Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, May 29, 2014 5:01 PM
To: Blansfield, Earl (NIH/NICHD) [E]
Subject: FW: BUDGET OF THE SUPPORT STUDY

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: Raju, Tonse (NIH/NICHD) [E]
Sent: Tuesday, May 27, 2014 8:32 AM
To: Clark, Bryan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hayunga, Eugene G. (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]
Subject: RE: BUDGET OF THE SUPPORT STUDY

Thanks Bryan. (b)(5)
Tonse

Tonse N.K. Raju, MD, DCH
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Phone: 301-402-1872, Fax: 301-496-3790
rajut@mail.nih.gov

From: Clark, Bryan (NIH/NICHD) [E]
Sent: Tuesday, May 27, 2014 8:30 AM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Hayunga, Eugene G. (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]
Subject: RE: BUDGET OF THE SUPPORT STUDY

Hi all,

I would (b)(5)
(b)(5)

(b)(5) Since, in this case, their would be mutual agreement considering the sharing of grant information, it would not need to be provided under FOIA but I'm including Earl (Blansfield) for more information.

Thanks,
Bryan

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Monday, May 26, 2014 3:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Hayunga, Eugene G. (NIH/NICHD) [E]; Clark, Bryan (NIH/NICHD) [E]
Subject: RE: BUDGET OF THE SUPPORT STUDY

Personally I (b)(5)
(b)(5)

I am copying Gene and Bryan to make sure that I am not speaking out of school ☺

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 7:30 PM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: Fwd: BUDGET OF THE SUPPORT STUDY

Mona
Can you advise?
Thanks

Sent from my iPhone

Begin forwarded message:

> **From:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
> **Date:** May 23, 2014 at 7:11:51 PM EDT
> **To:** Jesus Villar <(b)(6) @gmail.com>
> **Cc:** "Rosemary (NIH/NICHD) Higgins" <higginsr@mail.nih.gov>
> **Subject: Re: BUDGET OF THE SUPPORT STUDY**
>
> Dear Dr. Villar.
>
> This was a multicenter trial with ongoing support and additional capitation per patient enrollment.
>
> Dr. Higgins is the NICHD program officer of the Network. She may be able to give you more details.

Wally

Sent from my iPhone

On May 23, 2014, at 3:34 AM, "Jesus Villar" (b)(6) @gmail.com> wrote:

> Dear Dr. Carlo:
>
> I am preparaing a Research Grant for the European Union on a project that combine experimental and clinical research on acute lung injury.
> The clinical side involves the Designing of a Clinical Trials Network in patients with ARDS.
> One of the key issues in these types of grants is the detailed budget that I need to perform a couple of trials in the next 5 years.
>
> Since you were the Principal Investigator of the classical and clinically relevant SUPPORT Study, I would like to ask you if you can send me how did you distribute the budget granted to your team for performing the study. I asume that the budget includes salary support for the PI and the site investigators, salary support for fellows, project managers, etc.
>
> Thank you,
>
> Jesús Villar

--
Jesús Villar, MD, PhD, FCCM
CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III
Multidisciplinary Organ Dysfunction Evaluation Research Network,
Research Unit, Hospital Universitario Dr. Negrin
Barranco de la Ballena, s/n - 4th floor, south wing
35010 Las Palmas de Gran Canaria
Canary Islands, Spain
Phone: (+34) 928-449413
Fax: (+34) 928-449813
Cellular: (+34) 606 (b)(6)
e-mail: (b)(6) gmail.com

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 12:18 PM
To: Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Oh, sorry. Thanks!

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 12:18 PM
To: Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

She means the one attached, Renate.

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 12:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

I'm not sure which Carlo study it is from this list:
https://www.google.com/search?q=NEJM+Carlo+2010&oq=NEJM+Carlo+2010&aqs=chrome..69i57.6035j0j4&sourceid=chrome&es_sm=93&ie=UTF-8 Would you specify? (b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:46 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

The source of the numbers are as follows:

Percent Mortality:		
Higher saturation group	16.2 percent	(NEJM 2010 Carlo publication)
Lower saturation group	19.9 percent	(NEJM 2010 Carlo publication)
Infants treated outside of study	23.1 percent	
Non-enrolled/Eligible patients	24.1 percent	(Table 3 of the Rich study – enrolled, non-eligible)

I have to go back through to find the source of the 23.1 %.
Hope this helps

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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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: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Sorry, Rose. One more question. We had these numbers when the issue just broke, but they don't synch with what's in the Rich study. Should we j(b)(5)

Percent Mortality:

Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:32 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Enrolled infants had lower rates of complications and mortality. When adjusted for factors that impact morbidity and mortality (e.g. antenatal steroids, etc), infants in the trial had not greater risk than the unenrolled eligible infants.

Rosemary D. Higgins, MD
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Bethesda, MD 20892
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Just so I understand, in what way were they different? Are they saying the outcome numbers aren't really a fair representation?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:26 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

The papers are in the public domain. The Consent paper points out that the enrolled sample is somewhat different that those who were eligible but not enrolled.

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:24 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Thanks, Rose. Is there (b)(5)
(b)(5) I'm not sure I understand what the study is saying in terms of consent bias.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:09 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Here is the SUPPORT consent paper – see table 3 which compares the enrolled versus non-enrolled. The second paper (STOLL) is a paper looking at in-hospital outcomes for extremely premature infants. If you go to table 3, the mortality is broken out by week of gestation. The following mortality rates for infants 24-27 weeks are as follows:
24 weeks – 45%
25 weeks -28%
26 weeks – 16%
27 weeks – 12%

Hope this helps

Rose

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higginsr@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: FW: Misconduct of HHS demands investigation
Importance: High

Hi Rose and Bob:

HHS is working with Paul Basken of the Chronicle of Higher Education. Paul mentioned the deaths and I told Tait we should point out the stats on survival compared those not on the study. I have the QA below that we drafted but is there a paper or data point that I can link to from it or a reference I can cite?

How did mortality rates from the study compare to those of infants not in the study?

Infants in the study had a lower mortality rate than those not enrolled. Even after adjusting for characteristics of the non-enrolled infants, such as poorer health, infants in the study were still at no greater risk of death and other conditions associated with extreme prematurity.

Percent Mortality:	
Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

Thanks,
Renate

From: Sye, Tait (OS/ASPA)
Sent: Friday, May 23, 2014 10:49 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Renate-

Can you send me a link/citation for the line that the babies on the study did better than the babies off the study?

Thanks.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Thursday, May 22, 2014 9:20 PM
To: Sye, Tait (OS/ASPA)
Subject: Fw: Misconduct of HHS demands investigation

Actually, the babies on the study did better than the babies off the study. I think we need to point that out.

From: Paul Basken <paul.basken@chronicle.com>
Sent: Thursday, May 22, 2014 6:52 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

... and to be clear, the "some babies died" is badly phrased here, as there's apparently no hard data on that, just the expectation that many were exposed to a higher risk of death... plus the 11 families suing over various injuries...

From: Paul Basken
Sent: Thursday, May 22, 2014 6:35 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Tait, Renate... I have to say that after looking at this for another couple days, I'm getting a better sense of what the underlying complaint is here... I couldn't give this full attention two days ago while finishing off a few other things, but now that I see the emails describe how thoroughly Dr. Collins and others at NIH were apparently guiding OHRP on its response to the Support trial, I'd like to check back to be sure that's really all you have to say about it...

I do realize there's a legitimate argument out there about whether patients really need to be notified in cases where they are essentially being randomized into arms of a trial in which other real-life factors probably would have randomized them anyhow. But the important distinction here is that the treatment in this case was not just a replica of what might have randomly happened to these babies, but an artificially altered version of those real-life conditions designed to keep each baby getting a set dose of oxygen regardless of how it was responding to that level. And some of the babies died as a result of that.

And it's not just the universities that were responsible for setting up that protocol, but NIH officials who signed off on it. And so for top NIH officials -- including Dr. Collins -- to come to OHRP after the fact, and try to guide OHRP in how to respond, and to in fact pressure OHRP to change how it responded, seems to be a pretty serious charge, and one that deserves a bit more than a one-line response saying that NIH regularly works with OHRP to ensure patient protections.

Of course if that's still all you want to say about it, then we'll have no choice but to report it that way. But it does seem to leave some big questions hanging out there. It seems like the kind of thing Dr. Collins would want to answer directly, even if he is out of the country.

Thanks, Paul (202-466-1044)

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:30 PM

To: Paul Basken; Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

Not to sound like a broken record, but we are going to stick by our statement:

OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:29 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Thanks, Renate.. That's helpful... Would that then have made it somehow improper, or at least undesirable, for NIH officials to be coordinating with OHRP on a policy response?
Thanks, Paul

From: Myles, Renate (NIH/OD) [E] [mylesr@od.nih.gov]
Sent: Tuesday, May 20, 2014 4:26 PM
To: Paul Basken; Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Hi Paul:

One point of clarification: OHRP is part of HHS (not outside HHS). OHRP used to be under NIH and then was moved under HHS.

Thanks,
Renate

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:24 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

OK thanks, will see what they say on that question... I realize some folks are unhappy with OHRP, and I'm actually working on a piece about that, but just wondering if this particular complaint is a legally valid line of attack... Rep DeLauro in her statement said that this kind of thing is the reason why they moved OHRP out of HHS, so perhaps Congress did intend OHRP to have some freedom of movement, and this kind of coordination by HHS and NIH may seem contrary to the spirit somehow, but I'm not clear that it's legally prohibited... Thanks, Paul

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:13 PM
To: Paul Basken; Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

[OFF THE RECORD- good question]

Here is OHRP's compliance oversight procedures, including its legal authority:

http://www.hhs.gov/ohrp/compliance/evaluation/index.html

and, as I note in our statement:

OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:09 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Thanks... I'm trying to figure out what exactly is the alleged violation. Is it stated in law somewhere that OHRP is supposed to be fully independent of HHS and/or NIH?
Thanks, Paul

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:05 PM
To: Myles, Renate (NIH/OD) [E]; Paul Basken
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

Here is HHS statement regarding Public Citizen letter. Please attribute to HHS spokesperson:

"The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare and well-being of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

"In the wake of extensive scientific and public discussions since OHRP's March 2013 determination letter related to the SUPPORT study, OHRP became aware of different understandings of what is meant by "standard of care" and risks that must be disclosed to potential subjects in the research context.

"To further understanding of related issues, HHS solicited public comments and held a public meeting in August 2013 to gather feedback on this important issue. OHRP has been reviewing these comments, along with input from others parts of HHS, and is currently drafting guidance on the issue."

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Tuesday, May 20, 2014 3:36 PM
To: 'Paul Basken'
Cc: Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Hi Paul:

Thanks for checking. The response to the original PC Letter is coming from HHS OASPA (copying Tait Sye).

Best,
Renate

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 3:34 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Renate... Anything on this? Thanks, Paul (202-466-1044)

From: Karilyn Gower [mailto:kgower@citizen.org]
Sent: Tuesday, May 20, 2014 10:11 AM
To: Dianne Donovan
Subject: Misconduct of HHS demands investigation

Hi Dianne. I thought you or someone else at the Chronicle of Higher Education might be interested in the release below. Please let me know if you have any questions. Thanks!
-Kari

Karilyn Gower | Press Officer
TEL: 202.588.7779 | **CELL:** 630.913.4287
1600 20th St NW, Washington, DC 20009
http://www.citizen.org

PUBLICCITIZEN

Investigation Needed: Senior HHS Officials Facilitated NIH Interference With Investigation of the SUPPORT Study, Despite Direct Conflict of Interest

Deputy Secretary, Other High-Ranking HHS Officials Allowed NIH Director, Deputy Director to Review and Edit Office of Human Research Protections' Compliance Oversight Letter, Emails Show

May 20, 2014

Contact: Angela Bradbery (202) 588-7741
Karilyn Gower (202) 588-7779

WASHINGTON, D.C. – Public Citizen, joined by nine prominent scholars, today called for an immediate investigation by the U.S. Department of Health and Human Services (HHS) Office of Inspector General into the conduct of senior HHS officials, who, according to an email trail, permitted top National Institutes of Health (NIH) officials to edit drafts of a letter documenting findings of what should have been an independent inquiry into serious ethical lapses in a major NIH trial.

According to documents Public Citizen recently obtained under the Freedom of Information Act (FOIA), HHS officials in the immediate Office of the Secretary and Office of the Assistant Secretary for Health (OASH) knowingly allowed the director of NIH and other senior NIH officials to interfere with the independence of the Office for Human Research Protections' (OHRP's) ongoing compliance oversight investigation of the controversial SUPPORT study, Public Citizen said in a letter to the HHS inspector general.

In a separate letter to the HHS inspector general, U.S. Rep. Rosa DeLauro (D-Conn.) today echoed the call for an investigation.

Though heavily redacted, the documents Public Citizen obtained reveal that named NIH officials were, inappropriately, given multiple opportunities to review and edit drafts of a pending OHRP compliance oversight determination letter regarding the SUPPORT study, as well as apparently allowing NIH to influence the timing of the release of the letter, which occurred on June 4, 2013. This letter put on hold all compliance enforcement actions taken by OHRP that had been outlined in an earlier letter issued on Feb. 8, 2013, to the University of Alabama at Birmingham. This hold is still in effect.

The SUPPORT study was funded by the NIH at a cost of more $20 million, and NIH scientists were co-investigators on the study. The experimental study exposed 1,316 premature infants to increased risk of blindness, brain injury and death without informing parents of the risks to their babies or the true nature and purpose of the research.

"It is deeply disturbing and unacceptable that the NIH, which was involved in the development, approval, conduct and oversight of the SUPPORT study, was allowed to review and edit OHRP's compliance oversight letter," said Dr. Michael Carome, director of Public Citizen's Health Research Group. "The most troubling part is that numerous high-ranking officials facilitated this interference by senior NIH officials, despite the fact that NIH had obvious actual, direct conflicts of interest in the research under investigation."

"The emails obtained by Public Citizen strongly suggest that the NIH – apparently desperate to undo OHRP's earlier compliance oversight determinations – launched an aggressive campaign to undermine OHRP's regulatory authority and regrettably found several willing partners for this campaign at the highest levels of HHS," said renowned bioethicist Ruth Macklin, a professor at Albert Einstein College of Medicine and director of a training program in research ethics sponsored by the NIH Fogarty International Center.

Said DeLauro, "The very reason OHRP was administratively moved out of NIH was because of the long-recognized conflicts of interest that exist between NIH and OHRP. That move was intended to prevent exactly the type of NIH interference that has now apparently occurred. It appears that actions displayed by senior HHS leaders have compromised the integrity and independence of OHRP's ongoing investigation into the SUPPORT

study."

The series of email communications between NIH, the HHS secretary's office and OHRP paints a truly disturbing picture, Carome said. A sampling of some of the most revealing emails includes:

• Email on May 3, 2013, 4:54 PM

From: Jerry Menikoff (Director, OHRP):
Addressed to: Kathy Hudson (Deputy Director for Science, Outreach, and Policy, NIH); Howard Koh (Assistant Secretary for Health, HHS); Wanda Jones (Principal Deputy Assistant Secretary for Health, HHS); and Kirby Bumpus (OASH, HHS)
Subject: RE: Support study -
Message:

Kathy,

For your weekend enjoyment, **here is the revised version of the SUPPORT letter...** [Emphasis added]

• Email on May 12, 2013, 02:10 PM

From: Kathy Hudson (Deputy Director for Science, Outreach, and Policy, NIH)
Addressed to: Howard Koh (Assistant Secretary for Health, HHS) and Jerry Menikoff (Director, OHRP)
Subject: Suggested correction to OHRP-UAB draft letter [Emphasis added]

An apparent attachment is completely redacted.

A June 2, 2013, email, from Francis Collins, director of NIH, sent to many senior leaders of HHS – including the deputy secretary and chief of staff – thanked them "for the opportunity to weigh in on OHRP's letter to UAB [University of Alabama Birmingham] and the Federal Register Notice related to SUPPORT" and stated that the NIH is "grateful for the opportunity to work with such a dedicated team within HHS."

"This interference has seriously compromised the integrity and independence of OHRP's compliance oversight investigation into the SUPPORT study, fundamentally undermining OHRP's regulatory authority and almost certainly doing long-lasting and possibly irreparable harm to the status of this critically important regulatory agency, whose primary mission is to protect human subjects," said Carome.

Public Citizen and the nine prominent scholars in bioethics, law and history seek to ensure that all HHS officials who played a role in the corrupt conduct revealed by the HHS emails are held accountable and that appropriate corrective actions are taken to prevent such improper and unethical interference by NIH in the compliance oversight activities of OHRP from recurring.

In a separate letter to the HHS inspector general, DeLauro asked the inspector general "to assess whether OHRP needs to be relocated, and if so where, in order to prevent the type of NIH and other HHS interference that seem to have occurred in this episode."

View Public Citizen's letter.

View DeLauro's letter.

Read further email correspondence between NIH, the HHS secretary's office and OHRP (PDF).

###

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 12:18 PM
To: Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation
Attachments: Carlo SUPPORT 2010-05-16.pdf

She means the one attached, Renate.

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 12:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

I'm not sure which Carlo study it is from this list:
https://www.google.com/search?q=NEJM+Carlo+2010&oq=NEJM+Carlo+2010&aqs=chrome..69i57.6035j0j4&sourceid=chrome&es_sm=93&ie=UTF-8 Would you specify? (b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:46 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

The source of the numbers are as follows:

Percent Mortality:	
Higher saturation group	16.2 percent (NEJM 2010 Carlo publication)
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I have to go back through to find the source of the 23.1 %.
Hope this helps

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Sorry, Rose. One more question. We had these numbers when the issue just broke, but they don't synch with what's in the Rich study. Should we (b)(5)

Percent Mortality:

Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:32 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Enrolled infants had lower rates of complications and mortality. When adjusted for factors that impact morbidity and mortality (e.g. antenatal steroids, etc), infants in the trial had not greater risk than the unenrolled eligible infants.

Rosemary D. Higgins, MD
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From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Just so I understand, in what way were they different? Are they saying the outcome numbers aren't really a fair representation?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:26 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

The papers are in the public domain. The Consent paper points out that the enrolled sample is somewhat different that those who were eligible but not enrolled.

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From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:24 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Thanks, Rose. Is there (b)(5)
(b)(5) I'm not sure I understand what the study is saying in terms of consent bias.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:09 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation

Here is the SUPPORT consent paper – see table 3 which compares the enrolled versus non-enrolled. The second paper (STOLL) is a paper looking at in-hospital outcomes for extremely premature infants. If you go to table 3, the mortality is broken out by week of gestation. The following mortality rates for infants 24-27 weeks are as follows:
24 weeks – 45%
25 weeks -28%
26 weeks – 16%
27 weeks – 12%

Hope this helps

Rose

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From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: FW: Misconduct of HHS demands investigation
Importance: High

Hi Rose and Bob:

HHS is working with Paul Basken of the Chronicle of Higher Education. Paul mentioned the deaths and I told Tait we should point out the stats on survival compared those not on the study. I have the QA below that we drafted but is there a paper or data point that I can link to from it or a reference I can cite?

How did mortality rates from the study compare to those of infants not in the study?

Infants in the study had a lower mortality rate than those not enrolled. Even after adjusting for characteristics of the non-enrolled infants, such as poorer health, infants in the study were still at no greater risk of death and other conditions associated with extreme prematurity.

Percent Mortality:

Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

Thanks,
Renate

From: Sye, Tait (OS/ASPA)
Sent: Friday, May 23, 2014 10:49 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Renate-

Can you send me a link/citation for the line that the babies on the study did better than the babies off the study?

Thanks.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Thursday, May 22, 2014 9:20 PM
To: Sye, Tait (OS/ASPA)
Subject: Fw: Misconduct of HHS demands investigation

Actually, the babies on the study did better than the babies off the study. I think we need to point that out.

From: Paul Basken <paul.basken@chronicle.com>
Sent: Thursday, May 22, 2014 6:52 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

... and to be clear, the "some babies died" is badly phrased here, as there's apparently no hard data on that, just the expectation that many were exposed to a higher risk of death... plus the 11 families suing over various injuries...

From: Paul Basken
Sent: Thursday, May 22, 2014 6:35 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Tait, Renate... I have to say that after looking at this for another couple days, I'm getting a better sense of what the underlying complaint is here... I couldn't give this full attention two days ago while finishing off a few other things, but now that I see the emails describe how thoroughly Dr. Collins and others at NIH were apparently guiding OHRP on its response to the Support trial, I'd like to check back to be sure that's really all you have to say about it...

I do realize there's a legitimate argument out there about whether patients really need to be notified in cases where they are essentially being randomized into arms of a trial in which other real-life factors probably would have randomized them anyhow. But the important distinction here is that the treatment in this case was not just a replica of what might have randomly happened to these babies, but an artificially altered version of those real-life conditions designed to keep each baby getting a set dose of oxygen regardless of how it was responding to that level. And some of the babies died as a result of that.

And it's not just the universities that were responsible for setting up that protocol, but NIH officials who signed off on it. And so for top NIH officials -- including Dr. Collins -- to come to OHRP after the fact, and try to guide OHRP in how to respond, and to in fact pressure OHRP to change how it responded, seems to be a pretty serious charge, and one that deserves a bit more than a one-line response saying that NIH regularly works with OHRP to ensure patient protections.

Of course if that's still all you want to say about it, then we'll have no choice but to report it that way. But it does seem to leave some big questions hanging out there. It seems like the kind of thing Dr. Collins would want to answer directly, even if he is out of the country.

Thanks, Paul (202-466-1044)

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:30 PM
To: Paul Basken; Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

Not to sound like a broken record, but we are going to stick by our statement:

OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:29 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Thanks, Renate.. That's helpful... Would that then have made it somehow improper, or at least undesirable, for NIH officials to be coordinating with OHRP on a policy response?
Thanks, Paul

From: Myles, Renate (NIH/OD) [E] [mylesr@od.nih.gov]
Sent: Tuesday, May 20, 2014 4:26 PM
To: Paul Basken; Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Hi Paul:

One point of clarification: OHRP is part of HHS (not outside HHS). OHRP used to be under NIH and then was moved under HHS.

