edu; chauer@peds.med.miami.edu; mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michael.acanregui@providence.org; adas@rti.org; mgentz@rti.org; shintz@stanford.edu; emcgowan@tuftsmedicalcenter.org; Wade Rich; gary_myers@urmc.rochester.edu; Patricia.W.Evans@uth.tmc.edu; roy.heyne@utsouthwestern.edu; moshea@wfubmc.edu; alaptook@wihri.org; BVohr@wihri.org; richard.ehrenkranz@vale.edu
Subject: Re: New England Journal of Medicine 12-08506.R2
Date: Friday, September 21, 2012 1:23:50 PM

Nice work all!

Janell

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>>> "Vaucher, Yvonne" <yvaucher@ucsd.edu> 9/21/2012 9:21 AM >>>
Hooray!!!!!!! Thanks to everyone for all your help along the way.

On 9/21/12 7:34 AM, "Finer, Neil" <nfiner@ucsd.edu> wrote:

> Many thanks on behalf of all the authors
> Neil finer
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> Sent from my iPhone
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> On Sep 21, 2012, at 4:10 PM, "editorial@nejm.org" <editorial@nejm.org>
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From: Bell, Edward (Pediatrics)
To: Higgins, Rosemary (NIH/NICHD) [E]; "mperalta@peds.uab.edu"; "Yvonne Vaucher"; "nfiner@ucsd.edu"; "Wally Carlo (wacarlo@uab.edu)"; "Michele Walsh (mcw3@cwru.edu)"; "mgantz@rti.org"; "Abbot Laptook"; "Brad Yoder (Bradley.yoder@hsc.utah.edu)"; "Roger Faix (Roger.Faix@hsc.utah.edu)"; "Abhik Das (adas@rti.org)"; "Kurt Schibler [kurt.schibler@cchmc.org]"; "Wade Rich"; "Nancy Newman"; "Betty Vohr (bvohr@wihri.org)"; "Kimberly Yolton (kimberly.yolton@cchmc.org)"; "Roy Heyne (Roy.Heyne@utsouthwestern.edu)"; "(b)(6) @aol.com"; "Patricia.W.Evans@uth.tmc.edu"; "golds005@mc.duke.edu"; "Michael.Acarregui@providence.org"; "Adams-Chapman, Ira"; "(apappas@med.wayne.edu)"; "srhinz@stanford.edu"; "bpoindex@iupui.edu"; "Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org)"; "richard.ehrenkranz@yale.edu"; "Anna Bodnar (abodnar@utah.gov)"; "cbauer@peds.med.miami.edu"; "JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)"; "moshea@wfubmc.edu"; "Gary Myers (gary_myers@URMC.Rochester.edu)"
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Subject: RE: Combined SUPPORT Neurodevelopmental Outcome revision submitted to NEJM
Date: Friday, September 21, 2012 12:56:22 PM

Congratulations, Neil, Yvonne, et al!!!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 21, 2012 11:12 AM
To: 'mperalta@peds.uab.edu'; 'Yvonne Vaucher'; 'nfiner@ucsd.edu'; 'Wally Carlo (wacarlo@uab.edu)'; 'Michele Walsh (mcw3@cwru.edu)'; 'mgantz@rti.org'; 'Abbot Laptook'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; 'Roger Faix (Roger.Faix@hsc.utah.edu)'; 'Abhik Das (adas@rti.org)'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Wade Rich'; 'Nancy Newman'; 'Betty Vohr (bvohr@wihri.org)'; 'Kimberly Yolton (kimberly.yolton@cchmc.org)'; 'Roy Heyne (Roy.Heyne@utsouthwestern.edu)'; '(b)(6) @aol.com'; 'Patricia.W.Evans@uth.tmc.edu'; 'golds005@mc.duke.edu'; 'Michael.Acarregui@providence.org'; 'Adams-Chapman, Ira'; '(apappas@med.wayne.edu)'; 'srhinz@stanford.edu'; 'bpoindex@iupui.edu'; 'Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org)'; 'richard.ehrenkranz@yale.edu'; 'Anna Bodnar (abodnar@utah.gov)'; 'cbauer@peds.med.miami.edu'; 'JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)'; 'moshea@wfubmc.edu'; 'Gary Myers (gary_myers@URMC.Rochester.edu)'
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Subject: RE: Combined SUPPORT Neurodevelopmental Outcome revision submitted to NEJM

For those who are not on the masthead, I have attached the acceptance from the NEJM. This is under embargo so needs to stay confidential.

Thanks to all the sites and especially their staff for making this happen. Your commitment and perseverance is really appreciated!!!!

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 14, 2012 11:03 AM
To: mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Michele Walsh (mcw3@cwru.edu); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RICH; Nancy Newman; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Michael.Acarregui@providence.org; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; bpoindex@iupui.edu; Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary_myers@URMC.Rochester.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; Frantz, Ivan; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale_phelps@urmc.rochester.edu; carl_dangio@urmc.rochester.edu
Subject: Combined SUPPORT Neurodevelopmental Outcome revision submitted to NEJM

Hi

Attached is the SUPPORT FU paper resubmitted this week to NEJM. Please note, Dr. Brenda Poindexter's name has been added to the masthead (doesn't appear on the attached copy). This was done by the journal when the papers were combined into one. One we hear back from the journal I will let everyone know. Please keep the information confidential.

Thanks for all your help and commitment!!

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]
Subject: RE: New England Journal of Medicine 12-08506.R2
Date: Friday, September 21, 2012 12:36:00 PM

We are looking into this in two ways -

1. There is a proposal to look at this in depth in the NRN (i.e. before and after SUPPORT and less invasive or non-invasive ventilation prevalence in the NICU population).
2. We are also re-looking at BPD rates as our recruitment in the hydrocortisone for extubation is lagging - we don't know yet if BPD is decreased and if not, we may need to adjust entry criteria in that study.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Friday, September 21, 2012 12:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]
Subject: RE: New England Journal of Medicine 12-08506.R2

Dear Rose,
Congratulations :)

Are you finding that some of the SUPPORT sites are already changing practices on delivery room resuscitation based on the original publication of the primary outcome? The findings in this neurodevelopmental outcome paper will help further justify this potential approach to delivery room/NICU care.

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 21, 2012 10:31 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]

Subject: Fw: New England Journal of Medicine 12-08506.R2

Hi

Once again, thanks for all the SUPPORT for our SUPPORT trial.

I have alerted our folks who do press releases and we will likely do one for this.

With warmest regards,
Rose

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

From: editorial@nejm.org [mailto:editorial@nejm.org]

Sent: Friday, September 21, 2012 10:10 AM

To: yvaucher@ucsd.edu <yvaucher@ucsd.edu>; mperalta@peds.uab.edu <mperalta@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; michele.walsh@cwru.edu <michele.walsh@cwru.edu>; mgantz@rti.org <mgantz@rti.org>; alaptook@wihri.org <alaptook@wihri.org>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; roger.faix@hsc.utah.edu <roger.faix@hsc.utah.edu>; adas@rti.org <adas@rti.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; wrich@ucsd.edu <wrich@ucsd.edu>; nxs5@cwru.edu <nxs5@cwru.edu>; BVohr@wihri.org <BVohr@wihri.org>; kimberly.yolton@cchmc.org <kimberly.yolton@cchmc.org>; roy.heyne@utsouthwestern.edu <roy.heyne@utsouthwestern.edu>; (b)(6)@aol.com (b)(6)@aol.com>; Patricia.W.Evans@uth.tmc.edu <Patricia.W.Evans@uth.tmc.edu>; golds005@mc.duke.edu <golds005@mc.duke.edu>; michael.acarregui@providence.org <michael.acarregui@providence.org>; iadamsc@emory.edu <iadamsc@emory.edu>; apappas@med.wayne.edu <apappas@med.wayne.edu>; srhinz@stanford.edu <srhinz@stanford.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; adusick@pediatrics.wisc.edu <adusick@pediatrics.wisc.edu>; emcgowan@tuftsmedicalcenter.org <emcgowan@tuftsmedicalcenter.org>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; (b)(6)@gmail.com (b)(6)@gmail.com>; cbauer@peds.med.miami.edu <cbauer@peds.med.miami.edu>; jafuller@salud.unm.edu <jafuller@salud.unm.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; gary_myers@urmc.rochester.edu <gary_myers@urmc.rochester.edu>; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com (b)(6)@aol.com>

Subject: New England Journal of Medicine 12-08506.R2

Dear Dr. Finer and co-authors,

Thank you for the article, "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial," which the Journal is pleased to accept for publication.