Thanks,
Renate

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:24 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

OK thanks, will see what they say on that question... I realize some folks are unhappy with OHRP, and I'm actually working on a piece about that, but just wondering if this particular complaint is a legally valid line of attack... Rep DeLauro in her statement said that this kind of thing is the reason why they moved OHRP out of HHS, so perhaps Congress did intend OHRP to have some freedom of movement, and this kind of coordination by HHS and NIH may seem contrary to the spirit somehow, but I'm not clear that it's legally prohibited... Thanks, Paul

---

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:13 PM
To: Paul Basken; Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

[OFF THE RECORD- good question]

Here is OHRP's compliance oversight procedures, including its legal authority:

http://www.hhs.gov/ohrp/compliance/evaluation/index.html

and, as I note in our statement:

OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:09 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Thanks... I'm trying to figure out what exactly is the alleged violation. Is it stated in law somewhere that OHRP is supposed to be fully independent of HHS and/or NIH?
Thanks, Paul

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:05 PM
To: Myles, Renate (NIH/OD) [E]; Paul Basken
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

Here is HHS statement regarding Public Citizen letter. Please attribute to HHS spokesperson:

"The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare and well-being of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

"In the wake of extensive scientific and public discussions since OHRP's March 2013 determination letter related to the SUPPORT study, OHRP became aware of different understandings of what is meant by "standard of care" and risks that must be disclosed to potential subjects in the research context.

"To further understanding of related issues, HHS solicited public comments and held a public meeting in August 2013 to gather feedback on this important issue. OHRP has been reviewing these comments, along with input from others parts of HHS, and is currently drafting guidance on the issue."

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Tuesday, May 20, 2014 3:36 PM
To: 'Paul Basken'
Cc: Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Hi Paul:

Thanks for checking. The response to the original PC Letter is coming from HHS OASPA (copying Tait Sye).

Best,
Renate

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 3:34 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Renate... Anything on this? Thanks, Paul (202-466-1044)

From: Karilyn Gower [mailto:kgower@citizen.org]
Sent: Tuesday, May 20, 2014 10:11 AM
To: Dianne Donovan
Subject: Misconduct of HHS demands investigation

Hi Dianne. I thought you or someone else at the Chronicle of Higher Education might be interested in the release below. Please let me know if you have any questions. Thanks!
-Kari

Karilyn Gower | Press Officer
TEL: 202.588.7779 | **CELL:** (b)(6)
1600 20th St NW, Washington, DC 20009
http://www.citizen.org

PUBLICCITIZEN

Investigation Needed: Senior HHS Officials Facilitated NIH Interference With Investigation of the SUPPORT Study, Despite Direct Conflict of Interest

Deputy Secretary, Other High-Ranking HHS Officials Allowed NIH Director, Deputy Director to Review and Edit Office of Human Research Protections' Compliance Oversight Letter, Emails Show

May 20, 2014

Contact: Angela Bradbery (202) 588-7741
Karilyn Gower (202) 588-7779

WASHINGTON, D.C. – Public Citizen, joined by nine prominent scholars, today called for an immediate investigation by the U.S. Department of Health and Human Services (HHS) Office of Inspector General into the conduct of senior HHS officials, who, according to an email trail, permitted top National Institutes of Health

(NIH) officials to edit drafts of a letter documenting findings of what should have been an independent inquiry into serious ethical lapses in a major NIH trial.

According to documents Public Citizen recently obtained under the Freedom of Information Act (FOIA), HHS officials in the immediate Office of the Secretary and Office of the Assistant Secretary for Health (OASH) knowingly allowed the director of NIH and other senior NIH officials to interfere with the independence of the Office for Human Research Protections' (OHRP's) ongoing compliance oversight investigation of the controversial SUPPORT study, Public Citizen said in a letter to the HHS inspector general.

In a separate letter to the HHS inspector general, U.S. Rep. Rosa DeLauro (D-Conn.) today echoed the call for an investigation.

Though heavily redacted, the documents Public Citizen obtained reveal that named NIH officials were, inappropriately, given multiple opportunities to review and edit drafts of a pending OHRP compliance oversight determination letter regarding the SUPPORT study, as well as apparently allowing NIH to influence the timing of the release of the letter, which occurred on June 4, 2013. This letter put on hold all compliance enforcement actions taken by OHRP that had been outlined in an earlier letter issued on Feb. 8, 2013, to the University of Alabama at Birmingham. This hold is still in effect.

The SUPPORT study was funded by the NIH at a cost of more $20 million, and NIH scientists were co-investigators on the study. The experimental study exposed 1,316 premature infants to increased risk of blindness, brain injury and death without informing parents of the risks to their babies or the true nature and purpose of the research.

"It is deeply disturbing and unacceptable that the NIH, which was involved in the development, approval, conduct and oversight of the SUPPORT study, was allowed to review and edit OHRP's compliance oversight letter," said Dr. Michael Carome, director of Public Citizen's Health Research Group. "The most troubling part is that numerous high-ranking officials facilitated this interference by senior NIH officials, despite the fact that NIH had obvious actual, direct conflicts of interest in the research under investigation."

"The emails obtained by Public Citizen strongly suggest that the NIH – apparently desperate to undo OHRP's earlier compliance oversight determinations – launched an aggressive campaign to undermine OHRP's regulatory authority and regrettably found several willing partners for this campaign at the highest levels of HHS," said renowned bioethicist Ruth Macklin, a professor at Albert Einstein College of Medicine and director of a training program in research ethics sponsored by the NIH Fogarty International Center.

Said DeLauro, "The very reason OHRP was administratively moved out of NIH was because of the long-recognized conflicts of interest that exist between NIH and OHRP. That move was intended to prevent exactly the type of NIH interference that has now apparently occurred. It appears that actions displayed by senior HHS leaders have compromised the integrity and independence of OHRP's ongoing investigation into the SUPPORT study."

The series of email communications between NIH, the HHS secretary's office and OHRP paints a truly disturbing picture, Carome said. A sampling of some of the most revealing emails includes:

- **Email on May 3, 2013, 4:54 PM**

From: Jerry Menikoff (Director, OHRP):
Addressed to: Kathy Hudson (Deputy Director for Science, Outreach, and Policy, NIH); Howard Koh (Assistant Secretary for Health, HHS); Wanda Jones (Principal Deputy Assistant Secretary for Health, HHS); and Kirby Bumpus (OASH, HHS)

Subject: RE: Support study -
Message:

Kathy,

For your weekend enjoyment, **here is the revised version of the SUPPORT letter…** [Emphasis added]

• Email on May 12, 2013, 02:10 PM

From: Kathy Hudson (Deputy Director for Science, Outreach, and Policy, NIH)
Addressed to: Howard Koh (Assistant Secretary for Health, HHS) and Jerry Menikoff (Director, OHRP)
Subject: Suggested correction to OHRP-UAB draft letter [Emphasis added]

An apparent attachment is completely redacted.

A June 2, 2013, email, from Francis Collins, director of NIH, sent to many senior leaders of HHS – including the deputy secretary and chief of staff – thanked them "for the opportunity to weigh in on OHRP's letter to UAB [University of Alabama Birmingham] and the Federal Register Notice related to SUPPORT" and stated that the NIH is "grateful for the opportunity to work with such a dedicated team within HHS."

"This interference has seriously compromised the integrity and independence of OHRP's compliance oversight investigation into the SUPPORT study, fundamentally undermining OHRP's regulatory authority and almost certainly doing long-lasting and possibly irreparable harm to the status of this critically important regulatory agency, whose primary mission is to protect human subjects," said Carome.

Public Citizen and the nine prominent scholars in bioethics, law and history seek to ensure that all HHS officials who played a role in the corrupt conduct revealed by the HHS emails are held accountable and that appropriate corrective actions are taken to prevent such improper and unethical interference by NIH in the compliance oversight activities of OHRP from recurring.

In a separate letter to the HHS inspector general, DeLauro asked the inspector general "to assess whether OHRP needs to be relocated, and if so where, in order to prevent the type of NIH and other HHS interference that seem to have occurred in this episode."

View Public Citizen's letter.

View DeLauro's letter.

Read further email correspondence between NIH, the HHS secretary's office and OHRP (PDF).

###

ORIGINAL ARTICLE

Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

ABSTRACT

BACKGROUND

Previous studies have suggested that the incidence of retinopathy is lower in preterm infants with exposure to reduced levels of oxygenation than in those exposed to higher levels of oxygenation. However, it is unclear what range of oxygen saturation is appropriate to minimize retinopathy without increasing adverse outcomes.

METHODS

We performed a randomized trial with a 2-by-2 factorial design to compare target ranges of oxygen saturation of 85 to 89% or 91 to 95% among 1316 infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation. The primary outcome was a composite of severe retinopathy of prematurity (defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab), death before discharge from the hospital, or both. All infants were also randomly assigned to continuous positive airway pressure or intubation and surfactant.

RESULTS

The rates of severe retinopathy or death did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3% and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21). Death before discharge occurred more frequently in the lower-oxygen-saturation group (in 19.9% of infants vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; P=0.04), whereas severe retinopathy among survivors occurred less often in this group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; P<0.001). There were no significant differences in the rates of other adverse events.

CONCLUSIONS

A lower target range of oxygenation (85 to 89%), as compared with a higher range (91 to 95%), did not significantly decrease the composite outcome of severe retinopathy or death, but it resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern, since a lower target range of oxygen saturation is increasingly being advocated to prevent retinopathy of prematurity. (ClinicalTrials.gov number, NCT00233324.)

*The authors are listed in the Appendix. The affiliations of the authors and other investigators in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) Study Group of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development are listed in the Appendix. Address reprint requests to Dr. Waldemar A. Carlo at the University of Alabama at Birmingham, 176F Suite 9380, 619 S. 19th St., Birmingham, AL 35294-7335, or at wcarlo@peds.uab.edu.

This article (10.1056/NEJMoa0911781) was published on May 16, 2010, at NEJM.org.

N Engl J Med 2010.

Retinopathy of prematurity is an important cause of blindness and other visual disabilities in preterm infants. The incidence of retinopathy of prematurity was increased with exposure to unrestricted oxygen supplementation in preterm infants in randomized, controlled trials performed in the 1950s.[1] In the 1960s, this increase resulted in the practice of restricting the fraction of inspired oxygen (FiO_2) to no more than 0.50, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that levels of oxygen saturation previously thought to be at the upper end of the normal range may increase the risk of retinopathy of prematurity as compared with levels at the lower end of the normal range.[3-5] Oxygen toxicity may also increase the risk of death,[6,7] bronchopulmonary dysplasia,[8-10] periventricular leukomalacia,[11] cerebral palsy,[12] and other conditions. Although a multicenter observational study did not show a significant association between higher values for the partial pressure of arterial oxygen and retinopathy, a single-center cohort study involving transcutaneous oxygen monitoring provided support for an association between an increased risk of retinopathy[13] and exposure to arterial oxygen levels of 80 mm Hg or more.[14]

Pulse oximetry allows clinicians to continuously monitor levels of oxygen saturation and to target levels in a defined range. Associations between lower target levels of oxygen saturation and a lower incidence of retinopathy have been reported.[1-5] In a survey of 144 neonatal intensive care units (NICUs), the rate of retinal ablation surgery among very-low-birth-weight infants was increased among infants cared for in NICUs that used higher maximum target levels of oxygen saturation, as compared with infants in NICUs that used lower target levels. The rate of retinal ablation surgery was 3.3% in NICUs using target levels of 92% or higher and 1.4% in NICUs using target levels of less than 92%; the rate was 5.6% in NICUs using target levels of 98% or higher and 3.1% in NICUs using target levels of less than 98%.[3] In a retrospective study comparing outcomes at five NICUs, the incidence of severe retinopathy requiring ablation therapy was 27% in NICUs where the target saturation level was 88 to 98% and only 6% in NICUs where the target level was 70 to 90%.[3] Rates of death and cerebral palsy did not differ significantly among these NICUs. In three studies with a before-and-after design, the implementation of a policy of target levels of oxygen saturation of approximately 83 to 95% was associated with a substantial reduction in the incidence of retinopathy, as compared with the period before implementation of the policy; however, the actual levels of oxygen saturation achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] Although data from these studies suggest that maintenance of oxygenation at ranges lower than those previously used may decrease the incidence of retinopathy of prematurity, the safety of low target levels of oxygen saturation remains a concern.

We conducted the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a controlled, multicenter trial with a 2-by-2 factorial design, to compare two target levels of oxygen saturation and two ventilation approaches (continuous positive airway pressure [CPAP] initiated in the delivery room with a protocol-driven strategy of limited ventilation vs. intratracheal administration of surfactant with a protocol-driven strategy of conventional ventilation). The oxygen-saturation component of the trial tested the hypothesis that a lower target range of oxygen saturation (85 to 89%), as compared with a higher target range (91 to 95%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity or death among infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation. The ventilation part of this factorial-design trial, which was used to control the ventilation approach and test other hypotheses, is reported elsewhere in this issue of the *Journal*.[17]

METHODS

STUDY DESIGN

The study was conducted as part of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The study was approved by the institutional review board at each participating site and by RTI International, which is the independent data coordinating center for the Neonatal Research Network. Data collected at the study sites were transmitted to RTI International, which stored, managed, and analyzed the data for this

10.1056/NEJMoa0911781 NEJM.ORG

study. Written informed consent was obtained from the parent or guardian of each child before delivery.

PATIENTS

Infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation were eligible for enrollment at birth. Infants born in other hospitals and those known to have major congenital anomalies were excluded.

ENROLLMENT AND TREATMENT

Infants were enrolled from February 2005 through February 2009. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Using sealed, opaque envelopes, we randomly assigned infants before birth to a target range of oxygen saturation of 85 to 89% (the lower-oxygen-saturation group) or 91 to 95% (the higher-oxygen-saturation group). Infants who were part of multiple births were randomly assigned to the same group.

Blinding was maintained with the use of electronically altered pulse oximeters (Masimo Radical Pulse Oximeter) that showed saturation levels of 88 to 92% for both targets of oxygen saturation, with a maximum variation of 3%. For example, a reading of 90% corresponded to actual levels of oxygen saturation of 87% in the group assigned to lower oxygen saturation (85 to 89%) and 93% in the group assigned to higher oxygen saturation (91 to 95%). A previous trial used a fixed 3% absolute oxygen-saturation variation throughout the entire range of saturation levels to keep caregivers unaware of study-group assignments and to separate levels of oxygen saturation in preterm infants,[18] but the algorithm used in the current trial differed, since the oxygen-saturation reading gradually changed and reverted to actual (nonskewed) values when it was less than 84% or higher than 96% in both treatment groups. Limits of 85% and 95% that would trigger an alarm in the delivery system were suggested, but they could be changed for individual patients.

Targeting of levels of oxygen saturation with altered pulse oximetry was initiated within the first 2 hours after birth and was continued until 36 weeks of postmenstrual age or until the infant was breathing ambient air and did not require ventilator support or CPAP for more than 72 hours, whichever occurred first. Infants who were weaned to room air but who subsequently received oxygen supplementation before 36 weeks of postmenstrual age were placed back on the assigned study pulse oximeter. The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age. Adjustments in supplemental oxygen to maintain the target level of oxygen saturation between 88 and 92% were performed by the clinical staff rather than the research staff.

Data on oxygen saturation were electronically sampled every 10 seconds and downloaded by the data center. Readings of levels of oxygen saturation that were pooled (i.e., not separated according to treatment group) were provided quarterly to each center for feedback on compliance. Actual data on oxygen saturation were not provided to the clinicians or researchers but are used exclusively in this article. For the ventilation part of this trial with a 2-by-2 factorial design, participants were randomly assigned to CPAP with a protocol-driven limited ventilation strategy or to prophylactic early administration of surfactant with a protocol-driven conventional ventilation strategy.[17]

ASSESSMENTS

Research nurses recorded all data using standardized definitions included in the trial's manual of operations. Data collection, excluding examinations to detect retinopathy of prematurity, was completed at discharge. All surviving infants were followed by ophthalmologists trained in the diagnosis of retinopathy of prematurity. Examinations began by 33 weeks of postmenstrual age and continued until the study outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group[19,20]) was diagnosed if any of the following findings were present: in zone 1, stage 3 retinopathy of prematurity, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of retinopathy of prematurity; in zone 2, plus disease with stage 2 retinopathy of prematurity or plus disease with stage 3 retinopathy of

prematurity. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. The primary outcome was death before discharge or severe retinopathy as defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy. The original study protocol specified a primary outcome of death before 36 weeks of postmenstrual age, but this was changed to death before discharge before any data analyses were performed. All other outcomes reported were prespecified, including assessment of the need for oxygen at 36 weeks of postmenstrual age[21] and safety outcomes.

Figure 1 (facing page). Screening, Randomization, and Primary Outcome.

The numbers shown exclude infants of women who were screened during pregnancy but whose babies were not subsequently born at a study center between 24 weeks 0 days and 27 weeks 6 days of gestation. The outcome of severe retinopathy of prematurity (ROP) could not be determined in some infants because of loss to follow-up. CPAP denotes continuous positive airway pressure.

STATISTICAL ANALYSIS

The analysis for the oxygen-saturation part of this factorial trial compared the percentage of infants in each treatment group in whom the primary outcome of severe retinopathy or death occurred. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. We performed a post hoc survival analysis with the use of a Cox proportional-hazards model to compare mortality in the two oxygen-saturation groups, assuming that there were no subsequent deaths among the infants who were discharged. In the analysis of all outcomes, the results were adjusted, as prespecified, for stratification according to study center and gestational age, as well as for familial clustering due to random assignment of infants who were part of multiple births to the same treatment group. To compare the actual oxygen-saturation values in the two treatment groups, the median value during oxygen supplementation was determined for each infant. Those values were plotted according to treatment group, and the medians of the resulting distributions were compared with the use of a rank-sum test.

An absolute between-group difference of 10 percentage points in the rate of the composite primary outcome was considered clinically important. The sample-size calculations were based on the rate of death or threshold retinopathy of 47% in the Neonatal Research Network for the year 2000. We increased the sample size by a factor of 1.12 to allow for infants who were part of multiple births to be randomly assigned to the same treatment (since this introduced a clustering effect into the design), and we increased the sample size by an additional 17% to adjust for attrition after hospital discharge. We increased the sample size further to minimize type I error with the use of a conservative 2% level of significance. The result was a target sample of 1310 infants. The study was not powered to detect an interaction effect between the two factorial parts of the study.

Analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the 46 planned analyses of secondary outcomes according to treatment group, we would expect no more than three tests to have P values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for predefined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have P values of less than 0.05 on the basis of chance alone.

An independent data and safety monitoring committee appointed by the director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the data and safety monitoring committee, at the request of the investigators, evaluated the data on oxygen saturation to evaluate compliance with the protocol. The Lan–DeMets spend-

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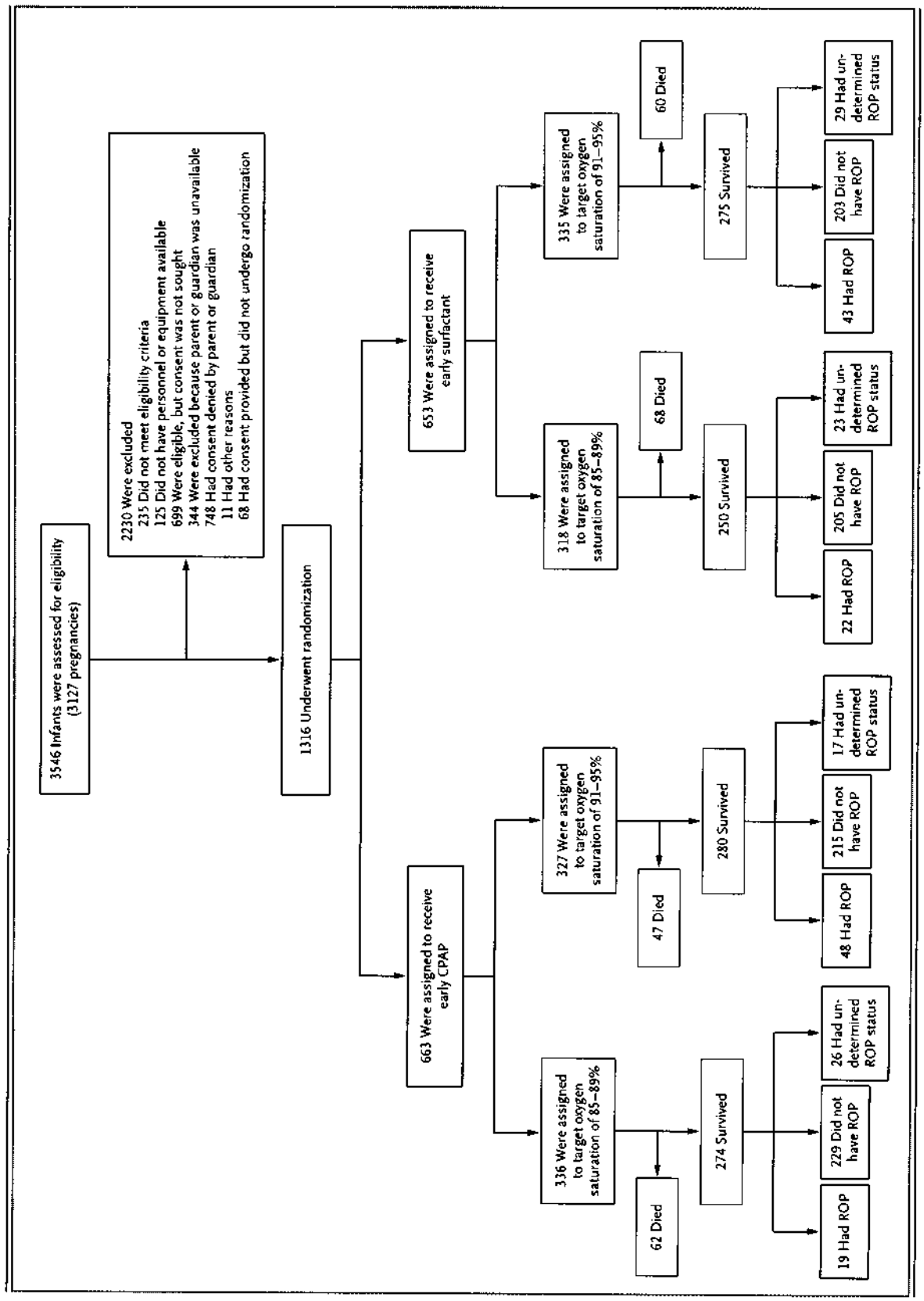
3546 Infants were assessed for eligibility (3127 pregnancies)
2230 Were excluded
235 Did not meet eligibility criteria
125 Did not have personnel or equipment available
699 Were eligible, but consent was not sought
344 Were excluded because parent or guardian was unavailable
748 Had consent denied by parent or guardian
11 Had other reasons
68 Had consent provided but did not undergo randomization
1316 Underwent randomization
663 Were assigned to receive early CPAP
336 Were assigned to target oxygen saturation of 85–89%
62 Died
274 Survived
19 Had ROP
229 Did not have ROP
26 Had undetermined ROP status
327 Were assigned to target oxygen saturation of 91–95%
47 Died
280 Survived
48 Had ROP
215 Did not have ROP
17 Had undetermined ROP status
653 Were assigned to receive early surfactant
318 Were assigned to target oxygen saturation of 85–89%
68 Died
250 Survived
22 Had ROP
205 Did not have ROP
23 Had undetermined ROP status
335 Were assigned to target oxygen saturation of 91–95%
60 Died
275 Survived
43 Had ROP
203 Did not have ROP
29 Had undetermined ROP status

Table 1. Baseline Characteristics of the Patients.