This acceptance is made with the understanding that neither the article itself nor any part of its essential substance, tables or figures has been published or will be submitted for publication elsewhere before it appears in the Journal. The acceptance is also made with the understanding that all the authors, the data, and its presentation meet the requirements as described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org).

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Sincerely yours,

Jeffrey M. Drazen, M.D.
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New England Journal of Medicine
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From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; "Sara Harris"
Subject: RE: Interview scheduling query: SUPPORT follow-up
Date: Friday, September 21, 2012 11:53:08 AM

Yeah, that is really a lot. We can only quote two of you in the release. (One needs to be you.)

But if you want them to be in on the interview conversation, then I don't think it will hurt.

We'll certainly mention them in the text of the release, though. And we can tell them that they can send out releases from their own institutions, but asking them to credit NICHD funding high up.

Does that sound ok to you?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 21, 2012 11:50 AM
To: 'Sara Harris'
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview scheduling query: SUPPORT follow-up

One question –

Drs. Finer and Carlo certainly led the trial. We have two very devoted follow up physicians (first and second authors on current paper), Drs. Vaucher and Peralta – is 4 + me too many to interview?? This really was a big group effort. Let me know.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
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higginsr@mail.nih.gov

From: Sara Harris [mailto:sharris@palladianpartners.com]
Sent: Friday, September 21, 2012 11:06 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: Interview scheduling query: SUPPORT follow-up

Dear Dr. Higgins,

Many thanks for forwarding the information on the SUPPORT trial follow-up accepted in *NEJM*. Bob and I would like to set up a time to talk with you about the findings in order to write up a news release.

Would you please suggest two or three times in the next couple of weeks when you would be available to talk by phone? With Council on Monday, sometime later in the week or into October may be best. I also noticed that Dr. Finer and Dr. Carlo were on the call for the earlier release. Please feel free to include them or either of the two first authors in this correspondence if you would like them to join the call. As usual, plan to set aside about 30 minutes to discuss the findings, approach, and any overarching messages you would like to emphasize.

Many thanks for your time! We look forward to talking with you soon.

All the best,
Sara

Sara Harris |MAIL: Palladian Partners, Inc. 8484 Georgia Ave., Suite 200 Silver Spring, MD 20910
|PH: 301-650-8660 ext. 289 |EMAIL: sharris@palladianpartners.com

From: Bauer, Charles R
To: "Vaucher, Yvonne"; Finer, Neil
Cc: mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; Rich. Wade; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpointex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
Subject: RE: New England Journal of Medicine 12-08506.R2
Date: Friday, September 21, 2012 12:03:24 PM

Yvonne, Miriam and Neil,

WOW!!!! Congratulations on a job superbly done. Thank you.

Charlie

Charles R Bauer, M.D.
Professor of Pediatrics, Obstetrics-Gynecology and Psychology
University of Miami School of Medicine
Department of Pediatrics
Division of Neonatology
(305) 243-5808
(305) 243-3501 FAX

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, September 21, 2012 11:21 AM
To: Finer, Neil; editorial@nejm.org
Cc: mperalta@peds.uab.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; Rich. Wade; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpointex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; Bauer, Charles R; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; higginsr@mail.nih.gov; (b)(6)@aol.com
Subject: Re: New England Journal of Medicine 12-08506.R2

Hooray!!!!!!!!!! Thanks to everyone for all your help along the way.

On 9/21/12 7:34 AM, "Finer, Neil" <nfiner@ucsd.edu> wrote:

>Many thanks on behalf of all the authors
>Neil finer
>
>Sent from my iPhone

>
>On Sep 21, 2012, at 4:10 PM, "editorial@nejm.org" <editorial@nejm.org>
>wrote:
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>>
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From: [Wally Carlo, M.D.](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: New England Journal of Medicine 12-08506.R2
Date: Friday, September 21, 2012 10:55:29 AM

Rose.

Thanks so much for stating this. I try hard to be a good team player and enjoy so much working with you in the NRN.

THANKS.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Fri, Sep 21, 2012 14:52:16 GMT+00:00
Subject: Re: New England Journal of Medicine 12-08506.R2

Wally-

I want to personally thank you for your unending and continued energy and commitment to this landmark study and follow up.

With warmest regards,
Rose

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Friday, September 21, 2012 10:15 AM
To: Das, Abhik <adas@rti.org>; yvaucher@ucsd.edu <yvaucher@ucsd.edu>; Myriam Peralta, M.D. <MPeralta@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: New England Journal of Medicine 12-08506.R2

Great job. A major contribution to medical knowledge.

Wally

-----Original message-----

From: "Das, Abhik" <adas@rti.org>
To: "yvaucher@ucsd.edu" <yvaucher@ucsd.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Gantz, Marie" <mgantz@rti.org>, "Higgins, Rosemary (NIH/NICHD) [E]" <rosemary.higgins@nih.hhs.gov>
Sent: Fri, Sep 21, 2012 14:13:13 GMT+00:00
Subject: RE: New England Journal of Medicine 12-08506.R2

Congratulations all around!

Thanks!

Abhik

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

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of
editorial@nejm.org

Sent: Friday, September 21, 2012 10:10 AM

To: yvaucher@ucsd.edu; mperalta@peds.uab.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu;
michele.walsh@cwru.edu; Gantz, Marie; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu;
roger.faix@hsc.utah.edu; Das, Abhik; kurt.schibler@cchmc.org; wrich@ucsd.edu;
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roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu;
gold005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu;
apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu;
adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org;
richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu;
jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu;
higginsr@mail.nih.gov; (b)(6)@aol.com

Subject: New England Journal of Medicine 12-08506.R2

Dear Dr. Finer and co-authors,

Thank you for the article, "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial," which the Journal is pleased to accept for publication.

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From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: New England Journal of Medicine 12-08506.R2
Date: Friday, September 21, 2012 10:41:39 AM

Sure. Just tell Sara which ones to get in touch with when she send the e-mail around.

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 21, 2012 10:41 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: New England Journal of Medicine 12-08506.R2

Should we also include the lead investigators (they are nice to work with)?

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

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, September 21, 2012 10:39 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: New England Journal of Medicine 12-08506.R2

OK. I'm getting the director's podcast ready and won't be able to look at until Monday. I sent it to Sara for scheduling, so you should be hearing from her soon.

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 21, 2012 10:29 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Fw: New England Journal of Medicine 12-08506.R2

Bob

This is a follow up paper to the NRN SuPPORT trial (co-funded by nhlbi). We should do a release.