Characteristic	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)
Birth weight — g	836±193	825±193
Gestational age — wk	26±1	26±1
Male sex — no./total no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group — no./total no. (%)†		
Non-Hispanic white	242/654 (37.0)	279/662 (42.1)
Non-Hispanic black	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other or unknown	23/654 (3.5)	24/662 (3.6)
Maternal use of antenatal corticosteroids — no./total no. (%)		
Any	633/654 (96.8)	632/661 (95.6)
Full course	477/651 (73.3)	462/658 (70.2)
Apgar score <3 at 5 min — no./total no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant treatment — no./total no. (%)	531/653 (81.3)	558/660 (84.5)
Multiple birth — no./total no. (%)	161/654 (24.6)	176/662 (26.6)

* Plus–minus values are means ±SD. P>0.05 for all comparisons.
† Race or ethnic group was reported by the mother or guardian of each child.

ing functions with Pocock and O'Brien–Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. In the final analysis, the nominal level of significance was 0.05. The monitored safety outcomes included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

CHARACTERISTICS OF THE STUDY SAMPLE

We enrolled 1316 infants in the study (Fig. 1). When 247 infants had been enrolled, enrollment was temporarily suspended on the basis of the recommendation of the data and safety monitoring committee and the decision of the director of the National Institute of Child Health and Human Development because of concern that readings of levels of oxygen saturation often exceeded the target levels. Separation of the oximetry data according to whether patients were breathing ambient air or receiving oxygen supplementation addressed this concern, because infants who did not require supplemental oxygen accounted for a large proportion of the high saturation levels. Resumption of enrollment was approved. The baseline characteristics of the two treatment groups were similar (Table 1).

PRIMARY OUTCOME

The rate of the composite primary outcome, severe retinopathy or death before discharge, did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3 and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21) (Table 2). Although the trial was not powered to detect an interaction between the level of oxygen saturation and the ventilation intervention, we prospectively planned to evaluate this interaction, and no significant interaction was found (P=0.57). Death before discharge occurred in 130 of 654 infants in the lower-oxygen-saturation group (19.9%) as compared with 107 of 662 infants in the higher-oxygen-saturation group (16.2%) (relative risk with lower oxygen saturation, 1.27; 95% CI, 1.01 to 1.60; P=0.04; number needed to harm, 27). The distribution of the major causes of death did not differ significantly between the two groups (see Table 1 in the Supplementary Appendix, available with the

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Table 2. Major Outcomes.*

Outcome	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)	Adjusted Relative Risk (95% CI)
	no./total no. (%)		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76–1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37–0.73)
Death			
Before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01–1.60)
By 36 wk postmenstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99–1.63)
BPD, defined by use of supplemental oxygen, at 36 wk	203/540 (37.6)	265/568 (46.7)	0.82 (0.72–0.93)
BPD, defined by use of supplemental oxygen, or death by 36 wk	317/654 (48.5)	359/662 (54.2)	0.91 (0.83–1.01)
BPD, physiological definition, at 36 wk†	205/540 (38.0)	237/568 (41.7)	0.92 (0.81–1.05)
BPD, physiological definition, or death by 36 wk†	319/654 (48.8)	331/662 (50.0)	0.99 (0.90–1.10)
Intraventricular hemorrhage, grade 3 or 4‡	83/630 (13.2)	81/640 (12.7)	1.06 (0.80–1.40)
Intraventricular hemorrhage, grade 3 or 4, or death‡	179/653 (27.4)	156/661 (23.6)	1.18 (0.99–1.42)
Periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49–1.42)
Periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96–1.45)
Necrotizing enterocolitis, stage ≥2§	76/641 (11.9)	70/649 (10.8)	1.11 (0.82–1.51)
Necrotizing enterocolitis, stage ≥2, or death§	176/654 (26.9)	155/662 (23.4)	1.18 (0.98–1.43)
Pneumothorax	47/654 (7.2)	43/662 (6.5)	1.12 (0.74–1.68)
Postnatal corticosteroids for BPD	61/636 (9.6)	69/644 (10.7)	0.91 (0.67–1.24)
Death			
By 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72–1.72)
By 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84–1.70)
Late-onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89–1.18)
Late-onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94–1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86–1.07)
Treatment for patent ductus arteriosus			
Medical	219/634 (34.5)	233/645 (36.1)	0.95 (0.82–1.09)
Surgical	73/641 (11.4)	68/648 (10.5)	1.09 (0.80–1.48)
Any air leaks in first 14 days	51/654 (7.8)	42/662 (6.3)	1.23 (0.83–1.83)

* Values were adjusted for stratification factors (study center and gestational-age group) as well as for familial clustering. BPD denotes bronchopulmonary dysplasia.

† The physiological definition of BPD includes, as a criterion, the receipt of more than 30% oxygen or the need for positive pressure support at 36 weeks or, in the case of infants requiring less than 30% oxygen, the need for any oxygen at 36 weeks after an attempt at oxygen withdrawal.

‡ There are four grades of intraventricular hemorrhage; higher grades indicate more severe bleeding.

§ There are three stages of necrotizing enterocolitis; higher stages indicate more severe necrotizing enterocolitis.

full text of this article at NEJM.org). Similar results were observed for both gestational-age strata. Survival analysis with the use of the unadjusted Kaplan–Meier method (Fig. 2) and a Cox proportional-hazards model produced similar results (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07). The rate of severe retinopathy among survivors who were discharged or transferred to another facility or who reached the age of 1 year was lower in the lower-oxygen-saturation group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; P<0.001; number needed to treat, 11). Although

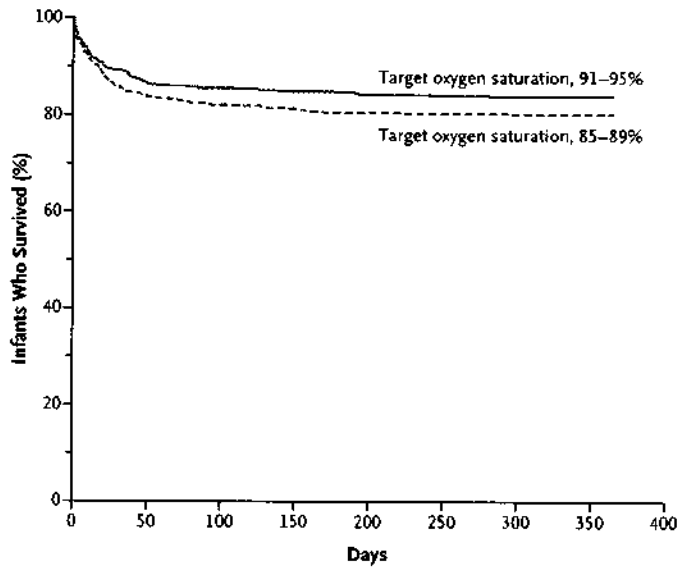

Figure 2. Kaplan–Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life.

Cox proportional-hazards analysis indicated that there was an increased hazard of death in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07). The analysis assumed that infants who were discharged or transferred from the hospital survived to 1 year of age.

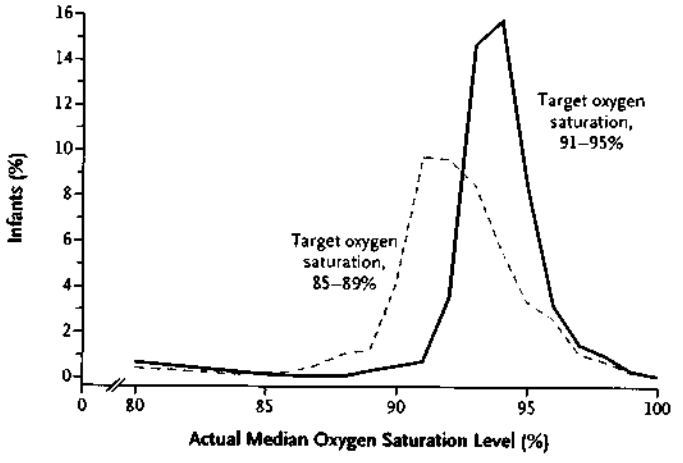

Figure 3. Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups.

The medians of the distributions were significantly different on the basis of a rank-sum test (P<0.001). The 80% level of oxygen saturation shown includes all values at or below 80%.

use of bevacizumab was among the criteria for this outcome, only three infants received bevacizumab, and these infants also had threshold retinopathy or surgical intervention for retinopathy. Three ophthalmologists adjudicated results for the patients who did not meet the criteria for retinopathy, and the results were materially unchanged (Table 2 in the Supplementary Appendix).

SECONDARY OUTCOMES

The rate of oxygen use at 36 weeks was reduced in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group (P=0.002), but the rates of bronchopulmonary dysplasia among survivors, as determined by the physiological test of oxygen saturation at 36 weeks, and the composite outcome of bronchopulmonary dysplasia or death by 36 weeks did not differ significantly between the treatment groups. Other prespecified major outcomes also did not differ significantly between the two groups (Table 2).

The median level of oxygen saturation in infants who were receiving oxygen supplementation in the two treatment groups differed substantially but, as expected, there was considerable overlap (Fig. 3). The actual median levels of oxygen saturation were slightly higher than targeted levels in both treatment groups. The duration of oxygen supplementation was shorter in the lower-oxygen-saturation group, but the duration of mechanical ventilation, CPAP, and nasal synchronized intermittent mandatory ventilation did not differ significantly (Table 3 in the Supplementary Appendix). Other measures of resource use also did not differ significantly between the two groups.

DISCUSSION

In this multicenter, randomized trial, we found no significant difference in the primary outcome — severe retinopathy or death — between infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) and those assigned to a higher target range (91 to 95%). Assessment of the individual components of the primary outcome showed that the lower target range of oxygen saturation increased the risk of in-hospital death, whereas it reduced the risk of severe retinopathy among survivors. These results were observed even though there was substantial overlap of actual levels of oxygen saturation between the two treatment groups. Previous trials of targeting of levels of oxygen saturation have shown similar difficulties in maintaining levels of oxygen saturation within a narrow target range.[18,22] Longer follow-up will be required to determine

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the effects of lower target ranges of oxygen saturation on functional visual and neurodevelopmental outcomes.

Despite the increase in mortality when restrictive oxygen supplementation was used in the 1950s and 1960s and the limited data from observational studies,[3-5,15,16] it is becoming common practice to use lower target ranges of oxygen saturation with the goal of reducing the risk of retinopathy of prematurity.[23] The results of this large randomized trial to test the effect of lower versus higher target ranges of oxygen saturation, in conjunction with the results of previous studies, add to the concern that oxygen restriction may increase the rate of death among preterm infants. The combined risk difference observed in the trials from the 1950s was an absolute increase in in-hospital mortality of 4.9 percentage points in the oxygen-restricted group,[1] which is close to the absolute increase of 3.7 percentage points in the rate of death before discharge in the lower-oxygen-saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants at least 2 weeks after birth[18] or after moderately severe retinopathy developed[22] did not show an increased risk of death or a significantly reduced risk of retinopathy in the lower-oxygen-saturation groups. However, the lower target ranges of oxygen saturation in these trials — 91 to 94% in one trial and 89 to 94% in the other — were closer to the target range in our higher-oxygen-saturation group. The increase in mortality in our trial may be related to the lower target ranges of levels of oxygen saturation, the use of oxygen restriction started soon after birth, or both. A meta-analysis of early restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a reduction in severe retinopathy (relative risk, 0.19; 95% CI, 0.07 to 0.50) with a nonsignificant trend toward increased mortality.[24] These trials were performed by limiting the FIO_2 concentration usually to less than 0.50, at a time before the continuous monitoring of arterial oxygen saturation was possible. To our knowledge, no other randomized, controlled trials of different target ranges of oxygen saturation in supplementation initiated soon after birth have been performed since the availability of continuous transcutaneous monitoring of oxygen saturation. Like the meta-analysis[24] and most nonrandomized studies,[3-5,15,16] our trial confirmed that lower target ranges of oxygenation result in a large reduction in the incidence of severe retinopathy among survivors. However, our data suggest that there is one additional death for approximately every two cases of severe retinopathy that are prevented. Several ongoing trials across the world address the same intervention tested in the current trial.[25]

In summary, a target range of oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, did not affect the combined outcome of severe retinopathy or death, but it increased mortality while substantially decreasing severe retinopathy among survivors. At the present time, caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality.

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APPENDIX

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Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 23, 2014 11:09 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Misconduct of HHS demands investigation
Attachments: RIch SUPPORT consent 2012.pdf; Stoll, GDB 2010.pdf

Here is the SUPPORT consent paper – see table 3 which compares the enrolled versus non-enrolled. The second paper (STOLL) is a paper looking at in-hospital outcomes for extremely premature infants. If you go to table 3, the mortality is broken out by week of gestation. The following mortality rates for infants 24-27 weeks are as follows:
24 weeks – 45%
25 weeks -28%
26 weeks – 16%
27 weeks – 12%

Hope this helps

Rose

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From: Myles, Renate (NIH/OD) [E]
Sent: Friday, May 23, 2014 11:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: FW: Misconduct of HHS demands investigation
Importance: High

Hi Rose and Bob:

HHS is working with Paul Basken of the Chronicle of Higher Education. Paul mentioned the deaths and I told Tait we should point out the stats on survival compared those not on the study. I have the QA below that we drafted but is there a paper or data point that I can link to from it or a reference I can cite?

How did mortality rates from the study compare to those of infants not in the study?

Infants in the study had a lower mortality rate than those not enrolled. Even after adjusting for characteristics of the non-enrolled infants, such as poorer health, infants in the study were still at no greater risk of death and other conditions associated with extreme prematurity.

Percent Mortality:	
Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

Thanks,
Renate

From: Sye, Tait (OS/ASPA)
Sent: Friday, May 23, 2014 10:49 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Renate-

Can you send me a link/citation for the line that the babies on the study did better than the babies off the study?

Thanks.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Thursday, May 22, 2014 9:20 PM
To: Sye, Tait (OS/ASPA)
Subject: Fw: Misconduct of HHS demands investigation

Actually, the babies on the study did better than the babies off the study. I think we need to point that out.

From: Paul Basken <paul.basken@chronicle.com>
Sent: Thursday, May 22, 2014 6:52 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

... and to be clear, the "some babies died" is badly phrased here, as there's apparently no hard data on that, just the expectation that many were exposed to a higher risk of death... plus the 11 families suing over various injuries...

From: Paul Basken
Sent: Thursday, May 22, 2014 6:35 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Tait, Renate... I have to say that after looking at this for another couple days, I'm getting a better sense of what the underlying complaint is here... I couldn't give this full attention two days ago while finishing off a few other things, but now that I see the emails describe how thoroughly Dr. Collins and others at NIH were apparently guiding OHRP on its response to the Support trial, I'd like to check back to be sure that's really all you have to say about it...

I do realize there's a legitimate argument out there about whether patients really need to be notified in cases where they are essentially being randomized into arms of a trial in which other real-life factors probably would have randomized them anyhow. But the important distinction here is that the treatment in this case was not just a replica of what might have randomly happened to these babies, but an artificially altered version of those real-life conditions designed to keep each baby getting a set dose of oxygen regardless of how it was responding to that level. And some of the babies died as a result of that.

And it's not just the universities that were responsible for setting up that protocol, but NIH officials who signed off on it. And so for top NIH officials -- including Dr. Collins -- to come to OHRP after the fact, and try to guide OHRP in how to respond, and to in fact pressure OHRP to change how it responded, seems to be a pretty serious charge, and one that deserves a bit more than a one-line response saying that NIH regularly works with OHRP to ensure patient protections.

Of course if that's still all you want to say about it, then we'll have no choice but to report it that way. But it does seem to leave some big questions hanging out there. It seems like the kind of thing Dr. Collins would want to answer directly, even if he is out of the country.

Thanks, Paul (202-466-1044)

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:30 PM
To: Paul Basken; Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

Not to sound like a broken record, but we are going to stick by our statement:

OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:29 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Thanks, Renate.. That's helpful... Would that then have made it somehow improper, or at least undesirable, for NIH officials to be coordinating with OHRP on a policy response?

Thanks, Paul

From: Myles, Renate (NIH/OD) [E] [mylesr@od.nih.gov]
Sent: Tuesday, May 20, 2014 4:26 PM
To: Paul Basken; Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Hi Paul:

One point of clarification: OHRP is part of HHS (not outside HHS). OHRP used to be under NIH and then was moved under HHS.

Thanks,
Renate

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:24 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

OK thanks, will see what they say on that question... I realize some folks are unhappy with OHRP, and I'm actually working on a piece about that, but just wondering if this particular complaint is a legally valid line of attack... Rep DeLauro in her statement said that this kind of thing is the reason why they moved OHRP out of HHS, so perhaps Congress did intend OHRP to have some freedom of movement, and this kind of coordination by HHS and NIH may seem contrary to the spirit somehow, but I'm not clear that it's legally prohibited... Thanks, Paul

---

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:13 PM
To: Paul Basken; Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

[OFF THE RECORD- good question]

Here is OHRP's compliance oversight procedures, including its legal authority:

http://www.hhs.gov/ohrp/compliance/evaluation/index.html

and, as I note in our statement:

OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 4:09 PM
To: Sye, Tait (OS/ASPA); Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Thanks... I'm trying to figure out what exactly is the alleged violation. Is it stated in law somewhere that OHRP is supposed to be fully independent of HHS and/or NIH?
Thanks, Paul

From: Sye, Tait (OS/ASPA) [Tait.Sye@hhs.gov]
Sent: Tuesday, May 20, 2014 4:05 PM
To: Myles, Renate (NIH/OD) [E]; Paul Basken
Subject: RE: Misconduct of HHS demands investigation

Hi Paul-

Here is HHS statement regarding Public Citizen letter. Please attribute to HHS spokesperson:

"The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare and well-being of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP regularly works with entities such as NIH, IRBs and others to ensure the protection of human subjects in research.

"In the wake of extensive scientific and public discussions since OHRP's March 2013 determination letter related to the SUPPORT study, OHRP became aware of different understandings of what is meant by "standard of care" and risks that must be disclosed to potential subjects in the research context.

"To further understanding of related issues, HHS solicited public comments and held a public meeting in August 2013 to gather feedback on this important issue. OHRP has been reviewing these comments, along with input from others parts of HHS, and is currently drafting guidance on the issue."

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Tuesday, May 20, 2014 3:36 PM
To: 'Paul Basken'
Cc: Sye, Tait (OS/ASPA)
Subject: RE: Misconduct of HHS demands investigation

Hi Paul:

Thanks for checking. The response to the original PC Letter is coming from HHS OASPA (copying Tait Sye).

Best,
Renate

From: Paul Basken [mailto:paul.basken@chronicle.com]
Sent: Tuesday, May 20, 2014 3:34 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Misconduct of HHS demands investigation

Renate... Anything on this? Thanks, Paul (202-466-1044)

From: Karilyn Gower [mailto:kgower@citizen.org]
Sent: Tuesday, May 20, 2014 10:11 AM
To: Dianne Donovan
Subject: Misconduct of HHS demands investigation

Hi Dianne. I thought you or someone else at the Chronicle of Higher Education might be interested in the release below. Please let me know if you have any questions. Thanks!
-Kari

Karilyn Gower | Press Officer
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PUBLICCITIZEN

Investigation Needed: Senior HHS Officials Facilitated NIH Interference With Investigation of the SUPPORT Study, Despite Direct Conflict of Interest

Deputy Secretary, Other High-Ranking HHS Officials Allowed NIH Director, Deputy Director to Review and Edit Office of Human Research Protections' Compliance Oversight Letter, Emails Show

May 20, 2014

Contact: Angela Bradbery (202) 588-7741
Karilyn Gower (202) 588-7779

WASHINGTON, D.C. – Public Citizen, joined by nine prominent scholars, today called for an immediate investigation by the U.S. Department of Health and Human Services (HHS) Office of Inspector General into the conduct of senior HHS officials, who, according to an email trail, permitted top National Institutes of Health (NIH) officials to edit drafts of a letter documenting findings of what should have been an independent inquiry into serious ethical lapses in a major NIH trial.