Rose

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

From: editorial@nejm.org [mailto:editorial@nejm.org]
Sent: Friday, September 21, 2012 10:10 AM
To: yvaucher@ucsd.edu <yvaucher@ucsd.edu>; mperalta@peds.uab.edu <mperalta@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; michele.walsh@cwru.edu <michele.walsh@cwru.edu>; mgantz@rti.org <mgantz@rti.org>; alaptook@wihri.org <alaptook@wihri.org>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; roger.faix@hsc.utah.edu <roger.faix@hsc.utah.edu>; adas@rti.org <adas@rti.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; wrich@ucsd.edu <wrich@ucsd.edu>; nxs5@cwru.edu <nxs5@cwru.edu>; BVohr@wihri.org <BVohr@wihri.org>; kimberly.yolton@cchmc.org <kimberly.yolton@cchmc.org>; roy.heyne@utsouthwestern.edu <roy.heyne@utsouthwestern.edu>; (b)(6)@aol.com <(b)(6)@aol.com>; Patricia.W.Evans@uth.tmc.edu <Patricia.W.Evans@uth.tmc.edu>; golds005@mc.duke.edu <golds005@mc.duke.edu>; michael.acarregui@providence.org <michael.acarregui@providence.org>; iadamsc@emory.edu <iadamsc@emory.edu>; apappas@med.wayne.edu <apappas@med.wayne.edu>; srhintz@stanford.edu <srhintz@stanford.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; adusick@pediatrics.wisc.edu <adusick@pediatrics.wisc.edu>; emcgowan@tuftsmedicalcenter.org <emcgowan@tuftsmedicalcenter.org>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; (b)(6)@gmail.com <(b)(6)@gmail.com>; cbauer@peds.med.miami.edu <cbauer@peds.med.miami.edu>; jafuller@salud.unm.edu <jafuller@salud.unm.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; gary_myers@urmc.rochester.edu <gary_myers@urmc.rochester.edu>; Higgins, Rosemary (NIH/NICHD) [E];

(b)(6)@aol.com <(b)(6)@aol.com>

Subject: New England Journal of Medicine 12-08506.R2

Dear Dr. Finer and co-authors,

Thank you for the article, "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial," which the Journal is pleased to accept for publication.

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Sincerely yours,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine

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Blansfield, Earl (NIH/NICHD) [E]

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com on behalf of editorial@nejm.org
Sent: Friday, September 21, 2012 10:10 AM
To: yvaucher@ucsd.edu; mperalta@peds.uab.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
Subject: New England Journal of Medicine 12-08506.R2
Attachments: Attached file: FinerSUPPORTfollowupFINAL-jmd.docx; Attached standard file: * Embargo-Guidelines-11.07.pdf

Dear Dr. Finer and co-authors,

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Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

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From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
To: ["Yvonne Vaucher"; "mperalta@peds.uab.edu"](#)
Subject: THANKS
Date: Friday, September 21, 2012 11:54:00 AM

Thanks so much to the two of you for working so hard and endlessly on this NEJM upcoming publication!

I really appreciate all your effort and hard work!!
With warmest regards
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]
Subject: Fw: New England Journal of Medicine 12-08506.R2
Date: Friday, September 21, 2012 10:30:37 AM
Attachments: FinerSUPPORTfollowupFINAL-jmd.docx
Embargo-Guidelines-11.07.pdf

Hi

Once again, thanks for all the SUPPORT for our SUPPORT trial.

I have alerted our folks who do press releases and we will likely do one for this.

With warmest regards,

Rose

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

From: editorial@nejm.org [mailto:editorial@nejm.org]

Sent: Friday, September 21, 2012 10:10 AM

To: yvaucher@ucsd.edu <yvaucher@ucsd.edu>; mperalta@peds.uab.edu <mperalta@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; michele.walsh@cwru.edu <michele.walsh@cwru.edu>; mgantz@rti.org <mgantz@rti.org>; alaptook@wihri.org <alaptook@wihri.org>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; roger.faix@hsc.utah.edu <roger.faix@hsc.utah.edu>; adas@rti.org <adas@rti.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; wrich@ucsd.edu <wrich@ucsd.edu>; nxs5@cwru.edu <nxs5@cwru.edu>; BVohr@wihri.org <BVohr@wihri.org>; kimberly.yolton@cchmc.org <kimberly.yolton@cchmc.org>; roy.heyne@utsouthwestern.edu <roy.heyne@utsouthwestern.edu>; (b)(6)@aol.com <(b)(6)@aol.com>; Patricia.W.Evans@uth.tmc.edu <Patricia.W.Evans@uth.tmc.edu>; golds005@mc.duke.edu <golds005@mc.duke.edu>; michael.acarregui@providence.org <michael.acarregui@providence.org>; iadamsc@emory.edu <iadamsc@emory.edu>; apappas@med.wayne.edu <apappas@med.wayne.edu>; srhinz@stanford.edu <srhinz@stanford.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; adusick@pediatrics.wisc.edu <adusick@pediatrics.wisc.edu>; emcgowan@tuftsmedicalcenter.org <emcgowan@tuftsmedicalcenter.org>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; (b)(6)@gmail.com <(b)(6)@gmail.com>; cbauer@peds.med.miami.edu <cbauer@peds.med.miami.edu>; jfuller@salud.unm.edu <jfuller@salud.unm.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; gary_myers@urmc.rochester.edu <gary_myers@urmc.rochester.edu>; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com <(b)(6)@aol.com>

Subject: New England Journal of Medicine 12-08506.R2

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Harvard Medical School

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From: Roger Faix
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised Title Page - New England Journal of Medicine 12-08506.R1
Date: Tuesday, September 18, 2012 12:39:40 PM

Done!

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, September 18, 2012 7:26 AM
To: Roger Faix; (b)(6)@aol.com; Betty Vohr (bvohr@wihri.org); Anna Bodnar (abodnar@utah.gov)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Revised Title Page - New England Journal of Medicine 12-08506.R1

Please forward the needed information to NEJM AS SOON AS POSSIBLE - today - please
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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6100 Executive Blvd., Room 4B03
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301-496-5575
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higginsr@mail.nih.gov

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From: onbehalf of +jripley+nejm.org@manuscriptcentral.com
[mailto: onbehalf of +jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Monday, September 17, 2012 5:27 PM
To: nfiner@ucsd.edu; bpoindex@iupui.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Revised Title Page - New England Journal of Medicine 12-08506.R1

Re: 12-08506.R1 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer:

Dr. Solomon is ready to make a decision on your manuscript, but before we can do so, we need a revised title page adding on Dr. Poindexter. It was my impression that she was accidentally left off the current manuscript when the previous two were combined. Please let me know if this is the case, and if so, please send a revised title page as soon as possible.

Before I can send your manuscript for a decision, I also need disclosure forms from Drs. Bodnar and Vohr, and copyright forms from Drs. Costello and Faix. I have emailed them.

We hope these issues will be resolved quickly, so we can move forward with your manuscript.

Thank you,

Julie
Editorial Assistant II

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From: Roger Faix
To: jripley@nejm.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: New England Journal of Medicine 12-08506.R1
Date: Tuesday, September 18, 2012 11:45:32 AM
Attachments: [NEJM copyright form - Finer follow-up 2012.pdf](#)

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Sent: Monday, September 17, 2012 2:52 PM
To: Roger Faix
Cc: archerst@mail.nih.gov
Subject: New England Journal of Medicine 12-08506.R1

Re: 12-08506.R1 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Faix:

Thank you for submitting your copyright form; However, we need it signed in pen. Please sign the attached form and either email it or fax it to 781-207-6529 as soon as possible.

Thank you.

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

AUTHORS: PLEASE RETURN THIS FORM TO:

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THE NEW ENGLAND JOURNAL OF MEDICINE
10 SHATTUCK STREET, BOSTON, MA 02115 U.S.A.
781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF Aug. / 14 / 2012

()

PRINTED NAME Roger G. Faix, M.D.

SIGNATURE Roger G. Faix, M.D. 

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com on behalf of editorial@nejm.org
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(b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu;
gary_myers@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
Subject: New England Journal of Medicine - 12-08506.R2
Date: Tuesday, September 18, 2012 9:52:47 AM

Dear Dr. Finer and co-authors,

Thank you for submitting your revision, of "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" to the New England Journal of Medicine.

Your submission will be forwarded to the editor, and may be sent out for review as necessary.

Please call us at 617-734-9800 if you have any questions.

Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School

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From: Rich, Wade
To: jripley@nejm.org; [Finer, Neil](mailto:Finer_Neil); bpoindex@iupui.edu
Cc: [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer_Stephanie); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins_Rosemary)
Subject: RE: Revised Title Page - New England Journal of Medicine 12-08506.R1
Date: Monday, September 17, 2012 5:54:00 PM
Attachments: [SUPPORTPaperResubmission Title Page.docx](#)

Attached is revised Title Page for 12-08506.R1 with Dr. Poindexter added. Please let me know if this format is OK.

Thank you.

Wade Rich for Neil Finer

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[<mailto:mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com>] On Behalf Of jripley@nejm.org
Sent: Monday, September 17, 2012 2:27 PM
To: [Finer, Neil](mailto:Finer_Neil); bpoindex@iupui.edu
Cc: archerst@mail.nih.gov; [Rich, Wade](mailto:Rich_Wade); higginsr@mail.nih.gov
Subject: Revised Title Page - New England Journal of Medicine 12-08506.R1

Re: 12-08506.R1 - Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Dear Dr. Finer:

Dr. Solomon is ready to make a decision on your manuscript, but before we can do so, we need a revised title page adding on Dr. Poindexter. It was my impression that she was accidently left off the current manuscript when the previous two were combined. Please let me know if this is the case, and if so, please send a revised title page as soon as possible.

Before I can send your manuscript for a decision, I also need disclosure forms from Drs. Bodnar and Vohr, and copyright forms from Drs. Costello and Faix. I have emailed them.

We hope these issues will be resolved quickly, so we can move forward with your manuscript.

Thank you,

Julie
Editorial Assistant II

New England Journal of Medicine
10 Shattuck Street
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Fax: (617) 739-9864
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Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Yvonne E. Vaucher, MD MPH¹; * Myriam Peralta-Carcelen, MD MPH²; * Neil N. Finer, MD¹; Waldemar A. Carlo, MD²; Michele C. Walsh, MD MS³; Marie G. Gantz, PhD⁴; Abbot R. Lupton, MD⁵; Bradley A. Yoder, MD⁶; Roger G. Faix, MD⁶; Abhik Das, PhD⁷; Kurt Schibler, MD⁸; Wade Rich, RRT¹; Nancy S. Newman, RN⁴; Betty R. Vohr, MD⁵; Kimberly Yolton, PhD⁸; Roy J. Heyne, MD⁹; Deanne E. Wilson-Costello, MD³; Patricia W. Evans, MD¹⁰; Ricki F. Goldstein, MD¹¹; Michael J. Acarregui, MD¹²; Ira Adams-Chapman, MD¹³; Athina Pappas, MD¹⁴; Susan R. Hintz, MD MS Epi¹⁵; Brenda Poindexter, MD¹⁶; Anna M. Dusick, MD FAAP¹⁶; Elisabeth C. McGowan, MD¹⁷; Richard A. Ehrenkranz, MD¹⁸; Anna Bodnar, MD⁶; Charles R. Bauer, MD¹⁹; Janell Fuller, MD²⁰; T. Michael O'Shea, MD MPH²¹; Gary J. Myers, MD²²; Rosemary D. Higgins, MD²³ for the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

*Both authors contributed equally to the manuscript

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¹⁸ Department of Pediatrics, Yale University School of Medicine, New Haven, CT

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Text Word count: 2688

Text: MeSH terms:

Cerebral palsy

Infant, Newborn

Infant, Low Birth Weight

Infant, Extremely Low Birth Weight

Infant, Premature

Infant, Extremely Low Gestational Age

Infant mortality

Intellectual disability

Intensive care, neonatal

Neurodevelopmental outcome

Oximetry

Randomized controlled trial

Continuous Positive Airway Pressure

Intubation, intratracheal

Pulmonary surfactants/therapeutic use

Oxygen inhalation therapy/methods

Oxygen administration & dosage

Retinopathy of prematurity, epidemiology

Child development

Developmental disabilities, epidemiology

Psychomotor disorders, epidemiology

Follow-up studies

From: [Poindexter, Brenda B](#)
To: [Ripley, Julie](#)
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Subject: Re: Required forms - New England Journal of Medicine 12-08506.R1
Date: Monday, September 17, 2012 5:41:34 PM

Yes, my name was accidentally left off first draft so this is first notice I have received. Will send first thing in the morning.

Thanks,
Brenda

Sent from my iPhone

On Sep 17, 2012, at 5:17 PM, "Ripley, Julie" <jripley@nejm.org> wrote:

> Dear Dr. Poindexter,

>

> I have not yet received the required forms from you for NEJM manuscript 12-08506. Please fax or email a copyright form, signed in pen, to 781-207-6529 and fill out and email the attached disclosure in its electronic format. If you could do so as soon as possible, we'd appreciate it.

>

> Best,

> Julie

>

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

> From: Archer, Stephanie (NIH/NICHD) [E] [<mailto:archerst@mail.nih.gov>]

> Sent: Wednesday, September 12, 2012 11:18 AM

> To: Ripley, Julie

> Cc: 'Wade Rich'; Higgins, Rosemary (NIH/NICHD) [E]; Yvonne Vaucher (yvaucher@ucsd.edu); Neil Finer (nfiner@ucsd.edu)

> Subject: RE: Required forms - New England Journal of Medicine 12-08506.R1

>

> Dear Ms. Ripley,

>

> I just emailed the files to you in 8 separate emails. I believe that Brenda Poindexter sent you her forms directly. If you do not have these, or are missing any others, please let me know.

>

> Thank you,

>

> Stephanie Archer

>

> Stephanie Wilson Archer

> The Eunice Kennedy Shriver National Institute of Child Health and Human Development Pregnancy & Perinatology Branch

> 6100 Executive Boulevard, Room 4B03

> Rockville, MD 20852

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> archerst@mail.nih.gov

>

>

>

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From: [Michael O'Shea](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Nancy Peters; \(kzaterka@rti.org\)](#)
Subject: RE: DSMB review of SUPPORT
Date: Tuesday, August 14, 2012 5:07:02 PM

Thanks very much, Rose.

Kris, could you send me any DSMB reports (just the summary letter for the PIs to submit to their IRBs) related to the SUPPORT Trial?

Thank you,

Mike

Michael O'Shea, MD, MPH
Professor of Pediatrics
Vice Chair for Research
Section Head for Neonatology
Wake Forest School of Medicine

Medical Center Blvd
Winston-Salem, NC 27157
phone 336-716-4663
FAX 336-716-2525

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, August 14, 2012 5:04 PM
To: Michael O'Shea
Cc: Nancy Peters; (kzaterka@rti.org)
Subject: RE: DSMB review of SUPPORT

Mike
Kris can provide the information
Thanks
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: Michael O'Shea [<mailto:moshea@wakehealth.edu>]
Sent: Tuesday, August 14, 2012 5:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Nancy Peters
Subject: DSMB review of SUPPORT

Rose,

Our IRB requests that we annually renew IRB approval for studies for which we are still writing manuscripts, so I am renewing our IRB approval for SUPPORT.

They are asking for any DSMB reports related to SUPPORT.

Is there someone at NICHD who could help me obtain a copy of these? None were sent to me, probably because we were out of the study after March 2006.