According to documents Public Citizen recently obtained under the Freedom of Information Act (FOIA), HHS officials in the immediate Office of the Secretary and Office of the Assistant Secretary for Health (OASH) knowingly allowed the director of NIH and other senior NIH officials to interfere with the independence of the Office for Human Research Protections' (OHRP's) ongoing compliance oversight investigation of the controversial SUPPORT study, Public Citizen said in a letter to the HHS inspector general.

In a separate letter to the HHS inspector general, U.S. Rep. Rosa DeLauro (D-Conn.) today echoed the call for an investigation.

Though heavily redacted, the documents Public Citizen obtained reveal that named NIH officials were, inappropriately, given multiple opportunities to review and edit drafts of a pending OHRP compliance oversight determination letter regarding the SUPPORT study, as well as apparently allowing NIH to influence the timing of the release of the letter, which occurred on June 4, 2013. This letter put on hold all compliance enforcement actions taken by OHRP that had been outlined in an earlier letter issued on Feb. 8, 2013, to the University of Alabama at Birmingham. This hold is still in effect.

The SUPPORT study was funded by the NIH at a cost of more $20 million, and NIH scientists were co-investigators on the study. The experimental study exposed 1,316 premature infants to increased risk of blindness, brain injury and death without informing parents of the risks to their babies or the true nature and purpose of the research.

"It is deeply disturbing and unacceptable that the NIH, which was involved in the development, approval, conduct and oversight of the SUPPORT study, was allowed to review and edit OHRP's compliance oversight letter," said Dr. Michael Carome, director of Public Citizen's Health Research Group. "The most troubling part is that numerous high-ranking officials facilitated this interference by senior NIH officials, despite the fact that NIH had obvious actual, direct conflicts of interest in the research under investigation."

"The emails obtained by Public Citizen strongly suggest that the NIH – apparently desperate to undo OHRP's earlier compliance oversight determinations – launched an aggressive campaign to undermine OHRP's regulatory authority and regrettably found several willing partners for this campaign at the highest levels of HHS," said renowned bioethicist Ruth Macklin, a professor at Albert Einstein College of Medicine and director of a training program in research ethics sponsored by the NIH Fogarty International Center.

Said DeLauro, "The very reason OHRP was administratively moved out of NIH was because of the long-recognized conflicts of interest that exist between NIH and OHRP. That move was intended to prevent exactly the type of NIH interference that has now apparently occurred. It appears that actions displayed by senior HHS leaders have compromised the integrity and independence of OHRP's ongoing investigation into the SUPPORT study."

The series of email communications between NIH, the HHS secretary's office and OHRP paints a truly disturbing picture, Carome said. A sampling of some of the most revealing emails includes:

• Email on May 3, 2013, 4:54 PM

From: Jerry Menikoff (Director, OHRP):
Addressed to: Kathy Hudson (Deputy Director for Science, Outreach, and Policy, NIH); Howard Koh (Assistant Secretary for Health, HHS); Wanda Jones (Principal Deputy Assistant Secretary for Health, HHS); and Kirby Bumpus (OASH, HHS)
Subject: RE: Support study -
Message:

Kathy,

For your weekend enjoyment, **here is the revised version of the SUPPORT letter...** [Emphasis added]

• Email on May 12, 2013, 02:10 PM

From: Kathy Hudson (Deputy Director for Science, Outreach, and Policy, NIH)
Addressed to: Howard Koh (Assistant Secretary for Health, HHS) and Jerry Menikoff (Director, OHRP)
Subject: Suggested correction to OHRP-UAB draft letter [Emphasis added]

An apparent attachment is completely redacted.

A June 2, 2013, email, from Francis Collins, director of NIH, sent to many senior leaders of HHS – including the deputy secretary and chief of staff – thanked them "for the opportunity to weigh in on OHRP's letter to UAB [University of Alabama Birmingham] and the Federal Register Notice related to SUPPORT" and stated that the NIH is "grateful for the opportunity to work with such a dedicated team within HHS."

"This interference has seriously compromised the integrity and independence of OHRP's compliance oversight investigation into the SUPPORT study, fundamentally undermining OHRP's regulatory authority and almost certainly doing long-lasting and possibly irreparable harm to the status of this critically important regulatory agency, whose primary mission is to protect human subjects," said Carome.

Public Citizen and the nine prominent scholars in bioethics, law and history seek to ensure that all HHS officials who played a role in the corrupt conduct revealed by the HHS emails are held accountable and that appropriate corrective actions are taken to prevent such improper and unethical interference by NIH in the compliance oversight activities of OHRP from recurring.

In a separate letter to the HHS inspector general, DeLauro asked the inspector general "to assess whether OHRP needs to be relocated, and if so where, in order to prevent the type of NIH and other HHS interference that seem to have occurred in this episode."

View Public Citizen's letter.

View DeLauro's letter.

Read further email correspondence between NIH, the HHS secretary's office and OHRP (PDF).

###

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

AUTHORS: Wade Rich, BSHS, RRT,[a] Neil N. Finer, MD,[a] Marie G. Gantz, PhD,[b] Nancy S. Newman, RN,[c] Angelita M. Hensman, RN, BSN,[d] Ellen C. Hale, RN, BS, CCRC,[e] Kathy J. Auten, MSHS,[f] Kurt Schibler, MD,[g] Roger G. Faix, MD,[h] Abbot R. Laptook, MD,[e] Bradley A. Yoder, MD,[h] Abhik Das, PhD,[b] and Seetha Shankaran, MD,[i] for the SUPPORT and Generic Database Subcommittees of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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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/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 ± SD)	26.2 ± 1.1	26.0 ± 1.2	<.001
Birth weight (g) (mean ± SD)	830.1 ± 193.2	812.5 ± 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.

TABLE 2 Delivery Room Status and Interventions

Variable	Enrolled (N = 1316), %	Nonenrolled (N = 3053), %	Unadjusted P
Apgar <3 at 1 min	24.4	31.9	<.001
Apgar <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.

Our findings suggest that using antenatal consent to conduct a trial such as SUPPORT under the constraints of preintervention informed consent creates a situation where population bias is a significant issue. We agree with the concerns expressed by Schmidt et al[4] 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 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.

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

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(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: The NICHD NRN has published periodic evaluations of morbidity and mortality rates for VLBW infants. Increased VLBW survival has paralleled improvements in prenatal, obsteric and neonatal care, but recent data suggest that a plateau in survival may have been reached.

WHAT THIS STUDY ADDS: This study is the first NRN study to report outcomes on the basis of GA-specific information, which should be particularly valuable to obstetricians and pediatricians as they counsel parents of high-risk infants.

OBJECTIVE: This report presents data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network on care of and morbidity and mortality rates for very low birth weight infants, according to gestational age (GA).

METHODS: Perinatal/neonatal data were collected for 9575 infants of extremely low GA (22–28 weeks) and very low birth weight (401–1500 g) who were born at network centers between January 1, 2003, and December 31, 2007.

RESULTS: Rates of survival to discharge increased with increasing GA (6% at 22 weeks and 92% at 28 weeks); 1060 infants died at ≤12 hours, with most early deaths occurring at 22 and 23 weeks (85% and 43%, respectively). Rates of prenatal steroid use (13% and 53%, respectively), cesarean section (7% and 24%, respectively), and delivery room intubation (19% and 68%, respectively) increased markedly between 22 and 23 weeks. Infants at the lowest GAs were at greatest risk for morbidities. Overall, 93% had respiratory distress syndrome, 46% patent ductus arteriosus, 16% severe intraventricular hemorrhage, 11% necrotizing enterocolitis, and 36% late-onset sepsis. The new severity-based definition of bronchopulmonary dysplasia classified more infants as having bronchopulmonary dysplasia than did the traditional definition of supplemental oxygen use at 36 weeks (68%, compared with 42%). More than one-half of infants with extremely low GAs had undetermined retinopathy status at the time of discharge. Center differences in management and outcomes were identified.

CONCLUSION: Although the majority of infants with GAs of ≥24 weeks survive, high rates of morbidity among survivors continue to be observed. *Pediatrics* 2010;126:443–456

Over the previous 2 decades, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) has monitored trends in morbidity and mortality rates among very low birth weight (VLBW) infants born at the university centers that constitute the NRN.[1–6] Increased VLBW infant survival rates have paralleled improvements in prenatal, obstetric, and neonatal care.[7,8] NRN data suggest that a plateau in VLBW infant survival rates might have been reached, despite increased use of prenatal corticosteroid treatment, prenatal antibiotic treatment, and early neonatal surfactant treatment.[6] Previous NRN reports presented patient characteristics, interventions, and outcomes according to birth weight (BW), with an upper limit of 1500 g. Such BW-specific data may be skewed by more-mature infants with growth restriction. The aim of this study was to evaluate management, hospital complications, and mortality rates among infants with gestational ages (GAs) of 22 to 28 weeks who were born at NRN centers between 2003 and 2007.

METHODS

Study Population and Clinical Outcomes

Infants born alive at NRN centers in 2003–2007 with GAs of 22⁰⁄₇ to 28⁶⁄₇ weeks and BWs of 401 to 1500 g were studied, including those with congenital anomalies. These infants were part of the NRN VLBW registry.[1–6]

Research personnel collected maternal pregnancy/delivery data soon after birth and infant data from birth to death, discharge/transfer, or 120 days of age ("status"). For infants with prolonged hospitalizations, limited information was collected up to 1 year. Definitions for maternal and infant characteristics were provided in a manual of operations. GA was determined as the best obstetric estimate by using ultrasonography and/or the date of the last menstrual period. Intrauterine growth restriction, defined as BW of <10th percentile for gender and GA, was determined by using growth charts published by Alexander et al.[9] Morbidities were defined in earlier publications,[1–6,10,11] including respiratory distress syndrome, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), early-onset and late-onset sepsis, necrotizing enterocolitis, patent ductus arteriosus, and retinopathy of prematurity (ROP). Respiratory distress syndrome was defined on the basis of clinical features and oxygen or respiratory support for ≥6 of the first 24 hours.

Three definitions of BPD were used, namely, traditional BPD (supplemental oxygen use at postmenstrual age [PMA] of 36 weeks); BPD determined by using the National Institutes of Health Workshop severity-based diagnostic criteria,[12] and BPD determined according to physiologic definition.[13] Surviving infants who were discharged or transferred before PMA of 36 weeks were classified on the basis of their status at 36 weeks, if status information was available, or oxygen use at discharge/transfer, if status information was not available. Unless noted otherwise, BPD refers to the traditional definition.

Revisions to data collection in 2006 included questions about maternal chorioamnionitis, placental pathologic conditions, nitric oxide use, and ibuprofen use and expanded data collection on birth resuscitation and neurologic, pulmonary, and ophthalmologic outcomes. In addition to ophthalmologic examination results and interventions, the following outcomes, defined in the manual of operations, were recorded: favorable in both eyes, severe ROP in either eye, or undetermined in either eye without severe ROP in either eye. Complete definitions are included in a footnote to Table 6. The registry was approved by the institutional review boards at each center.

Statistical Analyses

All infants were studied for assessment of maternal characteristics, neonatal demographic features, interventions performed soon after birth, and survival. Infants who died at ≤12 hours were excluded from analyses focused on morbidities diagnosed at >12 hours. For determination of rates of survival without morbidity, morbidity was defined as severe IVH (≥grade 3), PVL, BPD, necrotizing enterocolitis, ≥stage 3 ROP, or infection (early-onset sepsis, late-onset sepsis, or meningitis).

Statistical significance for unadjusted comparisons was determined by using χ^2 or Wilcoxon tests. Logistic or linear regression models were used to assess associations with GA, with adjustment for study center and infant BW, with statistical significance determined by using Wald χ^2 or F tests. Generalized logit regression models were used for comparisons involving categorical variables with >2 levels.

Risk of death and changes in clinical practice during the study period were assessed by using robust Poisson regression models[14] to produce correct SEs for the estimated relative risks (RRs). Additional adjustments for clustering according to center were not made because study center was treated as a fixed effect in these models, which also included effects for BW and GA. To assess linear trends, year was included as a continuous variable, with adjusted RRs for the change per year being reported. Initial models included terms for interactions between each GA and year, to assess whether yearly trends varied according to GA.

Nonsignificant interactions were removed, and the models were rerun.

Participating NRN Study Centers

The numbers of infants included from each center were as follows: University of Alabama, 805 infants; Brown University, 616 infants; University of California, San Diego, 528 infants; Case Western Reserve University, 415 infants; University of Cincinnati, 974 infants; Duke University, 426 infants; Emory University, 516 infants; Indiana University, 720 infants; University of Iowa, 99 infants; University of Miami, 515 infants; University of New Mexico, 97 infants; University of Rochester, 243 infants; Stanford University, 334 infants; University of Texas Southwestern Medical Center at Dallas, 488 infants; University of Texas Health Science Center at Houston, 765 infants; Tufts University, 137 infants; University of Utah, 269 infants; Wake Forest University, 465 infants; Wayne State University, 637 infants; Yale University, 526 infants.

RESULTS

Study Group

A total of 9575 infants with GAs of 22 to 28 weeks and BWs of 401 to 1500 g were born at NRN centers between January 1, 2003, and December 31, 2007, and are included in this study. Overall, 25% of the cohort subjects were multiple births.

Maternal and Infant Characteristics, Delivery Room Interventions, and Early Deaths

Rates of prenatal steroid use increased with increasing GA, from 13% at 22 weeks to 53% at 23 weeks and 85% to 87% at 24 to 28 weeks (Table 1). Rates of prenatal antibiotic use were lowest for mothers who delivered at 22 weeks (51%) and highest for those who delivered at 24 to 25 weeks (73%). Chorioamnionitis was documented more frequently in maternal records and confirmed more commonly by placental histologic findings at lower GAs. Overall, 59% of infants were born through cesarean section, with the steepest increase in cesarean section delivery rates between GAs of 22 and 24 weeks (7% at 22 weeks and 60% at 24 weeks).

With adjustment for center and BW, there were no differences in racial distribution according to GA (Table 2). Early neonatal interventions differed according to GA (Table 2). At 22 weeks, only 19% of infants underwent intubation and ventilation in the delivery room. Intubation rates increased to 68% at 23 weeks and 87% at 24 weeks and decreased at >24 weeks. Of 856 infants who received resuscitation drugs and/or chest compressions, 96% also underwent intubation. Rates of surfactant therapy increased from 17% at 22 weeks to 63% at 23 weeks and 90% at 24 weeks. The proportion of infants who died at ≤12 hours decreased with increasing GA, from 85% at 22 weeks to 1% to 2% at 27 to 28 weeks (Table 3). Risk of early death was significantly elevated for infants born at 22 to 24 weeks, compared with infants born at 28 weeks (22 weeks, adjusted RR: 15.76 [95% confidence interval [CI]: 10.13–24.52]; 23 weeks, adjusted RR: 9.88 [95% CI: 6.48–15.08]; 24 weeks, adjusted RR: 2.90 [95% CI: 1.90–4.43]), but not for infants born at 25 to 27 weeks.

Changes in Clinical Practices

Rates of prenatal steroid use increased by ~1% per year during the study period, and rates of cesarean section delivery increased by ~2% per year (Table 4). Rates of prenatal antibiotic use decreased by ~3% per year. These trends did not vary according to GA (year-GA interaction: for prenatal steroid therapy, $P = .47$; for cesarean section delivery, $P = .37$; for prenatal antibiotic treatment, $P = .66$). Rates of endotracheal intubation in the delivery room and surfactant therapy varied according to GA (year-GA interaction: $P < .01$ for each). Rates of intubation and surfactant therapy decreased for infants born at 28 weeks. During the study period, the proportion of infants receiving continuous positive airway pressure (CPAP) therapy at 24 hours increased among infants of ≥24 weeks, as did the proportion of infants who never underwent intubation. Although the adjusted RR for BPD decreased over time among infants who survived to PMA of 36 weeks, the change was clinically insignificant.

Neonatal Characteristics and Morbidities Among Infants Who Survived >12 Hours

Overall, 89% of infants born at GAs of 22 to 28 weeks survived >12 hours. Substantially more early survivors born at 22 to 24 weeks received resuscitation efforts (intubation, drug treatment, and/or chest compression) in the delivery room, compared with infants born at 22 to 24 weeks who died at ≤12 hours (22 weeks, 90% vs 7%; 24 weeks, 91% vs 59%). Significant differences in resuscitation efforts between those who survived >12 hours and those who did not were not seen among infants with GAs of 25 to 27 weeks. Among infants born at 28 weeks, a smaller proportion of those who survived >12 hours received resuscitation efforts in the delivery room, compared with those who died within 12 hours (48% vs 65%; $P = .05$).

Infants at the lowest GAs were at the greatest risk for morbidities of prematurity (Tables 5 and 6). Overall, 93% infants experienced respiratory distress. Rates of mechanical ventilation at 24 hours decreased from 96% at 22 weeks to 40% at 28 weeks, and rates of CPAP therapy at 24 hours increased from 0% at 22 weeks to 3% at 23 weeks, 8% at 24 weeks, and 38% at 28 weeks.

TABLE 1 Maternal Demographic Features and Perinatal Information According to GA for VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007 (Including Infants Who Died Within 12 Hours After Birth)

Characteristic	22 wk ($N = 421$)	23 wk ($N = 871$)	24 wk ($N = 1370$)	25 wk ($N = 1498$)	26 wk ($N = 1576$)	27 wk ($N = 1838$)	28 wk ($N = 2001$)	Total ($N = 9575$)
Mother's age, y[a]								
Mean (range)	27 (22–32)	27 (25–32)	27 (25–31)	27 (23–30)	27 (25–30)	27 (25–31)	27 (25–32)	27 (25–31)
SD (range)	6.9 (4.2–9.9)	6.4 (0.0–7.0)	6.5 (4.7–8.9)	6.6 (4.9–7.2)	6.5 (4.6–7.6)	6.7 (5.1–7.5)	6.8 (5.2–7.5)	6.6 (5.7–7.0)
High school degree, % (range)	68 (0–100)	69 (25–100)	72 (40–100)	70 (33–94)	72 (25–90)	70 (0–100)	72 (41–89)	71 (36–88)
Medical insurance, % (range)[b]								
Medicaid/public insurance	51 (20–100)	42 (20–100)	50 (15–71)	53 (33–69)	50 (29–71)	50 (24–81)	49 (19–78)	49 (29–69)
Private insurance	35 (0–67)	45 (0–67)	39 (9–76)	38 (6–62)	40 (5–69)	40 (3–67)	42 (4–79)	40 (6–63)
Self-pay/uninsured	13 (0–40)	13 (0–51)	11 (0–42)	8 (0–38)	9 (0–30)	9 (0–22)	8 (0–31)	9 (<1–31)
Other	<1 (0–13)	<1 (0–11)	<1 (0–10)	<1 (0–11)	<1 (0–10)	1 (0–15)	<1 (0–15)	<1 (0–13)
≥1 prenatal visit, % (range)[b]	88 (33–100)	92 (84–100)	93 (85–100)	94 (86–100)	93 (80–100)	95 (85–100)	95 (89–100)	94 (85–100)
Diabetes mellitus, % (range)[c]	3 (0–20)	3 (0–17)	3 (0–10)	4 (0–8)	5 (2–15)	5 (0–11)	6 (1–15)	5 (3–8)
Hypertension, % (range)[b]	8 (0–26)	10 (0–28)	14 (0–40)	20 (9–38)	25 (13–43)	27 (15–42)	31 (11–47)	22 (14–37)
Prepartum hemorrhage, % (range)[b]	21 (0–67)	27 (0–76)	21 (9–40)	22 (5–56)	19 (0–54)	17 (5–35)	16 (6–23)	20 (9–32)
Prenatal steroid treatment, % (range)[b]	13 (0–100)	53 (10–100)	85 (49–100)	86 (62–100)	86 (48–100)	87 (57–100)	86 (46–100)	80 (45–97)
Prenatal antibiotic treatment, % (range)[b]	51 (21–92)	65 (0–88)	73 (56–90)	73 (48–94)	68 (45–100)	66 (51–85)	64 (50–89)	67 (55–85)
ROM >24 h before delivery, % (range)[b]	22 (0–45)	22 (0–42)	25 (8–40)	26 (13–40)	28 (15–50)	25 (14–32)	24 (16–34)	25 (18–32)
Mode of delivery, % (range)[b]								
Vaginal, vertex	60 (20–100)	53 (0–75)	32 (20–56)	31 (19–44)	33 (11–43)	30 (14–44)	30 (12–48)	34 (18–43)
Vaginal, breech	32 (0–80)	23 (0–56)	7 (0–22)	4 (0–13)	3 (0–13)	2 (0–4)	2 (0–5)	6 (0–12)
Vaginal, not otherwise specified	<1 (0–33)	<1 (0–6)	0 (0–0)	<1 (0–5)	<1 (0–2)	<1 (0–1)	<1 (0–1)	<1 (0–1)
Cesarean section	7 (0–33)	24 (3–100)	60 (24–80)	65 (54–79)	65 (52–89)	68 (55–86)	68 (47–88)	59 (47–81)
Infants born in 2006–2007	$N = 159$	$N = 321$	$N = 493$	$N = 573$	$N = 583$	$N = 732$	$N = 771$	$N = 3632$
Chorioamnionitis documented in mother's medical record, % (range)[b]	28 (0–100)	26 (0–100)	20 (0–39)	19 (0–56)	19 (0–44)	15 (0–28)	14 (0–22)	18 (7–29)
Placental pathologic evaluation performed, % (range)	77 (36–100)	86 (50–100)	82 (50–100)	83 (62–100)	80 (46–100)	80 (44–100)	83 (0–100)	82 (58–100)
Placental pathologic evaluation	$N = 123$	$N = 272$	$N = 401$	$N = 475$	$N = 461$	$N = 585$	$N = 634$	$N = 2951$
Histologic chorioamnionitis, % (range)[b]	70 (25–100)	61 (0–100)	59 (0–100)	51 (25–100)	48 (0–73)	41 (23–61)	34 (8–57)	48 (26–73)

Ranges are across all participating NRN centers. Information was missing as follows: mother's age, 4 infants; mother's education, 2834 infants; mother's medical insurance, 300 infants; prenatal care, 8 infants; diabetes mellitus, 8 infants; hypertension, 10 infants; prepartum hemorrhage, 8 infants; prenatal steroid treatment, 27 infants; prenatal antibiotic treatment, 30 infants, rupture of membranes date and/or time, 228 infants; mode of delivery, 9 infants; chorioamnionitis, 9 infants; placental pathologic evaluation, 26 infants; histologic chorioamnionitis, 17 infants. P values were determined with the Wald χ^2 test for differences according to GA, with adjustment for center and BW. ROM indicates rupture of membranes.

[a] $P \leq .05$.

[b] $P \leq .001$.

[c] $P \leq .01$.

The risk of BPD was inversely related to GA at birth. Because of the inclusion of infants with mild BPD (oxygen therapy for ≥28 days but use of room air at 36 weeks), more infants were classified as having BPD with the new, severity-based, definition of BPD (new definition, 68%; traditional definition, 42%; physiologic definition, 40%).

Most infants who survived >12 hours underwent ≥1 cranial ultrasound evaluation within 28 days; 64% of results were normal (Table 6). Overall, 10% of sonograms indicated grade 1 IVH, 6% grade 2 IVH, 7% grade 3 IVH, 9% grade 4 IVH, 2% ventriculomegaly without IVH, and 2% other abnormalities. PVL was observed for 3% of infants with sonograms performed in the first 28 days and 4% with sonograms performed after 28 days. Rates of abnormal ultrasound findings decreased with increasing GA.

Sepsis was diagnosed more frequently at the lowest GA (rates of early-onset sepsis were 6% at 22 weeks and 1% at 28 weeks, and rates of late-onset sepsis were 58% at 22 weeks and 20% at 28 weeks); 11% of infants developed necrotizing enterocolitis (Table 6). Patent ductus arteriosus was diagnosed for 46% of infants, of whom 71% were treated with indomethacin, 13% ibuprofen (2006–2007), and 27% surgical closure. Among 7313 infants who were still in the hospital at 28 days, 94% underwent an ophthalmologic examination before hospital discharge, death, or transfer. Of the 6866 with examination findings, 59% were diagnosed as having ROP (96% at 22 weeks and 32% at 28 weeks), and 12% under-

TABLE 2 Infant Demographic Features and Delivery Information According to GA for VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007 (Including Infants Who Died Within 12 Hours After Birth)

Characteristic	22 wk ($N = 421$)	23 wk ($N = 871$)	24 wk ($N = 1370$)	25 wk ($N = 1498$)	26 wk ($N = 1576$)	27 wk ($N = 1838$)	28 wk ($N = 2001$)	Total ($N = 9575$)
BW, g[a]								
Mean (range)	511 (473–621)	581 (549–639)	651 (609–677)	744 (709–791)	854 (737–891)	960 (919–1009)	1082 (1022–1207)	836 (789–903)
SD (range)	66.9 (30.4–122)	92.0 (55.4–139)	105 (90.6–125)	135 (107–162)	163 (133–183)	189 (164–218)	206 (160–229)	241 (218–259)
Male, % (range)[a]	58 (0–93)	55 (43–100)	53 (40–70)	53 (46–81)	53 (45–63)	55 (37–66)	51 (36–58)	53 (47–58)
Race/ethnicity, % (range)								
Black, non-Hispanic	45 (0–100)	38 (0–81)	41 (0–85)	41 (0–81)	39 (4–86)	38 (2–89)	36 (0–87)	39 (3–84)
Black, Hispanic	0 (0–0)	1 (0–10)	<1 (0–10)	<1 (0–6)	<1 (0–5)	<1 (0–3)	<1 (0–5)	<1 (0–3)
White, non-Hispanic	30 (0–80)	37 (0–63)	34 (4–70)	34 (0–71)	36 (4–62)	40 (3–79)	41 (5–88)	37 (5–71)
White, Hispanic	19 (0–67)	20 (0–100)	18 (0–76)	19 (0–88)	19 (0–73)	18 (<1–74)	17 (0–67)	18 (1–70)
American Indian/ Alaska native	<1 (0–20)	0 (0–0)	<1 (0–40)	<1 (0–13)	<1 (0–28)	<1 (0–10)	<1 (0–30)	<1 (0–20)
Asian/Pacific islander	4 (0–43)	3 (0–54)	3 (0–37)	3 (0–23)	3 (0–21)	3 (0–19)	3 (0–23)	3 (0–27)
>1 race/other	1 (0–19)	1 (0–14)	2 (0–26)	1 (0–21)	2 (0–22)	<1 (0–9)	1 (0–11)	1 (0–17)
Intrauterine growth restriction, % (range)[a]	0 (0–0)	4 (0–16)	6 (0–30)	8 (0–14)	8 (1–20)	10 (5–15)	9 (0–15)	8 (5–10)
Multiple birth, % (range)[a]	28 (0–48)	30 (11–100)	25 (7–32)	21 (6–40)	22 (8–40)	25 (0–40)	28 (16–37)	25 (18–34)
Delivery room resuscitation, % (range)								
Endotracheal intubation[a]	19 (0–100)	68 (10–100)	87 (53–100)	82 (53–98)	75 (32–92)	65 (31–90)	47 (10–82)	67 (41–85)
Resuscitation drug[a]	3 (0–20)	8 (0–32)	9 (0–32)	6 (0–28)	5 (0–22)	4 (0–19)	2 (0–7)	5 (1–16)
Chest compression[a]	3 (0–40)	10 (0–24)	13 (0–40)	10 (1–37)	7 (0–22)	6 (0–15)	4 (0–14)	8 (2–19)
Apgar score of ≤3, % (range)[a]								
At 1 min[a]	89 (0–100)	73 (50–100)	53 (30–71)	44 (25–63)	36 (22–53)	32 (17–48)	23 (12–30)	42 (29–53)
At 5 min[a]	86 (0–100)	49 (0–89)	20 (0–40)	12 (3–25)	8 (0–22)	7 (1–14)	4 (0–9)	16 (3–25)
Admission temperature, °C[a,b]								
Mean (range)	34.7 (31.3–37.0)	35.0 (33.2–36.6)	35.4 (34.2–37.0)	35.8 (34.8–36.9)	36.1 (35.1–37.0)	36.2 (35.1–37.1)	36.2 (35.1–37.2)	35.9 (34.8–37.0)
SD (range)	1.7 (0.1–3.2)	1.7 (0.1–1.9)	1.4 (0.7–1.5)	1.1 (0.6–1.3)	1.0 (0.5–1.2)	0.9 (0.5–1.1)	0.9 (0.4–1.2)	1.2 (0.7–1.3)
Surfactant therapy, % (range)[a]	17 (0–100)	63 (10–100)	90 (58–100)	88 (72–100)	85 (56–100)	78 (43–94)	65 (41–86)	76 (58–88)

Ranges are across all participating NRN centers. Information was missing as follows: gender, 2 infants; race/ethnicity, 24 infants; intrauterine growth restriction, 2 infants; endotracheal intubation, 9 infants; resuscitation drug, 13 infants; chest compression, 13 infants; Apgar score at 1 minute, 78 infants; Apgar score at 5 minutes, 78 infants, temperature, 1097 infants.

[a] $P \leq .001$ from the Wald χ^2 test for differences according to GA, with adjustment for center and BW. Differences in BW were adjusted for center effects only. Race/ethnicity was tested as black, white, or other.

[b] Infant temperature at initial admission to the nursery for infants born in 2003–2005 and first temperature reading obtained within 60 minutes after birth for infants born in 2006–2007.

went treatment for ROP (50% at 22 weeks and 2% at 28 weeks). A total of 2630 infants evaluated in 2006–2007 had ROP outcomes recorded at the time of discharge or 120 days of age. Among those infants, 39% had favorable outcomes, 7% had unfavorable outcomes with severe ROP requiring treatment, and 53% had undetermined ROP outcomes (ie, had not reached the threshold for surgery or were still immature and required further examination) (Table 6).

Survival and Morbidity Rates (All 9575 Infants)

Rates of survival to discharge increased with increasing GA, from 6% at 22 weeks to 92% at 28 weeks (72% overall) (Fig 1 and Table 3). Infants born at 22 to 23 weeks had >3 times the risk of death, compared with infants born at 28 weeks (22 weeks, adjusted RR: 3.88 [95% CI: 3.18–4.73]; 23 weeks, adjusted RR: 3.56 [95% CI: 2.95–4.30]). RRs decreased but remained significant for infants born at 24 to 27 weeks, compared with 28 weeks (24 weeks, adjusted RR: 2.52 [95% CI: 2.10–3.04]; 27 weeks, adjusted RR: 1.23 [95% CI: 1.01–1.49]). Rates of survival to discharge according to GA did not change during the study period (Table 4).

Neonatal morbidities occurred frequently among survivors. Rates of survival with morbidity decreased from 100% at 22 weeks to 92% at 23 weeks, 91% at 24 weeks, 80% at 25 weeks, 66%

TABLE 3 Mortality Rates According to GA for VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007

	% (Range)							
	22 wk ($N = 421$)	23 wk ($N = 871$)	24 wk ($N = 1370$)	25 wk ($N = 1498$)	26 wk ($N = 1576$)	27 wk ($N = 1838$)	28 wk ($N = 2001$)	Total ($N = 9575$)
Survived	6 (0–50)	26 (2–53)	55 (20–100)	72 (50–90)	84 (61–100)	88 (76–100)	92 (88–100)	72 (55–95)
Died	94 (50–100)	74 (47–98)	45 (0–80)	28 (10–50)	16 (0–39)	12 (0–24)	8 (0–12)	28 (5–45)
Time of death[a]								
≤12 h	85 (0–100)	43 (0–80)	11 (0–44)	5 (0–19)	3 (0–11)	1 (0–5)	2 (0–7)	11 (1–25)
>12–24 h	2 (0–6)	3 (0–7)	2 (0–6)	<1 (0–3)	<1 (0–2)	<1 (0–2)	<1 (0–1)	1 (0–2)
>1–3 d	1 (0–8)	9 (0–30)	6 (0–11)	3 (0–25)	2 (0–8)	1 (0–6)	<1 (0–4)	3 (0–7)
4–7 d	2 (0–23)	4 (0–20)	4 (0–11)	3 (0–7)	1 (0–8)	1 (0–6)	<1 (0–2)	2 (0–5)
8–14 d	2 (0–50)	5 (0–50)	5 (0–20)	3 (0–9)	2 (0–6)	2 (0–19)	<1 (0–5)	3 (1–8)
15–28 d	1 (0–15)	4 (0–16)	7 (0–15)	4 (0–8)	3 (0–11)	2 (0–5)	2 (0–7)	3 (0–6)
≥29 d	1 (0–8)	6 (0–17)	10 (0–30)	8 (0–15)	5 (0–10)	4 (0–8)	2 (0–5)	5 (1–9)
Survived	$N = 25$	$N = 226$	$N = 748$	$N = 1078$	$N = 1319$	$N = 1616$	$N = 1847$	$N = 6859$
Survived without morbidity[b]	0 (0–0)	8 (0–14)	9 (0–18)	20 (0–43)	34 (0–49)	44 (19–65)	57 (6–74)	37 (7–50)
Died	$N = 396$	$N = 645$	$N = 622$	$N = 420$	$N = 257$	$N = 222$	$N = 154$	$N = 2716$
Respiratory support withheld/withdrawn before death[c]	82 (40–100)	77 (0–100)	66 (21–96)	68 (0–100)	73 (42–100)	66 (20–100)	60 (0–100)	72 (29–95)
Died at ≤12 h	$N = 359$	$N = 375$	$N = 147$	$N = 72$	$N = 46$	$N = 27$	$N = 34$	$N = 1060$
Respiratory support withheld/withdrawn before death[d]	85 (40–100)	85 (43–100)	79 (0–100)	86 (0–100)	78 (0–100)	85 (0–100)	79 (25–100)	84 (53–100)

Ranges are across all participating NRN centers.

[a] Proportions among all infants including survivors.

[b] Proportions among infants who survived. Morbidities included severe IVH, PVL, BPD, necrotizing enterocolitis, infections, and ROP stage ≥3.

[c] Proportions among infants who died. Data on respiratory support withheld/withdrawn were missing for 52 infants.

[d] Proportions among infants who died within 12 hours. Data on respiratory support withheld/withdrawn were missing for 2 infants.

at 26 weeks, 56% at 27 weeks, and 43% at 28 weeks. Infection and BPD were the most-frequent morbidities. Although unadjusted rates of survival without major morbidity seemed unchanged, the adjusted RR for survival without morbidity increased over time (Table 4). The median length of hospital stay among survivors was 84 days, and lengths of stay decreased with increasing GA, from 141 days at 22 weeks to 63 days at 28 weeks ($P < .001$). PMA at discharge decreased from 42 weeks for surviving infants born at GAs of 22 weeks to 37 weeks for those born at 28 weeks (Fig 2).

DISCUSSION

Although VLBW infant mortality rates in the United States decreased substantially in the 1980s and early 1990s,[5–6,15–18] most reports, including findings for this cohort, failed to demonstrate further progress in reducing neonatal morbidity and mortality rates.[6,16–19] In contrast, a population cohort of all preterm infants born at GAs of <27 weeks in Sweden in 2004–2007 demonstrated survival rates higher than rates reported for other countries or reported previously for Sweden.[20] Our study reviewed neonatal morbidity and mortality rates for a large cohort of extremely preterm infants, to evaluate changes in clinical practice and contemporary outcomes at US academic centers. Although previous reports from the NRN used BW as the reference for morbidity and survival rates, the current study assessed outcomes according to GA. Appreciation of GA-based outcomes is particularly valuable for prenatal counseling and physician/family decision-making.

The decisions to provide active obstetric care and to initiate neonatal intensive care for the most-immature infants remain controversial. Center differences in obstetric/early neonatal interventions were identified, but we did not collect sufficiently detailed information on decision-making processes to help explain differences. In our cohort, rates of active obstetric intervention, as indicated by prenatal steroid administration and cesarean section delivery, increased markedly after 23 weeks of gestation. Prenatal steroid use was almost twice as frequent for infants born at GAs of 24 to 28 weeks, compared with infants born earlier. Similarly, rates of neonatal interventions and intensive care, measured as active resuscitation with ventilation in the delivery room, increased substantially between 22 and 23 weeks (19% vs 68%). Rates of death at ≤12 hours, which in part reflect willingness to provide intensive care to the most-immature infants, decreased with increasing GA, from 85% of infants at 22 weeks to 2% of infants at 28 weeks.

In-hospital morbidity rates remain high among extremely preterm infants, and morbidities contribute

TABLE 4 Clinical Practice Indicators and Survival Rates According to Birth Year for 9575 VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007

Characteristic	Percent					Adjusted RR (95% CI)	*P*
	2003 (*N* = 1919)	2004 (*N* = 1992)	2005 (*N* = 2032)	2006 (*N* = 1900)	2007 (*N* = 1732)		
Prenatal steroid treatment, all infants	81	76	80	79	83	1.01 (1.00–1.02)	.01
Prenatal antibiotic treatment, all infants	72	68	68	63	66	0.97 (0.96–0.98)	<.001
Cesarean section, all infants	57	58	62	60	60	1.02 (1.00–1.03)	.01
Delivery room endotracheal intubation							
22 wk	17	22	21	16	19	0.98 (0.85–1.13)	.8
23 wk	69	67	67	68	67	0.99 (0.96–1.02)	.6
24 wk	89	89	88	83	86	0.98 (0.97–1.00)	.04
25 wk	86	86	79	81	77	0.97 (0.95–0.99)	<.001
26 wk	83	78	68	76	69	0.95 (0.94–0.97)	<.001
27 wk	69	70	64	58	61	0.96 (0.94–0.98)	<.001
28 wk	54	58	45	41	38	0.90 (0.87–0.93)	<.001
All infants	71	72	66	63	62		
Surfactant therapy							
22 wk	18	17	21	13	18	0.97 (0.83–1.13)	.7
23 wk	65	66	63	63	59	0.98 (0.94–1.01)	.2
24 wk	91	88	89	88	93	1.00 (0.99–1.01)	.9
25 wk	89	89	85	91	87	0.99 (0.98–1.00)	.2
26 wk	89	83	84	87	82	0.99 (0.97–1.00)	.045
27 wk	78	80	75	77	78	1.00 (0.98–1.01)	.6
28 wk	73	70	61	62	59	0.94 (0.92–0.96)	<.001
All infants	78	77	74	75	74		
Survived to discharge							
22 wk	6	7	5	3	8		
23 wk	27	21	33	27	21		
24 wk	56	53	55	55	54		
25 wk	71	72	70	75	71		
26 wk	82	87	82	83	84		
27 wk	88	86	88	88	91		
28 wk	94	89	93	93	92		
All infants	72	70	71	73	72	1.00 (0.99–1.01)	.3
Survived >12 h	*N* = 1709	*N* = 1762	*N* = 1818	*N* = 1689	*N* = 1537		
Never intubated, all infants who survived >12 h[a]	8	8	10	10	11	1.12 (1.07–1.18)	<.001
Necrotizing enterocolitis, all infants who survived >12 h	9	11	11	11	12	1.04 (0.99–1.09)	.1
Survived >24 h	*N* = 1685	*N* = 1738	*N* = 1785	*N* = 1678	*N* = 1532		
CPAP therapy at 24 h							
22 wk	0	0	0	0	0		
23 wk	5	4	4	1	1	0.73 (0.51–1.05)	.09
24 wk	5	7	11	6	8	1.09 (0.95–1.24)	.2
25 wk	12	14	22	18	23	1.16 (1.07–1.25)	<.001
26 wk	27	32	32	25	34	1.01 (0.96–1.07)	.6
27 wk	32	35	35	37	40	1.05 (1.0–1.09)	.04
28 wk	36	36	36	41	40	1.04 (1.0–1.08)	.06
All infants who survived >24 h	23	25	26	27	29		
Survived >72 h	*N* = 1626	*N* = 1672	*N* = 1721	*N* = 1631	*N* = 1478		
Late-onset sepsis, all infants who survived >72 h	36	38	37	36	33	0.98 (0.96–1.0)	.1
Cranial sonography performed within 28 d after birth	*N* = 1660	*N* = 1708	*N* = 1749	*N* = 1646	*N* = 1497		
Severe IVH, all infants with sonograms	16	16	14	17	16	0.96 (0.93–1.0)	.05
Infants who underwent cranial imaging before and/or after 28 d	*N* = 1685	*N* = 1714	*N* = 1752	*N* = 1651	*N* = 1500		
PVL, all infants with imaging findings	4	5	5	4	5	0.93 (0.87–1.0)	.06
Survived to PMA of 36 wk	*N* = 1426	*N* = 1455	*N* = 1483	*N* = 1421	*N* = 1280		
BPD, infants who survived to PMA of 36 wk	43	42	40	43	43	0.94 (0.92–0.95)	<.001
Survived to discharge	*N* = 1385	*N* = 1403	*N* = 1445	*N* = 1383	*N* = 1243		
Survived without morbidity[b]							
22 wk	0	0	0	0	0		
23 wk	14	10	3	5	9		
24 wk	5	10	10	8	11		
25 wk	22	20	21	17	20		
26 wk	32	38	34	31	34		
27 wk	44	44	46	42	44		
28 wk	58	55	62	55	54		
All infants who survived to discharge	37	37	38	35	36	1.04 (1.02–1.06)	<.001

Information was missing as follows: prenatal steroid treatment, 27 infants; prenatal antibiotic treatment, 30 infants; cesarean section delivery, 9 infants; delivery room endotracheal intubation, 9 infants; surfactant therapy, 10 infants; never intubated, 3 infants; necrotizing enterocolitis, 1 infant, CPAP therapy, 14 infants; late-onset sepsis, 2 infants; severe IVH, 9 infants; PVL, 1 infant; BPD, 42 infants; survived without morbidity, 32 infants. RRs and *P* values were determined for the change per year from a modified Poisson model that included effects for study center, infant BW and GA, and year and, where significant, effects for the year-GA interaction (delivery room intubation, surfactant therapy and CPAP therapy at 24 h). RRs are shown for all infants overall in cases in which the year-GA interaction was not significant and separately for infants born at each GA in cases in which the interaction was significant. The year-GA interaction could not be assessed for the category of never intubated because of small sample sizes.

[a] Never used conventional or high-frequency ventilator or underwent nasal synchronized intermittent mandatory ventilation.

[b] Morbidities included BPD, severe IVH, PVL, necrotizing enterocolitis, ROP stage ≥3, and infections (early-onset sepsis, late-onset sepsis, or meningitis). Proportions were determined among survivors. Of the 25 surviving infants born at GA of 22 weeks, none survived without major morbidity.