Thank you,

Mike

Michael O'Shea, MD, MPH
Professor of Pediatrics
Vice Chair for Research
Section Head for Neonatology
Wake Forest School of Medicine

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Winston-Salem, NC 27157
phone 336-716-4663
FAX 336-716-2525

From: Patricia Evans
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Combined SUPPORT Neurodevelopmental Outcome revision submitted to NEJM
Date: Friday, September 14, 2012 2:35:06 PM

Thank you, Rose. I appreciate it. Hope you're doing well too. Have a great weekend.

Patricia

On Sep 14, 2012 10:57 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov> wrote:

Patricia

I am sending to your newer email – keep your fingers crossed. Hope you are doing well!
Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research
Network

Pregnancy and Perinatology Branch

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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 14, 2012 11:03 AM
To: mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsf.edu; Wally Carlo (wacarlo@uab.edu);
Michele Walsh (mcw3@cwru.edu); mgantz@rti.org; Abbot Laptook; Brad Yoder
(Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt

Schibler [kurt.schibler@cchmc.org]; Wade Rich; Nancy Newman; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com); Patricia.W.Evans@uth.tmc.edu; gold005@mc.duke.edu; Michael.Acarregui@providence.org; Adams-Chapman, Ira; (apappas@med.wayne.edu); shhintz@stanford.edu; bpoindex@iupui.edu; Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary_myers@URMC.Rochester.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; gold008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edwardbell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; Frantz, Ivan; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale_phelps@urmc.rochester.edu; carl_dangio@urmc.rochester.edu
Subject: Combined SUPPORT Neurodevelopmental Outcome revision submitted to NEJM

Hi

Attached is the SUPPORT FU paper resubmitted this week to NEJM. Please note, Dr. Brenda Poindexter's name has been added to the masthead (doesn't appear on the attached copy). This was done by the journal when the papers were combined into one. One we hear back from the journal< I will let everyone know. Please keep the information confidential.

Thanks for all your help and commitment!!
Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Kennedy, Kathleen A
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu
Cc: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins, Rosemary (NIH/NICHD) [E])
Subject: Another revision
Date: Wednesday, September 12, 2012 8:26:02 PM
Attachments: [ROP Natural History Study Manuscript \(revised after subcommittee comments\).doc](#)

Lisa, here's a summary of what we "discussed" yesterday and the additional comments/requests from the other reviews.

I think it might look better (less busy and cluttered) if we could stack the bars (same colors) for ROP. We would still have separate bars for Died before exam and Severe ROP or death. If we do this, I think we need to separate out "ROP less than severe" from "Any ROP". (We don't want to stack Severe ROP on top of Any ROP that includes Severe ROP.) So we'd have stacked bars of No ROP, ROP less than severe, and Severe ROP. The legend might need to be somewhere else (off to the side or at the bottom of the graph) though.

Don't worry about changing Figure 3. Several people have suggested that it's redundant with Table 3 and should be removed.

Brad Yoder asked for clarification on the statement "Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP." I've added "Among infants who had one exam without stage 3 ROP or plus disease and vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP." I based that on a prior email from you. Marie has said in her comments that this wasn't stated in the study protocol but it was "implied". I'm not sure how best to get a clear resolution on this. My guess is that it never came up because the ophthalmologists would, on clinical grounds, schedule a follow-up exam if the baby had stage 3 ROP or plus disease even if they thought the vessels were in Zone III (if that ever happened). I've asked Dale how we can best convey to the reader what was really done.

Could you please check the denominators again in Table 2? I have a comment from you in a prior version that mentions changes to the denominator for the sepsis variables but the ones that have missing data listed in the table are fungal sepsis and intraventricular hemorrhage (not late onset sepsis). Is that right?

Neil and others have asked about statistical comparisons of the data in Table 2. I don't think it's necessary but I wouldn't be surprised if the reviewers ask for it. I ran the numbers and added this: "Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP)." Let me know if that's ok with you. Dale suggested, and I agree, that it would be better to express "Days of supplemental oxygen" as medians and IQRs.

Marie asked about comparing (statistically) the curves in Figure 5 (Figure 4 in the revision) to support the statement (based on eyeball) that the vessels matured later in infant with Mild/Moderate ROP as compared to no ROP. I think we'd have to combine the GA groups together to do that but, if it's feasible, it would be worth trying to do that. Marie also asked about doing a statistical comparison of the curves in each of the graphs in Figure 4. Is that possible? It would be fantastic to have confidence intervals for all of this [Table 3 and Figure 4 (Figure 3 in the revision)], but I don't see how that would be feasible. Can you explain to me why the curves in Figure 4 (Figure 3 in the revision) appear to separate from the baseline of 0 before the min age of severe ROP in Table 3? That doesn't seem right to me, unless smoothing the curve makes it look like that. I've added a few sentences on analysis to the Methods. Could you please revise those when we decide how we're going to modify this?

Dale, the attached revision is my attempt to do what everyone asked whenever feasible. The changes that I made in response to other people's suggestions are highlighted in yellow. I'd appreciate it if you'd look at those parts to see if you agree with the changes. I wasn't able to make all the changes that you suggested to the What's new? and the Abstract because of the word limits. The biggest changes have to do with incorporating 2 new similar papers (we really need to get this done and published before there are more) and trying to clarify the Discussion about postmenstrual vs chronologic age. It didn't even make sense to me after I'd taken a break from it for a while. We may need to tweak the wording some more when Lisa finishes the analyses but I don't think there will be major changes. As always, I look forward to your comments on this.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [<mailto:wrage@rti.org>]
Sent: Tuesday, September 11, 2012 11:13 AM
To: Kennedy, Kathleen A
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)

Hi Kathleen,
See below:

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Tuesday, September 11, 2012 11:41 AM
To: Wrage, Lisa Ann
Subject: FW: Onset of ROP Observational Study (SUPPORT Secondary)

Could you please take a look at Abhik's comments #5 and #7?

For number 5, if it's doable, I think it might look better (less busy and cluttered) if we could stack the bars (same colors) for ROP. We would still have separate bars for Died before exam and Severe ROP or death. If we do this, I think we need to separate out "ROP less than severe" from "Any ROP". (We don't want to stack Severe ROP on top of Any ROP that includes Severe ROP.) So we'd have stacked bars of No ROP, ROP less than severe, and Severe ROP.

Lisa: I like the graph as it is, but he may have been thinking that stacking would eliminate possible confusion around that issue of including severe ROP in both bars. Since the ROP bar might get kind of long I may have to switch % to the X axis and GA to the Y axis, not sure, and it might look weird, but it also might be fine, I will just try it and see what you think.

For number 7, I don't know if the other line can be dotted such that it's distinguishable from the solid line. If that can be accomplished, it might be worth doing.

Lisa: It should be able to be dotted. I am assuming that you mean to include all infants with any ROP

in that line??

Thanks.

Lisa

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Das, Abhik [<mailto:adas@rti.org>]
Sent: Friday, July 27, 2012 12:28 PM
To: Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: Onset of ROP Observational Study (SUPPORT Secondary)

Kathleen:

This looks very good. I only have a few minor comments/suggestions in the attached.

Thanks

Abhik

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]
Sent: Friday, July 27, 2012 9:53 AM
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHHospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Archer, Stephanie
Subject: Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School

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Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

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Comment [KKA1]: 2804 words excluding title page, abstract, tables, subtitles, figures, figure legends, and references; needs to be <=3000

Abbreviations:

GA – gestational age
PMA – postmenstrual age
ROP – retinopathy of prematurity
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

Keywords

retinopathy of prematurity, screening, extremely preterm infants

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What's Known on this Subject

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

Comment [KKA2]: 40/40 words

What This Study Adds

Our data support the timing of examinations in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. We did not replicate the observation that the onset of ROP is more closely correlated with postmenstrual than chronological age.

Comment [KKA3]: 40/40 words

Abstract

Objective: Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997 and treated for threshold ROP. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

Patients and Methods: Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was a primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

Results: 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had a final ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

Conclusions: Our contemporary data support continued use of the 2006 guidelines. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines^{1,2} are based on natural history data from the CRYO-ROP³ and LIGHT-ROP⁴ studies. The CRYO-ROP study⁵ remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.⁶ Over the past two decades, survival of lower birth weight infants has increased.^{7,8} For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.⁷ The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.⁴ Based on the results of the ET-ROP study, earlier treatment is now recommended.⁹ With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP, defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP Study¹⁰ and a population-based cohort study of infants born 2004-2007 in Sweden¹¹ reported the age of onset of stages 1, 2, and 3 ROP; the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from the Canadian Neonatal Network reported the age of onset of Type 1 ROP in a cohort of 214 infants \leq 27 weeks gestation;¹² this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort¹³ reported that "No preterm infants required treatment before the 33th postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for treatable ROP so that appropriate follow-up can be arranged (particularly

Comment [KKA4]: 249 words, needs to be \leq 250 Dale, I can't add anything more to the abstract without removing something.

Comment [KKA5]: Dale, I've searched before for newer references for this statement. If we want a reference to support a statement that survival has improved, we need a report of survival for the same cohort (by either BW or GA) in two different time periods. This is the most recent report of that kind that I could find. I added the newer reference even though it doesn't support this statement because it reports survival of ELGA infants during the time of the SUPPORT trial.

for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27^{6/7} weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)¹⁴ to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O₂ saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24^{0/7} – 27^{6/7} weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab); or no severe ROP (full vascularization to the ora serrata or vascularization in zone III on 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up was curtailed at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in the either eye.

Categorical outcomes were compared by Chi squared test; continuous outcomes were compared by t-test. Survival (cumulative incidence) curves were compared by log rank test.

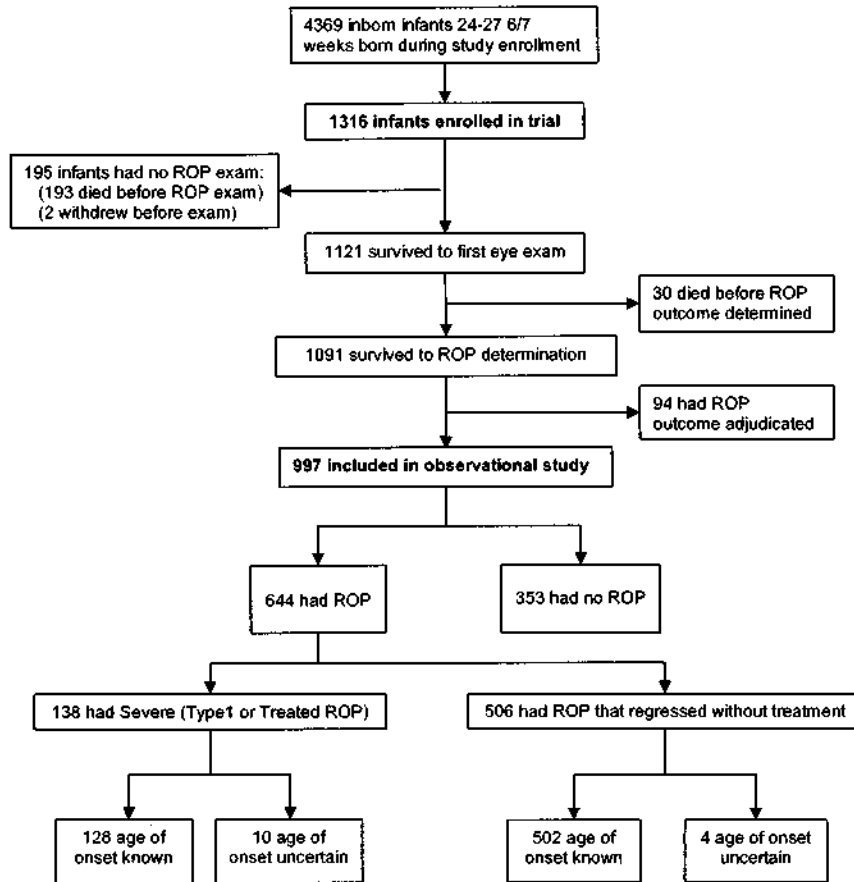
Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-five percent (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of subjects in the original trial and current analysis

Comment [KKA6]: Lisa included this in one of her emails. Marie says it was implied rather than stated. I asked Lisa about it. Dale, what do you think would best convey what we really did to the reader?

Comment [KKA7]: Lisa will need to revise this when she updates the analyses. I was viewing this as a descriptive rather than a hypothesis-testing study. Many on the subcommittee requested these analyses and I suspect we'll get similar requests from reviewers.



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)		
		All ROP Outcomes	By ROP Outcome Category	
			No ROP	Any ROP ¹

n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA ² [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

¹ Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

² based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all 1316 infants in SUPPORT Trial



Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/treated) ROP

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p < 0.05$ for all comparisons of no ROP vs any ROP).

Table 2. Risk factors for ROP

Risk Factor	No ROP	Any ROP ¹	Severe (Treated or Type 1) ROP
n	353	644	138
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [(n (%))]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23 ^a (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98 ^a (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

Comment [KKA8]: I had this backwards. It's been that way for a while; I'm surprised that none of us noticed it before.

Comment [KKA9]: I agree that Neil's observation is interesting but we don't have the data we need to address that question. I don't think we record the date of PDA surgery. There is a date recorded for first episode of NEC and it's coded as medical vs surgical NEC but that's not exactly the same as recording the date of NEC surgery. Even if we had that dates, and we could look at progression of ROP before and after surgery, I don't know what we would compare it to.

Comment [KKA10]: I asked Lisa to give us medians and IQRs for this.

¹ Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).
² missing data for 1 infant

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

Table 3. Postmenstrual and chronological age of onset¹ of any stage ROP (among infants with ROP age of onset determined)

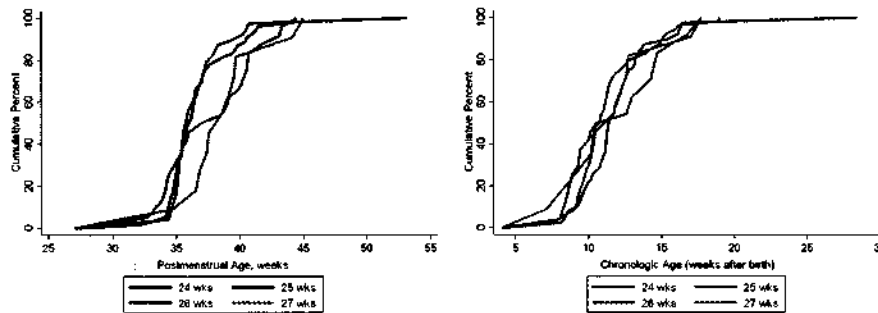
ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min ²	1%	5%	25%	50%	75%	95%	99%	Max ²	min	1%	5%	25%	50%	75%	95%	99%	max
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP ³	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type I/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

Comment [KKA11]: I don't think I'm following what's confusing about this. Is there some question about how ROP (any stage, any zone) would be defined? Maybe I'm missing something but that seems obvious to me. It thought the question was about whether a baby whose first exam had Type 1 or 2 ROP would also have that exam date as the date for onset of "Any ROP".

¹ Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.
² Min = minimum age at which designated severity of ROP was identified; max = maximum age.
³ Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 3.