TABLE 5 Pulmonary Morbidities According to GA for VLBW Infants Who Were Born in NRN Centers Between January 1, 2003, and December 31, 2007, and Survived >12 Hours After Birth

Characteristic	% (Range)							
	22 wk (N = 62)	23 wk (N = 496)	24 wk (N = 1223)	25 wk (N = 1426)	26 wk (N = 1530)	27 wk (N = 1811)	28 wk (N = 1967)	Total (N = 8515)
Respiratory distress syndrome[a]	95 (75–100)	98 (75–100)	98 (64–100)	97 (77–100)	94 (61–100)	90 (50–100)	86 (55–100)	93 (60–99)
Surfactant therapy[a]	97 (50–100)	97 (90–100)	95 (83–100)	90 (72–100)	86 (58–100)	78 (43–95)	65 (41–86)	82 (64–93)
Pneumothorax	15 (0–40)	11 (0–33)	11 (0–23)	9 (4–20)	7 (0–15)	5 (0–14)	4 (0–9)	7 (3–13)
Pulmonary hemorrhage[b]	16 (0–50)	15 (0–50)	13 (6–40)	10 (3–28)	7 (2–20)	4 (0–14)	3 (0–7)	7 (3–18)
Postnatal steroid treatment[a]	15 (0–50)	18 (0–50)	20 (0–60)	14 (0–44)	9 (0–30)	6 (0–14)	2 (0–6)	10 (0–24)
Never intubated[a,c]	0 (0–0)	<1 (0–6)	<1 (0–2)	2 (0–8)	5 (0–14)	12 (0–40)	23 (6–44)	9 (2–22)
Respiratory support at 24 h for infants who survived >24 h	N = 55	N = 471	N = 1192	N = 1414	N = 1520	N = 1804	N = 1962	N = 8418
Conventional or high-frequency ventilation[a,d]	96 (0–100)	94 (83–100)	89 (71–100)	76 (57–95)	61 (43–92)	49 (21–74)	40 (20–61)	62 (47–83)
Nasal SIMV[b,d]	0 (0–0)	<1 (0–6)	2 (0–16)	3 (0–20)	3 (0–18)	2 (0–12)	3 (0–16)	3 (0–14)
CPAP therapy[a,d]	0 (0–0)	3 (0–10)	8 (0–29)	18 (5–30)	30 (5–49)	36 (12–79)	38 (17–66)	26 (8–46)
Use of oxygen alone[a,d]	2 (0–100)	1 (0–6)	1 (0–7)	2 (0–7)	2 (0–13)	3 (0–10)	5 (0–15)	3 (<1–9)
Infants who survived to PMA of 36 wk	N = 27	N = 241	N = 790	N = 1121	N = 1344	N = 1648	N = 1852	N = 7023
BPD (oxygen use at 36 wk)[a,e]	85 (0–100)	73 (35–100)	69 (31–100)	55 (20–100)	44 (19–100)	34 (13–76)	23 (9–88)	42 (20–89)
Infants in hospital at PMA of 36 wk or discharged/transferred at 33–36 wk	N = 27	N = 231	N = 774	N = 1088	N = 1284	N = 1565	N = 1739	N = 6708
Severity-based BPD[a,f]								
Mild BPD	15 (0–100)	26 (0–50)	26 (0–67)	37 (0–62)	35 (0–58)	28 (0–52)	16 (0–35)	27 (5–38)
Moderate BPD	30 (0–100)	35 (0–100)	34 (0–68)	29 (9–70)	26 (5–71)	20 (4–55)	15 (0–57)	23 (8–60)
Severe BPD	56 (0–100)	39 (0–100)	37 (0–100)	26 (3–86)	17 (4–44)	13 (0–30)	8 (0–29)	18 (3–40)
Infants born in 2006–2007	N = 19	N = 174	N = 438	N = 547	N = 566	N = 728	N = 754	N = 3226
Inhaled nitric oxide treatment[b,g]	11 (0–50)	8 (0–50)	10 (0–54)	8 (0–27)	7 (0–25)	3 (0–12)	3 (0–14)	6 (0–19)
Infants who survived to PMA of 36 wk	N = 9	N = 83	N = 274	N = 422	N = 482	N = 650	N = 691	N = 2611
BPD by physiologic definition[a,h]	89 (50–100)	70 (0–100)	68 (0–100)	55 (19–100)	44 (6–100)	31 (0–100)	22 (0–100)	40 (15–82)

Ranges are across all participating NRN centers. Proportions are among all infants who survived >12 hours, except as noted. Information was missing as follows: respiratory distress syndrome, 5 infants; surfactant treatment, 7 infants; pulmonary hemorrhage, 2 infants; postnatal steroid treatment, 41 infants; never intubated, 3 infants; ventilator use at 24 hours, 13 infants; nasal synchronized intermittent mandatory ventilation at 24 hours, 14 infants; CPAP at 24 hours, 14 infants; oxygen alone at 24 hours, 14 infants; nitric oxide use, 1 infant. P values were determined with the Wald χ^2 test for differences according to GA, with adjustment for center and BW or, for nasal synchronized intermittent mandatory ventilation and inhaled nitric oxide use, with adjustment for BW only. SIMV indicates synchronized intermittent mandatory ventilation.

[a] $P \leq .001$.

[b] $P \leq .05$.

[c] Never used conventional or high-frequency ventilator or underwent nasal synchronized intermittent mandatory ventilation.

[d] Proportions among infants who survived >24 hours after birth. Use of oxygen alone at 24 hours was defined as receiving supplemental oxygen without conventional or high-frequency ventilation, nasal synchronized intermittent mandatory ventilation, or CPAP therapy.

[e] Proportions among infants who survived to PMA of 36 weeks and had nonmissing outcome data (N values shown). BPD could not be determined for 42 infants.

[f] Proportions among infants who were still in the hospital at PMA of 36 weeks or, if discharged or transferred before 36 weeks, were in the hospital for ≥28 days and until PMA of 33 weeks. N values are shown for infants with nonmissing outcome data. Severity-based BPD could not be determined for 68 infants. More information about severity-based BPD is presented in the text.

[g] Proportions among infants born in 2006–2007.

[h] Proportions among infants born in 2006–2007 who survived to PMA of 36 weeks and had nonmissing outcome data (N values shown). BPD according to the physiologic definition could not be determined for 90 infants. Information on how BPD was determined according to the physiologic definition is presented in the text.

to adverse neurodevelopmental outcomes. The majority of infants studied experienced a major complication during the initial hospitalization, with the risk of morbidity being inversely related to GA at birth. Center differences in the proportions of infants with specific morbidities were noted. At the lowest GAs (22–24 weeks), small numbers of infants at some centers contributed to the variability. The registry does not collect data on the reasons behind the choice of interventions for individual infants and has limited data on the severity of illness at birth, information that might permit more-detailed evaluation and understanding of center differences. Reducing the high rates of in-hospital morbidity among extremely low GA infants who are provided ongoing intensive care remains a challenge for clinicians and investigators.

To reduce rates of BPD, attention is being paid to avoidance of intubation, less prophylactic use of surfactant, and alternative modes of respiratory support. Rates of endotracheal intubation in the delivery room decreased in recent years among infants of >24 weeks, with a corresponding increase in CPAP therapy use at 24 hours of life. At GA of 28 weeks, use of surfactant decreased in the most-recent years. Furthermore, the proportion of infants who survived >12 hours without ever undergoing intubation and ventilation increased with increasing GA and

TABLE 6 Rates of Infections and Other Morbidities According to GA for VLBW Infants Who Were Born in NRN Centers Between January 1, 2003, and December 31, 2007, and Survived >12 Hours After Birth

Characteristic	% (Range)							
	22 wk ($N = 62$)	23 wk ($N = 496$)	24 wk ($N = 1223$)	25 wk ($N = 1426$)	26 wk ($N = 1530$)	27 wk ($N = 1811$)	28 wk ($N = 1967$)	Total ($N = 8515$)
Early-onset sepsis[a]	6 (0–67)	4 (0–20)	4 (0–9)	2 (0–7)	2 (0–6)	2 (0–6)	1 (0–4)	2 (<1–4)
Meningitis[b]	0 (0–0)	5 (0–25)	3 (0–12)	4 (0–15)	3 (0–9)	1 (0–5)	1 (0–5)	3 (0–8)
Late-onset sepsis[a,c]	58 (0–100)	62 (0–86)	55 (29–74)	46 (24–67)	35 (14–53)	27 (15–52)	20 (4–36)	36 (18–51)
NEC[b]	5 (0–33)	12 (0–50)	15 (0–22)	13 (5–24)	9 (0–25)	10 (0–21)	8 (3–20)	11 (4–19)
NEC managed medically[d]	67 (50–100)	31 (0–100)	39 (0–100)	52 (10–100)	48 (17–100)	47 (23–75)	58 (0–100)	48 (21–100)
NEC treated surgically[d]	33 (0–50)	69 (0–100)	61 (0–100)	48 (0–90)	52 (0–83)	53 (25–77)	42 (0–100)	52 (0–79)
PDA[a]	55 (13–100)	54 (21–100)	60 (31–80)	55 (25–92)	48 (21–88)	42 (14–80)	32 (13–60)	46 (26–78)
Indomethacin therapy for PDA[e,f]	82 (0–100)	73 (0–100)	76 (25–96)	72 (29–94)	69 (7–94)	68 (37–94)	67 (31–95)	71 (33–91)
Surgical treatment of PDA[a,e]	50 (0–100)	43 (0–77)	40 (13–62)	33 (13–65)	24 (6–44)	16 (0–33)	12 (0–33)	27 (10–41)
Infants in hospital at 28 d	$N = 30$	$N = 277$	$N = 874$	$N = 1197$	$N = 1386$	$N = 1683$	$N = 1866$	$N = 7313$
ROP examination performed[a,g]	93 (50–100)	91 (71–100)	93 (50–100)	94 (78–100)	96 (67–100)	95 (87–100)	92 (68–99)	94 (82–99)
ROP diagnosed[a,h]	96 (50–100)	88 (0–100)	89 (50–100)	79 (29–94)	65 (20–81)	49 (18–75)	32 (5–56)	59 (35–75)
ROP stage ≥3[a,h]	57 (0–100)	48 (0–100)	42 (25–77)	25 (11–54)	14 (0–29)	7 (0–14)	3 (0–11)	16 (6–28)
Intervention/surgical treatment for ROP[a,h]	50 (0–100)	40 (0–100)	35 (17–58)	17 (0–40)	8 (0–21)	4 (0–9)	2 (0–7)	12 (4–22)
Infants in hospital with weight measured at PMA of 36 wk	$N = 24$	$N = 215$	$N = 736$	$N = 976$	$N = 1106$	$N = 1231$	$N = 1204$	$N = 5492$
Growth failure at 36 wk[a,i]	92 (50–100)	91 (0–100)	85 (67–100)	83 (63–100)	79 (33–98)	76 (42–98)	73 (44–96)	79 (59–97)
Cranial ultrasonography performed within 28 d after birth	85 (50–100)	92 (67–100)	95 (87–100)	97 (85–100)	98 (92–100)	98 (94–100)	98 (90–100)	97 (93–100)
Sonogram findings within 28 d[a,j]	$N = 53$	$N = 454$	$N = 1163$	$N = 1385$	$N = 1499$	$N = 1781$	$N = 1925$	$N = 8260$
Normal	32 (0–100)	41 (13–74)	49 (14–70)	57 (30–84)	65 (36–90)	70 (50–83)	77 (50–91)	64 (43–79)
IVH grade 1	13 (0–40)	9 (0–50)	11 (0–43)	9 (0–17)	11 (0–23)	10 (5–24)	10 (0–32)	10 (5–23)
IVH grade 2	13 (0–50)	9 (0–25)	9 (0–29)	8 (2–19)	5 (0–14)	5 (0–14)	4 (0–25)	6 (2–12)
IVH grade 3	8 (0–33)	15 (0–47)	12 (5–20)	8 (0–15)	7 (0–14)	6 (0–15)	4 (0–10)	7 (3–13)
IVH grade 4	30 (0–67)	21 (0–50)	14 (0–33)	13 (3–36)	7 (0–31)	5 (1–17)	3 (0–15)	9 (4–23)
Ventriculomegaly, no IVH	4 (0–33)	3 (0–13)	3 (0–6)	3 (0–6)	2 (0–9)	2 (0–6)	1 (0–5)	2 (0–4)
PVL within 28 d[b,k]	6 (0–33)	4 (0–25)	3 (0–11)	4 (0–18)	3 (0–8)	2 (0–8)	2 (0–5)	3 (<1–6)
Infants born in 2006–2007	$N = 19$	$N = 174$	$N = 438$	$N = 547$	$N = 566$	$N = 728$	$N = 754$	$N = 3226$
PDA[a,l]	53 (0–100)	52 (13–100)	56 (0–100)	55 (20–100)	51 (12–100)	43 (0–80)	34 (0–63)	47 (23–78)
Ibuprofen therapy for PDA[l]	0 (0–0)	13 (0–64)	16 (0–50)	16 (0–60)	13 (0–64)	12 (0–44)	11 (0–60)	13 (0–52)
Infants in hospital at 28 d	$N = 11$	$N = 92$	$N = 320$	$N = 471$	$N = 508$	$N = 678$	$N = 718$	$N = 2798$
ROP examination performed[f,m]	91 (50–100)	91 (71–100)	92 (50–100)	94 (75–100)	95 (67–100)	96 (82–100)	93 (68–100)	94 (82–100)
ROP outcome at status[a,n]								
Determined, favorable in both eyes	10 (0–100)	27 (0–100)	28 (0–62)	31 (0–86)	38 (0–100)	46 (0–100)	46 (5–100)	39 (8–83)
Determined, severe ROP in either eye	30 (0–100)	30 (0–100)	21 (0–67)	11 (0–38)	5 (0–25)	3 (0–9)	<1 (0–9)	7 (0–20)
Undetermined ROP status in either eye (neither had severe ROP)	60 (0–100)	43 (0–100)	51 (0–82)	58 (14–100)	57 (0–100)	51 (0–100)	53 (0–95)	53 (8–88)

Ranges are across all participating NRN centers. Proportions are among all infants who survived >12 hours, except as noted. Information was missing as follows: patent ductus arteriosus, 4 infants; indomethacin therapy for patent ductus arteriosus, 38 infants; surgical treatment for patent ductus arteriosus, 2 infants; necrotizing enterocolitis, 1 infant; early-onset sepsis, 1 infant; meningitis, 1 infant; late-onset sepsis, 2 infants; ROP examination performed, 1 infant; ROP, 1 infant; ROP stage ≥3, 7 infants; intervention/surgical treatment for ROP, 32 infants. *P* values were determined with the Wald χ^2 test for differences according to GA, with adjustment for center and BW or, for early-onset sepsis, meningitis, and ibuprofen therapy for patent ductus arteriosus, with adjustment for BW only. PDA indicates patent ductus arteriosus; NEC, necrotizing enterocolitis.

[a] $P \leq .001$.

[b] $P \leq .01$.

[c] Proportions among infants who survived >3 days after birth.

[d] Proportions among infants with necrotizing enterocolitis.

[e] Proportions among infants with patent ductus arteriosus

[f] $P \leq .05$.

[g] Proportions among infants who were still in the hospital at 28 days of life.

[h] Proportions among infants who were still in the hospital at 28 days and underwent a ROP examination.

[i] Growth failure was defined as <10th percentile for gender at PMA of 36 weeks. Proportions were determined among infants who were alive and in the hospital at PMA of 36 weeks and who had weight measurements at PMA of 35 to 37 weeks. Among those in the hospital at 36 weeks, weight data were missing for 101 infants with other measurements taken at PMA of 36 weeks, weight was measured but not in the 35- to 37-week period for 21 infants, and growth failure could not be determined for 2 infants with missing gender information.

[j] From the sonogram with the most-severe findings. Proportions were determined among those who had sonograms performed within 28 days after birth. Categories shown are mutually exclusive. Some infants with IVH also had PVL, that is, 18 (2%) of 832 infants with grade 1 IVH, 21 (4%) of 506 infants with grade 2 IVH, 31 (5%) of 598 infants with grade 3 IVH, and 117 (16%) of 710 infants with grade 4 IVH. Ten (6%) of 173 infants with ventriculomegaly and no IVH also had PVL.

[k] Proportions indicate the proportions of infants with PVL overall, with and without IVH, among infants who had sonograms performed within 28 days after birth.

[l] Proportions were determined among infants born in 2006–2007. Ibuprofen treatment proportions are among infants who had patent ductus arteriosus. Information was missing as follows: patent ductus arteriosus, 1 infant; ibuprofen treatment, 1 infant.

[m] Proportions among infants born in 2006–2007 who were still in the hospital at 28 days of life. Information was missing for ROP examination for 1 infant.

[n] Proportions among infants born in 2006–2007 who were still in the hospital at 28 days and had ROP examinations performed. An assessment of ophthalmologic outcome at the time of status was made as follows: (1) favorable, defined as one of the following in each eye: vessels mature, vessels in zone III in 2 consecutive examinations, acute ROP of stage 1 or 2 in zone III in 2 consecutive examinations, or ROP in zone II or zone III but determined to be clearly regressing; (2) unfavorable, defined as severe ROP on the basis of one of the following in either eye: received surgical treatment for ROP, met criteria for undergoing surgery, or retinal detachment resulting from ROP; or (3) undetermined outcome, defined as one of the following in either eye: immature vessels in zone I or zone II, immature vessels reaching zone III in any single examination, stage 1 or 2 ROP in zone III at any single examination, stage 2 or 3 ROP in zone II or III not regressing, or active ROP in zone I or zone II. Data on outcome at status was missing for 13 infants

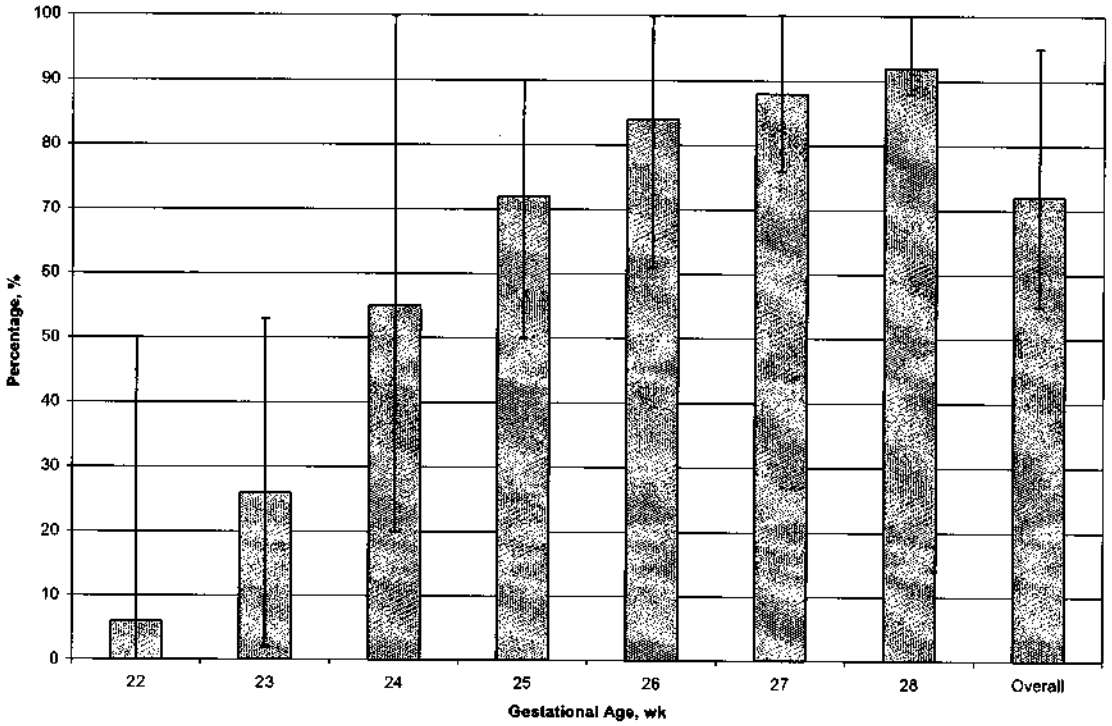
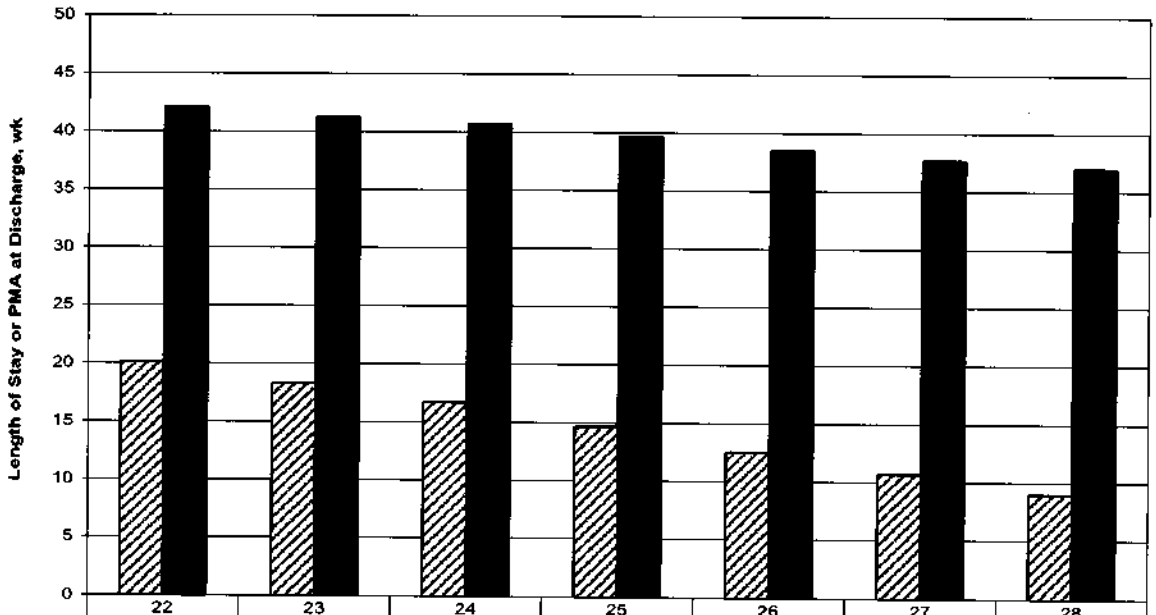


FIGURE 1
Survival to discharge according to GA among 9575 VLBW infants born in NICHD NRN centers between January 1, 2003, and December 31, 2007. The thin lines indicate ranges across centers.



	22	23	24	25	26	27	28
Length of stay	20.1	18.3	16.7	14.7	12.6	10.7	9.0
PMA at discharge	42.1	41.3	40.7	39.7	38.6	37.7	37.0

FIGURE 2
Median length of hospitalization (in weeks) and median PMA at discharge (in weeks) according to GA at birth among 6859 VLBW infants who were born in NICHD NRN centers between January 1, 2003, and December 31, 2007, and survived to discharge.

more-recent year of birth. With substantially increased use of CPAP therapy, it was surprising that overall rates of BPD were unchanged, although the adjusted RR for BPD decreased over the study period.