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth



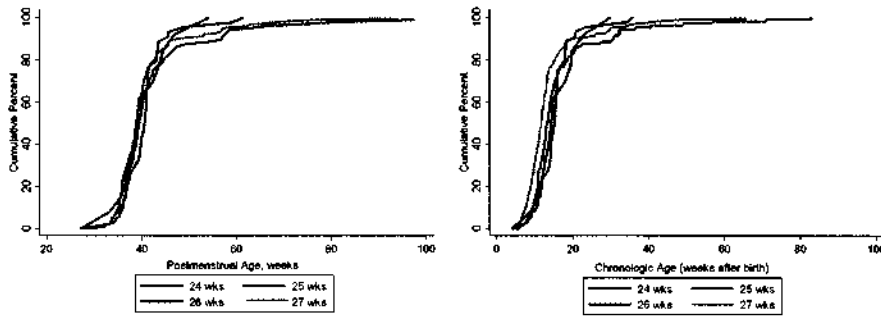
In contrast to prior studies, our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP

and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam without stage 3 ROP or plus disease and vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

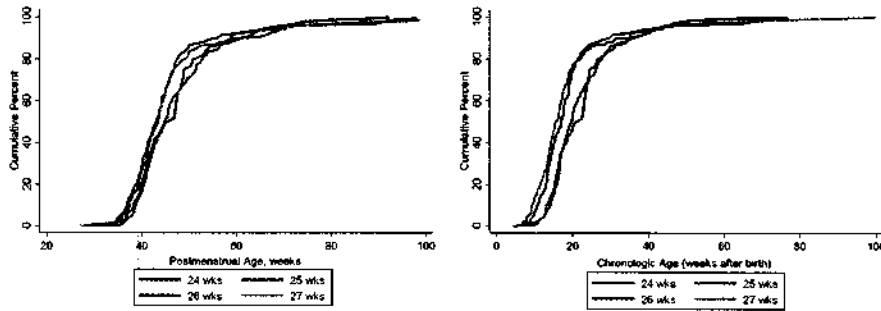
Comment [KKA12]: Added in response to Brad Yoder's comment. Need to verify with Lisa and Dale.

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

No ROP on any exam



Mild/Moderate ROP



In general, retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP.

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP; weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)

Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge).

Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,⁹ so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,³ lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,¹ albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤ 1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.¹⁵ Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age¹⁶ and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum (< 750 g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,¹¹ which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al¹² included 23-27 week infants; infants ≤ 25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants > 25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (23-24 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest age of onset of Type 1 ROP is more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian Network study,¹² the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al¹³ that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronological age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the

Comment [KKA13]: I added this at Abbot's suggestion. I'm not that happy with it. Your thoughts?

Comment [KKA14]: They didn't stratify randomization but they stratified by BW when they reported the timing of onset of ROP in the natural history paper.

potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.¹⁷ The SUPPORT Trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.¹⁷

Conclusion

Current screening guidelines, published in 2006,¹ recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at ≥ 35 weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Dr. Marie Gantz, and Ms. Wrage (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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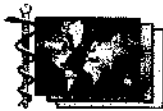
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This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) _____ 2. Surname (Last Name) _____ 3. Effective Date (07-August-2008)
4. Are you the corresponding author? Yes No
5. Manuscript Title _____
6. Manuscript Identifying Number (if you know it) _____

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
2. Consulting fee or honorarium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

* This means money that your institution received for your efforts on this study.
 ** Use this section to provide any needed explanation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD
9. Royalties	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
10. Payment for development of educational presentations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
11. Stock/stock options	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
13. Other (err on the side of full disclosure)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

SAVE



ICMJE Form for Disclosure of Potential Conflicts of Interest

Evaluation and Feedback

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: **CONFIDENTIAL SUPPORT FU PAPER AND NEJM**
Date: Tuesday, September 11, 2012 8:50:20 PM

Please resend. Than ks.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 11, 2012 5:31 PM
To: Vaucher, Yvonne
Subject: Re: **CONFIDENTIAL SUPPORT FU PAPER AND NEJM**

I think Stephanie sent you a series of emails with the documents attached. Let me know if we need to resend

Thanks
Rose

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, September 11, 2012 08:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: **CONFIDENTIAL SUPPORT FU PAPER AND NEJM**

Hi Rose,

This is the email I misinterpreted as meaning that you would submit the forms centrally. Sorry.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 13, 2012 1:46 PM
To: mperalta@peds.uab.edu; Vaucher, Yvonne; Finer, Neil; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Rich, Wade; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary_myers@URMC.Rochester.edu); bpoindex@iupui.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.F.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edwardbell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale_phelps@urmc.rochester.edu; carl_dangio@urmc.rochester.edu
Subject: **CONFIDENTIAL SUPPORT FU PAPER AND NEJM**
Importance: High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can

be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

In the meantime, I need everyone listed in the "TO" line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

From: [Vaucher, Yvonne](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)
Cc: [Rich, Wade](#); [Finer, Neil](#); [Vaucher, Yvonne](#)
Subject: RE: New England Journal of Medicine 12-08506
Date: Tuesday, September 11, 2012 6:00:16 PM

From previous correspondence I misunderstood that the "original" author forms were sent by the authors to the NEJM and the "copies" came to me, but as this was not the case, please resend and we will upload from here.

From Rose's correspondence with Julie from the NEJM (8/13-8/15) it appeared that Brenda's name was left off as an administrative error and we did not need to submit anything else to include her; however, I realize that we do need a new author list as the submitted title page does not include Brenda although at one point it did. Can Stephanie please send another updated author/institution list?

Yvonne

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

From: Finer, Neil
Sent: Tuesday, September 11, 2012 2:44 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne; Rich, Wade
Subject: RE: New England Journal of Medicine 12-08506

Thanks

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

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, September 11, 2012 2:26 PM
To: Finer, Neil
Subject: Re: New England Journal of Medicine 12-08506

Ok

We also had all of the author forms and I think they got emailed to Yvonne- I can resend if needed.

Thanks for all the effort and commitment to this!
Rose

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]
Sent: Tuesday, September 11, 2012 05:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: New England Journal of Medicine 12-08506

We are working on this - we will let you know if we need more details Neil

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

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]
Sent: Tuesday, September 11, 2012 2:23 PM
To: Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: New England Journal of Medicine 12-08506

Neil

Please make sure brenda gets added.

Stephanie can help if needed!

Thanks

Rose

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

From: Ripley, Julie [mailto:jripley@nejm.org]

Sent: Tuesday, September 11, 2012 05:01 PM

To: Higgins, Rosemary (NIH/NICHD) [E]

Cc: 'nfiner@ucsd.edu' <nfiner@ucsd.edu>

Subject: RE: New England Journal of Medicine 12-08506

Hi Dr. Higgins and Dr. Finer,

Thank you for your resubmission. I noticed that Dr. Poindexter was not added to the title page of your revised manuscript. If you could please add her and send me the revised file, I will upload it and add her as an author in our system.

Thank you,

Julie

Editorial Assistant

New England Journal of Medicine

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

From: Ripley, Julie

Sent: Wednesday, August 15, 2012 1:33 PM

To: 'Higgins, Rosemary (NIH/NICHD) [E]'

Cc: 'nfiner@ucsd.edu'

Subject: RE: New England Journal of Medicine 12-08506

Hi Rose,

I spoke with my manager and we will not need any paperwork to add this author since this was basically an administrative error. We will need a new title page for the manuscript, however, with her included. You can send this to me and I will add it to the manuscript.

Once I've received the revised title page, I will add her in our system.

Thanks!

Julie

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Monday, August 13, 2012 4:26 PM

To: Ripley, Julie (b)(6)@aol.com

Subject: RE: New England Journal of Medicine 12-08506

Hi

Dr. Anna Dusick died. Dr. Brenda Poindexter's name was inadvertently left off of the author line when the two papers were merged. She was originally listed on Dr. Peralta's submission 12-01618.

Thanks so much for your help

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy
and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Monday, August 13, 2012 4:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; [b)(6)]@aol.com
Subject: New England Journal of Medicine 12-08506

Re: 12-08506 - Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Dear Dr. Higgins:

Thank you for calling earlier today. I was told one of the authors of this manuscript is now deceased. Which author is it?

I will also ask my manager if we need change of author forms to "add" the author that was forgotten when the manuscripts merged. What is the name of that author?

Sincerely,

Julie Ripley
Editorial Assistant

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: New England Journal of Medicine 12-08506
Date: Tuesday, September 11, 2012 5:41:50 PM

Rose,

Where does Brenda go on the author list ?

wade

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

From: Finer, Neil
Sent: Tuesday, September 11, 2012 2:23 PM
To: Rich, Wade
Subject: FW: New England Journal of Medicine 12-08506

Can you add Brenda??

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

From: Ripley, Julie [mailto:jripley@nejm.org]
Sent: Tuesday, September 11, 2012 2:02 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Finer, Neil
Subject: RE: New England Journal of Medicine 12-08506

Hi Dr. Higgins and Dr. Finer,

Thank you for your resubmission. I noticed that Dr. Poindexter was not added to the title page of your revised manuscript. If you could please add her and send me the revised file, I will upload it and add her as an author in our system.

Thank you,
Julie

Editorial Assistant
New England Journal of Medicine

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

From: Ripley, Julie
Sent: Wednesday, August 15, 2012 1:33 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: 'nfiner@ucsd.edu'
Subject: RE: New England Journal of Medicine 12-08506

Hi Rose,

I spoke with my manager and we will not need any paperwork to add this author since this was basically an administrative error. We will need a new title page for the manuscript, however, with her included. You can send this to me and I will add it to the manuscript.

Once I've received the revised title page, I will add her in our system.

Thanks!
Julie

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 13, 2012 4:26 PM
To: Ripley, Julie; (b)(6)@aol.com
Subject: RE: New England Journal of Medicine 12-08506

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Thanks so much for your help

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Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org
Sent: Monday, August 13, 2012 4:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com
Subject: New England Journal of Medicine 12-08506

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<http://www.nejm.org>

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From: Finer, Neil
To: Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org
Subject: RE: New England Journal of Medicine - 12-08506.R1
Date: Tuesday, September 11, 2012 5:19:57 PM

This was great team effort
Many thanks to everyone
I hope we are done with this paper!
To a great team!!
Neil

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

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]
Sent: Tuesday, September 11, 2012 12:35 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org
Subject: FW: New England Journal of Medicine - 12-08506.R1

Dear Neil, Yvonne, Myriam, Rose and Abhik:

Great accomplishment.

Three NEJM papers from one trial. This must be record for the NRN and many trials. The largest ventilator trial; a factorial design! Huge impacts on patient care and survival will follow!!! Already I have heard comments that this is one of the most important trials ever in neonatology.

This would have never happened without your leadership as well as the excellent work by you and each member of the team.

Wally

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

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com
[<mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com>] On Behalf Of editorial@nejm.org
Sent: Tuesday, September 11, 2012 2:21 PM
To: yvaucher@ucsd.edu; Myriam Peralta, M.D.; nfiner@ucsd.edu; Wally Carlo, M.D.; michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com); Patricia.W.Evans@uth.tmc.edu; gold005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; adusick@pediatrics.wisc.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; [\(b\)\(6\)@gmail.com](mailto:(b)(6)@gmail.com); cbauer@peds.med.miami.edu; jfuller@salud.unm.edu; moshea@wfubmc.edu; gary_myers@urmc.rochester.edu; higginsr@mail.nih.gov; [\(b\)\(6\)@aol.com](mailto:(b)(6)@aol.com)
Subject: New England Journal of Medicine - 12-08506.R1

Dear Dr. Finer and co-authors,

Thank you for submitting your revision, of "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial" to the New England Journal of Medicine.

Your submission will be forwarded to the editor, and may be sent out for review as necessary.

Please call us at 617-734-9800 if you have any questions.

Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
<http://www.nejm.org>

From: [Vaucher, Yvonne](#)
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#); [Gantz, Marie](#); wacarfo@uab.edu; [Myriam Peralta, M.D.](#); [Finer, Neil](#); [Vaucher, Yvonne](#)
Subject: Combined SUPPORT Neurodevelopmental Outcome revision submitted to NEJM
Date: Tuesday, September 11, 2012 3:24:59 PM
Attachments: [SUPPORTWebAppendix_091112Final.docx](#)
[SUPPORTConsortDiagram_11Sept2012_RV7.pdf](#)
[SUPPORTEditorialReply4tr091012Final.doc](#)
[SUPPORTPaperResubmission091112CleanTablesNEJM2Final_MG.docx](#)
[SUPPORTPaperResubmission091112CleanHighlightedTablesNEJM2Final_MG.docx](#)

All,

Here it is as submitted to the NEJM. Let's hope we are near the end of the revisions.
Thanks for all your help!

Yvonne

From: Vaucher, Yvonne
Sent: Tuesday, September 11, 2012 12:06 PM
To: Rich, Wade
Subject:

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

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Investigators

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Methodology for limited ventilator strategy

CPAP Arm:

NICU management: CPAP infants could be intubated if they met any of the following criteria: an $\text{FiO}_2 > .50$ required to maintain an indicated $\text{SpO}_2 > 88\%$ for one hour, an arterial $\text{PaCO}_2 > 65$ torr documented on a single blood gas within 1 hour prior to intubation, or 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 within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $\text{PaCO}_2 < 65$ torr with a $\text{pH} > 7.20$, an $\text{SpO}_2 > 88\%$ with an $\text{FiO}_2 < 50\%$, a mean airway pressure (MAP) < 10 cm H₂O, ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be extubated within 24 hours of meeting all of the following criteria: $\text{PaCO}_2 < 50$ torr and $\text{pH} > 7.30$, $\text{FiO}_2 \leq .35$ with a $\text{SpO}_2 > 88\%$, a MAP < 8 cm H₂O, ventilator rate < 20 bpm, an amplitude $< 2X$ MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could 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.¹

Methodology for oximeter blinding strategy

4.1.1 Randomization and Masking, Storing and Assigning Oximeters

Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the 26 - 27 6/7 week gestational age group.... Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO_2 arm of the study. They will be specified as one of the following:

- **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue or Orange** OR
- **Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue or Orange**.

The **Blue/Orange codes** will designate an assignment to either the **Low (85% - 89%)** or **High (91% -95%)** SpO_2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the

sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form**).

Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know"**. Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO₂) are available to accommodate the delivery. Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.²

Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u> <u>Saturation</u>	<u>Higher</u> <u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) ^δ	849±186	852±193	858±186	844±192
Gestational age (weeks) ^δ	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10 th %) ^ε	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male ^ε	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White ^ε	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black ^ε	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic ^ε	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown ^ε	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation ^ε	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any ^ε	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section ^ε	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only ^ε	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married ^ε	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents ^ε	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education< high school	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

degree [€]				
Income < \$30,000/year [€]	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language [€]	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP [€]	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD [¶] [€]	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL [€]	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC [€]	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis [€]	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids [€]	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) ^δ	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

^δ Mean ± SD

[€] no./total no.(%)

[¶] At 36 weeks postmenstrual age

*p<0.05, ** p<0.01, ***p<0.001 (Comparison for groups within each intervention arm)

Comparisons adjusted for stratification by center and gestational age and for familial clustering

Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT

<u>24 0/7-25 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07
<u>26 0/7-27 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31

Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS

<u>24 0/7-25 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22

<u>26 0/7-27 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22

Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level \geq 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral pal	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78
Hearing impairment	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)