This is the first study to report ophthalmologic status as favorable, unfavorable, or undetermined at the time of the last in-hospital examination. Although 7% of all infants had severe ROP, the rate was 30% for infants with GAs of 22/23 weeks. Of concern, 53% of infants had undetermined ophthalmologic status at the last examination before discharge. This finding has implications for discharge planning and underscores the importance of a medical home, to ensure careful ophthalmologic follow-up monitoring of these vulnerable infants after discharge home or transport to a community hospital.

Although ours is not a population-based study, we included all extremely low gestation births at 20 academic centers across the United States that together represent >110 000 live births per year, an annual birth cohort equal in size to the Swedish national cohort described recently.[20] The rate of extremely low gestation birth was fivefold higher in our NRN cohort (~10 births at <27 weeks per 1000 infants) than in the Swedish cohort (2.3 births at <27 weeks per 1000 infants). This remarkable difference may be explained in part by Sweden's universal health insurance, with free prenatal care and associated social services, as well as an ethnically more homogeneous and somewhat older pregnant population. The high rates of prematurity in our cohort underscore the importance of the current health care debate in the United States. Survival rates for extremely low gestation infants born at NRN centers are lower than those reported from Sweden. For nearly all infants in the Swedish cohort, GA was estimated on the basis of ultrasound findings. The authors of the Swedish study noted that a limitation of the use of ultrasonography to determine GA is that erroneously low GAs might be estimated for infants with growth restriction. Given the decrease in mortality rates with increasing GA, underestimation of GA by as little as 1 week might explain in part the difference in mortality rates between the 2 cohorts. Greater use of prenatal steroid treatment at all GAs and of surfactant therapy at 22 to 23 weeks also might have contributed to differences between the 2 cohorts.

During the 5-year study period, there was no substantial improvement in rates of survival to discharge for extremely low gestation infants born at NRN centers. However, each additional week of GA at birth had substantial survival advantage; the most marked changes were between GAs of 22 and 25 weeks, with survival rates increasing from 6% to 72%. Furthermore, rates of survival to discharge without major morbidities increased dramatically between 22 and 25 weeks, with continued steady improvement for each additional week of gestation. PMA at discharge for VLBW infants, a proxy measure of length of stay and a reflection of the cost of care, was inversely related to GA at birth. Each additional week of GA at birth reduced PMA at discharge by almost 1 week and total length of hospital stay by ~2 weeks, a reflection of both severity of illness and complications of prematurity among these very immature infants. Although adjusted RRs for survival without morbidity increased over time, the burden of in-hospital complications remained high. Retrospective analyses of center differences and benchmarking studies to identify best performance have been unable to identify modifiable practices that consistently improve outcomes, which underscores the need for hypothesis-driven clinical trials to assess the efficacy of current neonatal interventions.[21–24] Clinicians and investigators are challenged to identify and to test currently available interventions and resources that yield consistently lower morbidity and mortality rates at some centers, so that we can improve rates of survival without major morbidities and reduce long-term neurodevelopmental impairments for all infants.

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(Continued from first page)

KEY WORDS
extremely low gestation, very low birth weight, morbidity, death

ABBREVIATIONS
VLBW—very low birth weight
BPD—bronchopulmonary dysplasia
BW—birth weight
CI—confidence interval
GA—gestational age
IVH—intraventricular hemorrhage
ROP—retinopathy of prematurity
RR—relative risk
NICHD—National Institute of Child Health and Human Development
NRN—Neonatal Research Network
CPAP—continuous positive airway pressure
PVL—periventricular leukomalacia
PMA—postmenstrual age

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Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network

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Subject:	SUPPORT Subcommittee Call to Review PAS Abstract - Availability Request
Date:	Thursday, May 22, 2014 11:55:52 AM
Attachments:	Aliaga - Prediction of retinopathy of prematurity in premature infants - ROP NRN proposal 5.15.14.docx

Dear all,

We need to set up a SUPPORT subcommittee call to review the attached abstract: Aliaga – Prediction of Retinopathy of Prematurity in Premature Infants.

Please provide your availability for the dates below on this Doodle poll (http://doodle.com/xqbxcyqq9r2ghgw2):

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Thanks,
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NICHD Neonatal Research Network Protocol Proposal

Title: Prediction of retinopathy of prematurity in premature infants

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A. Abstract

Retinopathy of prematurity (ROP) is a common morbidity in premature infants and is the leading cause of blindness in premature infants. Current predictive models estimate ROP risk primarily based on gestational age, birth weight, and postnatal growth. The development of a predictive model for ROP using prenatal and early postnatal risk factors will allow for individualized patient risk assessment early in postnatal life. Individualized risk assessment will inform provider decision-making regarding modification of exposure to risk factors (e.g., individualized oxygen saturation targets) and design of future trials (e.g. estimate baseline risk in trials).

B. Statement of the problem

ROP is a common morbidity in premature infants < 28 weeks' gestation and leads to lifelong morbidities, including blindness.[1] Approximately 60% of premature infants born at ≤ 28 weeks' gestation develop ROP.[2] The incidence of ROP increases with decreasing gestational age; at 25 weeks' gestation and lower the risk rises to > 80%.[2] Although there are on-going efforts to modify exposure to postnatal risk factors (e.g. days on mechanical ventilation, oxygen exposure, sepsis), ROP remains an important morbidity of premature birth. Randomized controlled trials (RCTs) provide high-level evidence regarding the effectiveness of an intervention at a group level. However, treatment effects (and harm) may differ based on individual patient characteristics. Given emerging evidence on prevention and treatment of ROP, with targeting lower oxygen saturation goals in the neonatal intensive care unit (NICU) decreasing the risk of ROP[3,4] and new treatments such as bevacizumab[5], a predictive model for ROP applied early in postnatal life will help guide individual patient treatment strategies. The development of a predictive model for ROP is a necessary step in the development of a clinical prediction guide. Subsequent model development, which incorporates risks of benefit and harm of interventions, will aid in analyses of existing data and planning prospective clinical trials that will lead to individualized treatment recommendations.

C. Hypotheses

Hypothesis 1: Using predictors available in the NRN Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) database we will be able to predict the risk of severe ROP in survivors on postnatal days 1, 7, 14, and 28. The width of the 95% confidence interval will be < 10%. A parsimonious model with < 8 clinically available predictors including postnatal day will result in a prediction model with area under the receiver operating characteristic (ROC) curve of 0.85 (95% CI; 0.80 – 0.90).

Hypothesis 2: We will successfully validate a predictive model for severe ROP using the SUPPORT database.

D. Specific Aims

Specific Aim 1: Develop early postnatal age predictive models for severe ROP. Using data from the NRN SUPPORT database, we will develop models to predict severe ROP in survivors on postnatal days 1, 7, 14, and 28.

We will examine maternal and neonatal risk factors for ROP based on previously published data, including: exposure to antenatal steroids, pregnancy associated hypertension, chorioamnionitis, gestational age, birth weight, sex, small for gestational age, multiple gestation, respiratory support, postnatal growth, and early and late onset sepsis/meningitis.

Specific Aim 2: Validate the predictive model for severe ROP described in Aim 1.

We will internally validate the predictive model of ROP. For internal validation, we will divide the cohort from the NRN SUPPORT Database into 2/3 model development and 1/3 testing cohorts.

E. Rationale/Justification

The rational for this proposal is to develop a predictive model of ROP that will serve to create a clinical prediction guide for individual assessment of ROP risk. This model will be a critical component to estimate the size of treatment benefit of a given intervention (i.e., is the benefit enough to justify the risk of harm?). The size of treatment benefit, or the patient's clinically important difference, will help guide individualized treatment recommendations early in postnatal life.[6] Using clinical prediction guides might provide individualized treatment recommendations based balancing risk of benefit (e.g. 48% decrease in severe ROP[3]) with risk of harm (e.g. 27% increase in mortality[3]) of a given intervention (e.g. oxygen saturation target of 85 – 89%).[6]

F. Background/Previous Studies

ROP is a common morbidity of preterm birth. ROP most often occurs in infants ≤ 28 weeks' gestation. Severe ROP often leads to long-term visual impairment, including blindness in ~ 10% of those with most severe ROP.[1,7,8] In the US, any stage of ROP is found in 59% of premature infants ≤ 28 weeks' gestation, with severe ROP in 16%.[2]

The pathophysiology of ROP involves the interruption of normal retinal development, subsequently leading to abnormal vascularization of the retina.[1,7] The development of ROP consists of two postnatal phases: cessation of retinal vessel growth and retinal neovascularization. The two phases of ROP are driven by preterm birth and the postnatal exposure of the developing retina to harmful factors (e.g. oxygen, inflammation).[1]

Gestational age, small for gestational age status, and time on supplemental oxygen are strong clinical risk factors for ROP (Neonatal Research Network Data, Gantz et al., in preparation). Routine screening in the US is recommended for all premature infants ≤ 30 weeks' gestation or ≤ 1500 g birth weight.[9] Current guidelines recommend that ROP screening begin at 31 weeks post-menstrual age for infants < 28 weeks' gestational age at birth. NRN SUPPORT data corroborates these guidelines.[10] The risk of severe ROP increases exponentially for each decreasing week of gestational age. Other consistently reported major risk factors for ROP include oxygen exposure, poor postnatal growth, hyperglycemia, and sepsis.[3,11-17] Screening for ROP does not begin until 4 to 6 weeks after birth and disease severe enough to require treatment usually does not occur until closer to term corrected gestational age. Therefore, there is a wide window of opportunity for preventive interventions in those infants at greatest risk for the disease.

Current predictive models for ROP aid in screening recommendations and incorporate postnatal data (e.g. gestational age, birth weight, postnatal growth) to examine ROP risk.[18-21] Researchers have examined the ability of models of illness severity to predict ROP (e.g. CRIB score, SNAPPE-II).[22-26] However, these are mostly international single center studies and are limited by small sample size and varying definitions of ROP outcomes (e.g. ROP in survivors, ROP warranting surgery). Other studies have focused on predicting disease progression in infants already diagnosed with ROP.[27,28] ROP predictive models that incorporate prenatal and early postnatal risk factors are lacking. Previous studies have focused on determining risk factors for ROP and do not focus on predicting individual-level ROP risk. Predictive models have not been developed or tested in their ability to contribute to individualized treatment recommendations (e.g. oxygen saturation targets at birth) in order to modify the development ROP in a given infant.

G. Methods/Procedures

i) Description of study design: This is a retrospective study of infants enrolled in the NRN SUPPORT Study.

ii) Definition of study population: We will include data from infants enrolled in the NRN SUPPORT Study (24 – 27 6/7th weeks' gestation) for the development and testing cohorts for internal validation.

iii) Description of study intervention: N/A

iv) Precise definition of outcomes: The primary outcome is risk of severe ROP in survivors on postnatal day 1, 7, 14, and 28. Infants who die prior to that day's model will not be included. Severe ROP is defined as any of the

following in any eye: ≥ Stage 3 ROP, plus disease with any stage, ophthalmologic surgery, or use of bevacizumab for retinopathy.

v) Statistical analysis plan: We will outline a set of *a priori* risk factors for inclusion in each postnatal day model based on their known association with the outcomes of ROP or death (see Table 1 below). We will develop a series of logistic regression models for each postnatal day (1, 7, 14, and 28) using stepwise forward selection or other regression models as appropriate.

Table 1. Predictors of ROP for model development

Predictor	Severe ROP	
	Day 1	*Subsequent days*
Maternal age	X	X
Gestational age at birth	X	X
Birth weight	X	X
Small for gestational age	X	X
Sex	X	X
Race/ethnicity	X	X
Multiple gestation	X	X
Maternal hypertensive disorder pregnancy	X	X
Chorioamnionitis	X	X
Surfactant use	X	X
Antenatal corticosteroids	X	X
1 min Apgar score	X	X
5 min Apgar score	X	X
Sepsis/meningitis	X	X
Level of respiratory support	X	X
SUPPORT saturation target	X	X
Highest FiO2	X	X
Time on supplemental oxygen	X	X
NEC		X
BPD		X
Postnatal corticosteroids for BPD		X
IVH grade 3 - 4	X	X
Postnatal growth (day 28)		X

vi) Sample size estimate based upon primary outcome: The SUPPORT Study enrolled 1316 infants born between 24 0/7th and 27 6/7th weeks of gestation. The incidence of severe ROP in survivors was 13%.[8] The sample size of the SUPPORT Database is such that the precision of a 95% confidence interval is no wider than 2%.

vii) Available population/compatibility with ongoing protocols: Since this proposal is for a retrospective study, there is no conflict with ongoing protocols.

viii) Estimate of projected recruitment time: N/A.

H. Risks/Benefits, with estimate of frequency/severity of risks: None

I. Budget estimate: RTI statistical support.

J. Future directions:

Subsequent work will include the development of a clinical prediction guide for risk of harm in the management of ROP (e.g. mortality if exposed to lower oxygen saturation target). The development of a clinical prediction guides for ROP is an important step toward developing a model for individualized treatment recommendations based on input regarding risk of benefit(s), risk of harm(s) of a given intervention, as well as incorporating individual patient/family values.

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27. Hardy RJ, Palmer EA, Dobson V, et al. Risk analysis of prethreshold retinopathy of prematurity. *Archives of ophthalmology.* Dec 2003;121(12):1697-1701.
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From: Gabrio, Jenna
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT PAS Abstract
Date: Thursday, May 22, 2014 11:33:33 AM

Hi Rose,

I believe there is only one Abstract for the SUPPORT committee to review: Aliaga – Prediction of retinopathy of prematurity in premature infants. I don't believe we have a call set up for this yet. Should we go ahead and set one up? Or can they review by email?

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
202-728-1946

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Childress, Kerri (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: Re: Topics Symposium in Ethics in Research Saturday May 3rd 2:45 to 4:45 PM
Date: Friday, May 02, 2014 10:00:43 AM

Sure, nice to know what (b)(5)

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

> On May 2, 2014, at 9:51 AM, "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov> wrote:
>
> Good enough, however (b)(5) Working with Rose now on a couple TPs and will give a heads up to OD, just in case.
>
> -----Original Message-----
> From: Guttmacher, Alan (NIH/NICHD) [E]
> Sent: Friday, May 02, 2014 9:49 AM
> To: Higgins, Rosemary (NIH/NICHD) [E]
> Cc: Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
> Subject: Re: Topics Symposium in Ethics in Research Saturday May 3rd 2:45 to 4:45 PM
>
> I do not think (b)(5)
(b)(5)
>
> Alan E. Guttmacher, M.D.
> Director
> Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health
>
>> On May 2, 2014, at 9:31 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:
>>
>> FYI
>>
>> Rosemary D. Higgins, MD
>> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal
>> Research Network Pregnancy and Perinatology Branch 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: Childress, Kerri (NIH/NICHD) [E]
>> Sent: Friday, May 02, 2014 9:26 AM

>> To: Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E];
>> Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E];
>> Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bock,
>> Robert (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]
>> Cc: Rowe, Mona (NIH/NICHD) [E]
>> Subject: RE: Topics Symposium in Ethics in Research Saturday May 3rd
>> 2:45 to 4:45 PM
>>
>> You are aware (b)(5)

(b)(5)

(b)(5) Some of my other concerns, although there are many:
>>
>> Tuskegee and the press -- a bullfighter? Not sure I understand the symbolism.
>>
>> They fooled the NY Times? Really, he is going to say this in public? You don't think the NY Times will have something to say about this?
>>
>> NIH Criticizes OHRP -- Again, in public?
>>
>> Conspiracy theories??
>>
>> We can address these issues in a way that will (b)(5) These slides are talking about an issue that falls on our plate and (b)(5) would think. (b)(5) Just let me know.
>>
>> Kerri
>>
>> -----Original Message-----
>> From: Higgins, Rosemary (NIH/NICHD) [E]
>> Sent: Friday, May 02, 2014 8:47 AM
>> To: Raju, Tonse (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E];
>> Spong, Catherine (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Devaney,
>> Stephanie (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]; Childress, Kerri
>> (NIH/NICHD) [E]
>> Subject: FW: Topics Symposium in Ethics in Research Saturday May 3rd
>> 2:45 to 4:45 PM
>>
>> Hi
>> This will be presented tomorrow at PAS in Vancouver
>>
>> Rose
>>
>> Rosemary D. Higgins, MD
>> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal
>> Research Network Pregnancy and Perinatology Branch 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: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
>> Sent: Friday, May 02, 2014 8:34 AM
>> To: Higgins, Rosemary (NIH/NICHD) [E]
>> Subject: FW: Topics Symposium in Ethics in Research Saturday May 3rd
>> 2:45 to 4:45 PM
>>
>> Rose
>> John Lantos Slides for Ethics talk tomorrow that I am Chairing with
>> Carl Seetha
>>
>> _____
>> From: Lantos, John [jlantos@cmh.edu]
>> Sent: Friday, May 02, 2014 7:06 AM
>> To: Robin Steinhorn; Shankaran, Seetha
>> Cc: Fanaroff, Jonathan; carl_dangio@urmc.rochester.edu; Alan
>> Fleischman
>> Subject: RE: Topics Symposium in Ethics in Research Saturday May 3rd
>> 2:45 to 4:45 PM
>>
>> Here are my slides. This should all fit together well. I will argue that the controversy over SUPPORT was generated by clever use of traditional media by Public Citizen and was NOT a phenomenon of social media. I'll suggest that getting an article and an editorial in the New York TImes about something still counts more that a lot of Facebook postings and tweets and that it, in fact, drives the Facebook posting and tweets. It also leads to NPR and AP picking up the story. Only a few newspapers (or websites) actually do any original investigative reporting anymore. Those that do, do it badly. So a good and clever Public Relations effort can lead even the best newspapers down the garden path.
>>
>> Focus on social media may distract us.
>>
>> I assume that we should just bring our slides on a stick, yes?
>>
>> John
>> John D. Lantos
>> Children's Mercy Hospital
>> 2401 Gillham Road, KCMO 64108
>> 816-701-5283
>> jlantos@cmh.edu
>>
>> Asst: Mary Ellen Hudson: mhudson@cmh.edu
>>
>> Are you interested in an on-line certificate program in Pediatric Bioethics?
>> Visit the the CMH Bioethics Center web page: http://www.childrensmercy.org/cmbc.
>> We are now accepting applications for 2014-15.
>> _____
>> From: Robin Steinhorn [rsteinhorn@ucdavis.edu]
>> Sent: Thursday, May 01, 2014 21:37
>> To: Shankaran, Seetha
>> Cc: Fanaroff, Jonathan; carl_dangio@urmc.rochester.edu; Alan
>> Fleischman; Lantos, John
>> Subject: Re: Topics Symposium in Ethics in Research Saturday May 3rd
>> 2:45 to 4:45 PM
>>
>> Hi Seetha,
>>
>> Here are my slides, let me know if there is something else you want me to address. I am very excited about this session!

>>
>> Robin
>>
>> 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.
>>
>> _____
>>
>> This document may include proprietary and confidential information of Wayne State University Physician Group and may only be read by those person(s) to whom it is addressed. If you have received this e-mail message in error, please notify us immediately. This document may not be reproduced, copied, distributed, published, modified or furnished to third parties, without prior written consent of Wayne State University Physician Group. Thank you.
>> <FW: Topics Symposium in Ethics in Research Saturday May 3rd 2:45 to
>> 4:45 PM.eml>

From:	Higgins, Rosemary (NIH/NICHD) [E]
To:	Rowe, Mona (NIH/NICHD) [E]
Subject:	FW: Final Support Internal QA April 18 3
Date:	Friday, May 02, 2014 9:56:59 AM
Attachments:	Final Support Internal QA April 18 3.docx

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 02, 2014 9:44 AM
To: Childress, Kerri (NIH/NICHD) [E]
Subject: Final Support Internal QA April 18 3

Kerri
Here is what we have

My cell (works in the US) – (b)(6)
NIH IPHone – 301-905-6112 – will work in Canada once I get there.

I am leaving on a 250 PM flight this afternoon. I have a layover in Denver from 645-930 PM ET and arrive after midnight ET in Vancouver.

Thanks
Rose

Page 0080 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0081 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0082 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Topics Symposium in Ethics in Research Saturday May 3rd 2:45 to 4:45 PM
Date: Friday, May 02, 2014 8:34:46 AM
Attachments: PAS2014 - Media - social and antisocial.pptx

Rose
John Lantos Slides for Ethics talk tomorrow that I am Chairing with Carl
Seetha

From: Lantos, John [jlantos@cmh.edu]
Sent: Friday, May 02, 2014 7:06 AM
To: Robin Steinhorn; Shankaran, Seetha
Cc: Fanaroff, Jonathan; carl_dangio@urmc.rochester.edu; Alan Fleischman
Subject: RE: Topics Symposium in Ethics in Research Saturday May 3rd 2:45 to 4:45 PM

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Focus on social media may distract us.

I assume that we should just bring our slides on a stick, yes?

John
John D. Lantos
Children's Mercy Hospital
2401 Gillham Road, KCMO 64108
816-701-5283
jlantos@cmh.edu

Asst: Mary Ellen Hudson: mhudson@cmh.edu

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We are now accepting applications for 2014-15.

From: Robin Steinhorn [rsteinhorn@ucdavis.edu]
Sent: Thursday, May 01, 2014 21:37
To: Shankaran, Seetha
Cc: Fanaroff, Jonathan; carl_dangio@urmc.rochester.edu; Alan Fleischman; Lantos, John
Subject: Re: Topics Symposium in Ethics in Research Saturday May 3rd 2:45 to 4:45 PM

Hi Seetha,

Here are my slides, let me know if there is something else you want me to address. I am very excited about this session!

Robin

Social and Anti-Social Media in the SUPPORT controversy

John D. Lantos M.D.
Children's Mercy Bioethics Center
Children's Mercy Hospital
Kansas City, MO

BEST CHILDREN'S HOSPITALS U.S.News 2013-14

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

Bioethics Center
CHILDREN'S MERCY KANSAS CITY

Two controversies over SUPPORT

- OHRP criticisms: mild, not newsworthy.
- Would have been forgotten.
- Controversy began when "Public Citizen" waged a brilliant media campaign to reshape the story.

What did OHRP say?

- "The IRB approved informed consent documents for this study failed to include…a description of any reasonably foreseeable risks and discomforts."
    - OHRP letter to UAB, March 7, 2013

Bioethics Center

What did they ask?

- "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)."

Bioethics Center

What did Public Citizen say?

- The study should never have been done
- We already knew the results
- Consent forms inadequate
- Babies were killed, blinded, and maimed
- Investigation crushed by political pressure

Public Citizen goes to war

- "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)."
- SUPPORT "highly unethical." "Exposed 1,316 extremely premature infants to increased risks of either death or retinal damage."

– April 10, Public Citizen letter to HHS Sec'y Sebelius

Public Citizen allegations

- The study could expose babies to:
  - increased risk of brain injury.
  - increased risk of retinopathy and/or blindness.
  - increased risk of death.
- Doctors individualized clinical decisions would have resulted in better outcomes than doctors following the study protocol.
  - http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6357&blogid=140#ixzz2pMzHA1uZ

Bioethics Center

In fact…

- No increase in brain injury
- Less retinopathy, no blindness
- Decreased mortality
- Neonatologists didn't individualize oxygen therapy, all followed protocols.

Bioethics Center

What did experts in neonatology say?

When I institute treatment according to a protocol, it is because that protocol is consistent with my fiduciary obligation to provide optimal treatment. Treatment under another different protocol could also be consistent with those obligations.

If I am unsure which is better, then using either protocol is consistent with my obligations to my patients.

- Barrington, AJOB, 2013

Individualized care?

Some centers do not have a protocol. In these there may be great variability between doctors. You could call this "individualized care" but, in reality, it is haphazard variation in practice, which is due to a lack of good data.

- Barrington, AJOB 2013

So how did PC "sell" it?

Bioethics Center

They played the Tuskegee card

- Asked Sec'y Sibelius to write a personal apology to all parents of study babies.
- Clever, deliberate invocation of Tuskegee and the apology by Pres. Clinton.

The United States government did something that was wrong -- deeply, profoundly, morally wrong. The American people are sorry -- for the loss, for the years of hurt. I apologize and I am sorry that this apology has been so long in coming.

President Bill Clinton and Herman Shaw, age 95, one of the men who was in the Tuskegee syphilis study, May 16, 1997.

Tuskegee and the press

Bioethics Center

They fooled the NY Times

The New York Times

April 10, 2013

Study of Babies Did Not Disclose Risks, U.S. Finds

By SABRINA TAVERNISE

A federal agency has found that a number of prestigious universities failed to tell more than a thousand families in a government-financed study of oxygen levels for extremely premature babies that the risks could include increased chances of blindness or death.

None of the families have yet been notified of the findings from the Office for Human Research Protections, which safeguards people who participate in government-financed research. But the agency's conclusions were listed in great detail in a letter last month to the University of Alabama at Birmingham, the lead site in the study. In all, 23 academic institutions took part, including Stanford, Duke and Yale.

Tavernise's facebook page

"I'm looking for families who participated in a study on the effects of oxygen levels on premature babies. If you are interested in sharing your story, please leave a comment below."

-April 10, 2013

https://www.facebook.com/nytimesscience/posts/127620190763854

Some parents responded

- "I am the parent of a VLBW boy born is 2002 and probably not in this study. The 'state of the art' at the time was not fact based. I am glad for this study even with its problems. This study may allow future preemie parents to have some facts to back up a choice that may leave their child blind."
    - -mcgerm, USA. NYT reader comments

Some parents responded

"My nearly 4 yo was involved in this study-he was in the low oxygen group. He lived, has sight but has significant neurological impairment. We tried to beg off the study (the alarms associated with it were *extremely* grating) but each time a researcher reminded us of the importance of the data. I feel kind of sick after reading this."

- Katie, Cincinnati.

Note:

- In low oxygen arm
- He lived (mortality higher in low O2 arm)
- He has sight (probably because he was in the low O2 arm)
- And is neurologically impaired (no difference between arms, lower overall)

Note:

- Tevernise never wrote a follow-up article
  - No parents
  - No report on the NEJM or NIH response
  - Nothing on the retraction by OHRP
  - Nothing on the HHS public meeting
- Shameful journalistic ethics

The New York Times

April 15, 2013

An Ethical Breakdown

By THE EDITORIAL BOARD

Despite reforms to protect patients from being harmed by medical research in recent decades, 23 academic institutions authorized a research project that failed to meet the most basic standard: providing an informed consent document to parents that accurately described the risks and benefits of the research to be conducted on extremely premature babies.

Then it got worse

A lead editorial in the *New York Times* echoed Public Citizen's concerns and called the failure to disclose risks "startling and deplorable."

– The Editorial Board of the New York Times. An Ethical Breakdown. April 15, 2013

Bioethics Center

NEJM fires back

- Informed consent document spelled out the risks and benefits "clearly and succinctly."
- Consent form "addressed the prevalent knowledge fairly and reasonably."
- "OHRP investigation cast a pall over the conduct of clinical research to answer important questions in daily practice."
    - April 18, 2013; NEJM

NIH criticizes OHRP

- "The babies included in SUPPORT were, of course, facing substantial risks because of prematurity… but their care was never compromised for the sake of the study."

  – Hudson, Guttmacher, Collins, In Support of SUPPORT — A View from the NIH. NEJM, 2013

Led to OHRP retraction

- "OHRP has become aware of widespread misunderstanding about the risks that are required to be disclosed in order to obtain informed consent."
- "We have put on hold all compliance actions against UAB relating to the SUPPORT case."
- "We will conduct an open public meeting…"
  - OHRP letter to UAB, June 5, 2013

Public Citizen's interpretation?

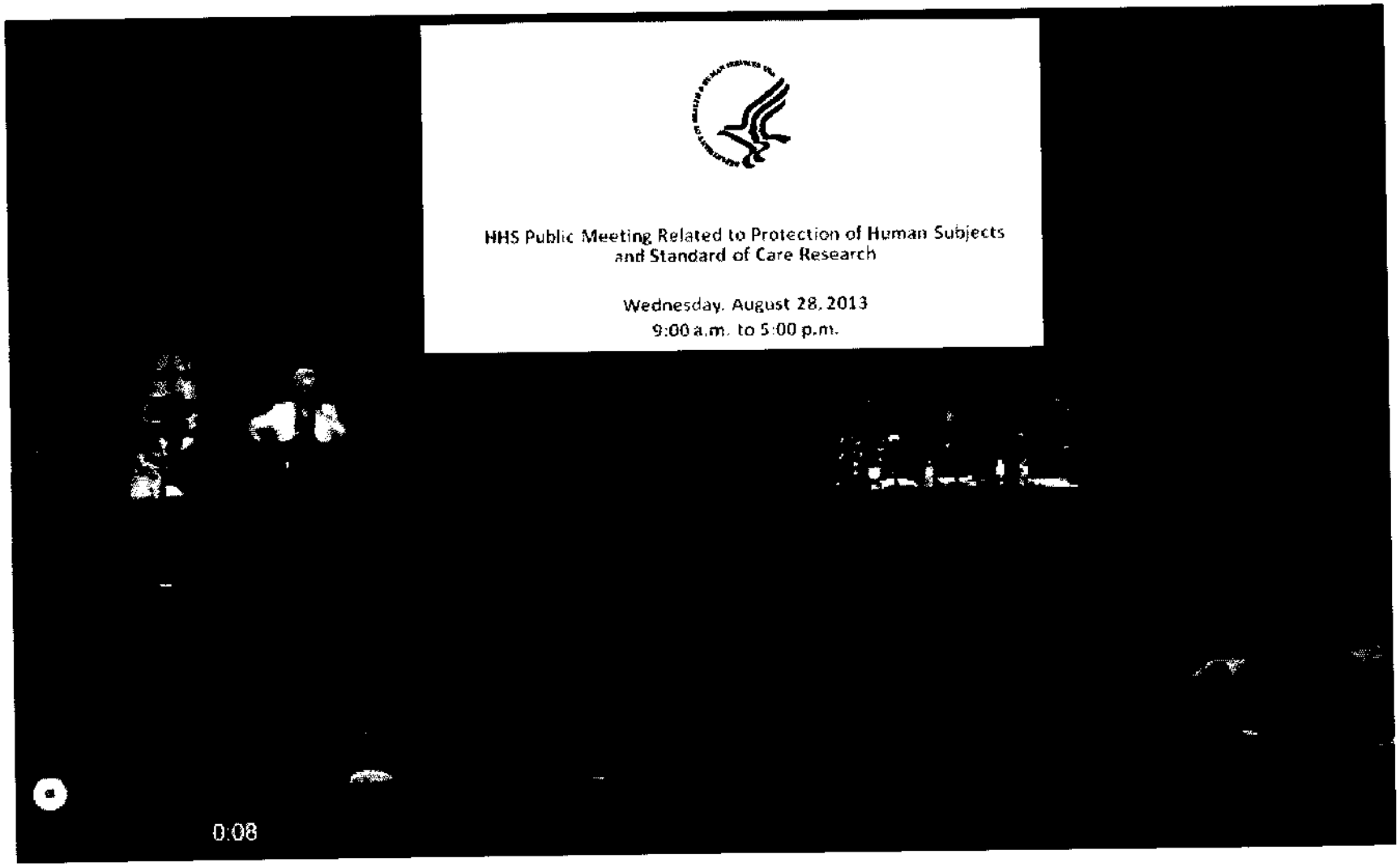
The Office for Human Research Protections bows to political pressure and puts enforcement actions on hold.

-June 5, 2013, Public Citizen

This became the new "trope"

- The medical-industrial complex is trying to suppress the truth and to continue to harm babies for their own nefarious ends.

Public meeting at HHS



Conspiracy theories

- "Soon after OHRP's findings regarding SUPPORT came to public attention a group of individuals within the medical research establishment launched a well orchestrated attack against OHRP in defense of the SUPPORT study."
    - Carome, HHS Open meeting

Note

- No names
- No evidence
- No rationale

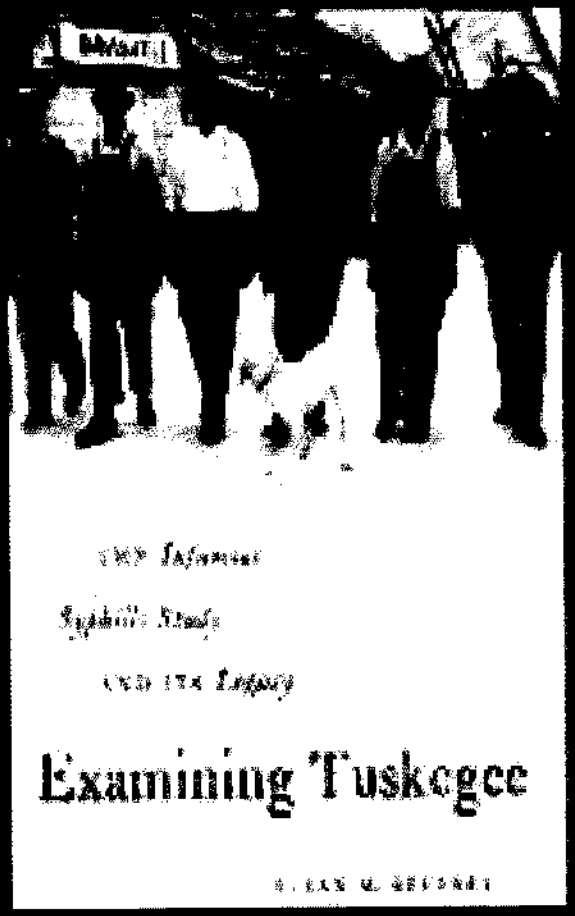
Tuskegee at HHS meeting

- Alice Drefer opened her remarks thus:

  "These remarks are jointly authored by Susan M. Reverby...I expect you are familiar with her work including her award winning books on the Tuskegee Syphilis Study…."

  – Alice Dreger, comments at HHS Public Meeting

Susan M. Reverby, PhD
Marion Butler McLean Professor
Wellesley College



Refs to Tuskegee

- "Although we are not saying that the SUPPORT study is akin to the Tuskegee study, and we would discourage over-using the Tuskegee Study as a metaphor, we should understand that the Tuskegee study was in many ways understood to be a kind of standard of care research…"

  – Alice Dreger, Northwestern U, at HHS Public Meeting

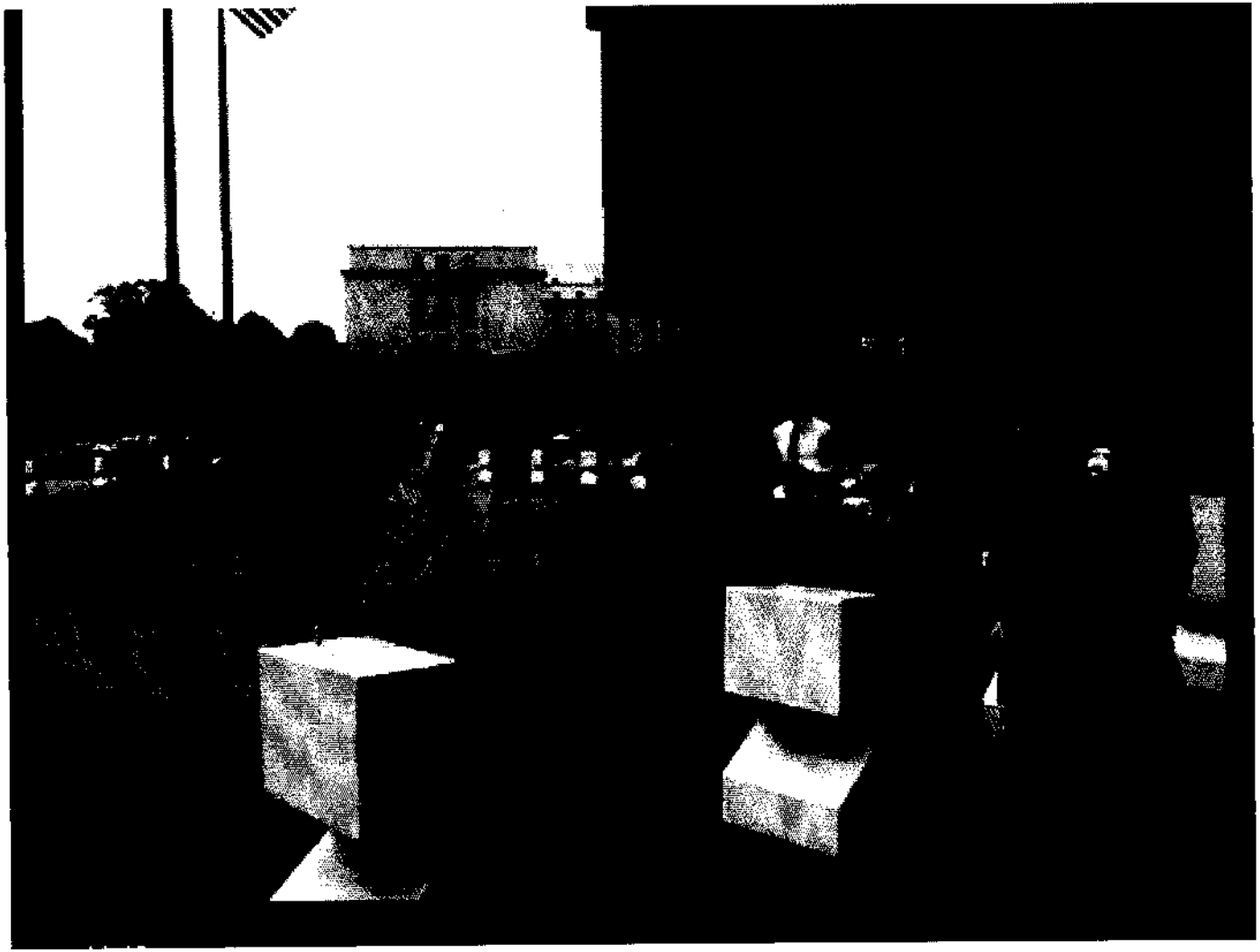
Michael Carome slightly more subtle

Human Subjects Protections at a Crossroads

- The history of human experimentation over the past century is filled with victims of unethical research conducted without adequate informed consent.
- Prior revelations of unethical research ultimately led to strengthening of human subjects protections. The opposite may occur in the wake of the SUPPORT study disclosures.

Manipulating the media

- Press conference on the steps of HHS.
- Didn't get a permit permit.
- 150th anniversary of "I have a dream."
- Obama was speaking at Lincoln Memorial.
- Security was tight all over town.



The story that got missed

- How did Public Citizen find out?
- Dr. Carome had been at OHRP?
- Was this all carefully planned for years?
- Did he take the government documents
- Conflicts of interest? Will they make money from a lawsuit against UAB?

Board of Directors: Public Citizen

- Mark Chavez, JD, Stanford Public Interest Law Foundation.
- Jason Adkins JD has actively investigated and litigated major class action cases on behalf of consumers.
- Robert C. Fellmeth JD, Center for Public Interest Law at UCSD.
- Andrew S. Friedman, JD, devoted primarily to litigation of major class action cases.
- Joy Howell, Cambridge Strategic Partners, a public affairs and public relations consulting firm.

Who Supports Public Citizen?

- Hard to know
- They demand that politicians disclose all their donations….

www.citizen.org

Disclosure Eclipse

Nearly Half of Outside Groups Kept Donors Secret in 2010; Top 10 Groups Revealed Sources of Only One in Four Dollars Spent

November 18, 2010

Who Supports Public Citizen?

- Hard to know
- They demand that politicians disclose all their donations….
- But they don't reveal their own donors!

Public Citizen's Form 990

Name of organization: PUBLIC CITIZEN FOUNDATION, INC

Employer identification number: 52-1263996

Part I Contributors (see instructions). Use duplicate copies of Part I if additional space is needed.

(a) No.	(b) Name, address, and ZIP + 4	(c) Total contributions	(d) Type of contribution
1		$ 300,000.	Person [X] Payroll [ ] Noncash [ ] (Complete Part II if there is a noncash contribution.)
2		$ 750,000.	Person [X] Payroll [ ] Noncash [ ] (Complete Part II if there is a noncash contribution.)
3		$ 400,000.	Person [X] Payroll [ ] Noncash [ ] (Complete Part II if there is a noncash contribution.)
4		$ 250,000.	Person [X] Payroll [ ] Noncash [ ] (Complete Part II if there is a noncash contribution.)

Conclusions

- Controversy created by Public Citizen
- Masters of public relations
- Motives unclear, probably self-serving
- Conflicts of interest undisclosed.

Bigger battles ahead

- Class action lawsuit led by anti-research crusader Alan Milstein, currently suing
  - Fred Hutchinson Cancer Research Center
  - Ohio State, over a neurology study
  - University of Oklahoma
  - UCLA over a study of anti-psychotics
    - Philadelphia Inquirer, May 20, 2002

Alan Milstein

- Milstein has become something of a human-research historian, lecturer and gadfly. He decries "trivial" trials of redundant drugs, researchers with financial conflicts of interest, and the "myth" that patients give informed consent.
    - Philly.com, May 20, 2002

Milstein on Informed Consent

- There is a real "disconnect" between what the researchers tell the subjects, what the subject understands, and what the document says.

Bioethics Center

Milstein on Informed Consent

- "Suppose the document said: "This is a human experiment. We want you to be a human guinea pig. You are to have no rights and no say. We are using your body to see if this drug works.""
    - Parkinson Pipeline Project, Attorney Alan Milstein: Breaking Ground in Medical Research Law. http://www.pdpipeline.org/2011/GDNF/gdnf_GRC_milstein.htm

Stay Tuned

The lawsuit is going forward. The media circus is about to begin!

Bioethics Center

From:	Archer, Stephanie (NIH/NICHD) [E]
To:	"Zaterka-Baxter, Kristin"
Cc:	"Michele C. Walsh (mcw3@cwru.edu)"; Julie Di Fiore (jmd3@case.edu); Higgins, Rosemary (NIH/NICHD) [E]
Subject:	RE: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality
Date:	Monday, April 28, 2014 4:18:35 PM

Yes, this passed via email vote March 26th.

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, April 28, 2014 3:58 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: 'Michele C. Walsh (mcw3@cwru.edu)'; Julie Di Fiore (jmd3@case.edu); Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality

HI Stephanie,

I see Roses email addresses the Support SubC but when Michele talked about last month's call, I assume she might have meant the SC because we have not had a Support call in quite some time. These revised were requested in Feb of 2014 with Roses email being sent March 2014 (modified proposal attached and Roses email). DO you have anything later than Jan that I may have missed?

Thanks
KRIS

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Monday, April 28, 2014 3:47 PM
To: Zaterka-Baxter, Kristin
Cc: 'Michele C. Walsh (mcw3@cwru.edu)'; Julie Di Fiore (jmd3@case.edu); Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT SECONDARY REQUEST -Specific Aims IH and mortality

Hi Kris,

This was a SUPPORT vote, not an SC vote, from January. The subcommittee approved it.

Stephanie

Stephanie Wilson Archer
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 09, 2013 11:29 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; bpoindex@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); 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 (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:	Luc Brion
To:	Gantz, Marie; Luc Brion; Myra Wyckoff; Mambarambath Jaleel; Das, Abhik; "doctorlevan@gmail.com"; Roy Heyne; Wrage, Lisa Ann; "Pablo.Sanchez@nationwidechildrens.org"; "nfiner@ucsd.edu"; "Wally Carlo (WCarlo@peds.uab.edu)"; Higgins, Rosemary (NIH/NICHD) [E]; "Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)"
Subject:	FW: Archives of Disease in Childhood - Manuscript ID fetalneonatal-2014-306057.R1
Date:	Saturday, April 19, 2014 12:22:10 AM
Attachments:	s1-in1721100411469633 29-1939656818Hwf-1766607715IdV752126477172110 04PDF_HI0001.pdf

Dear Colleagues:
Thanks a lot for all the comments and suggestions.
I attach the manuscript that was submitted to ADC.
Best regards
Luc

Luc P. Brion, MD
Professor of Pediatrics
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-----Original Message-----
From: onbehalfof+info.adc+bmj.com@manuscriptcentral.com [mailto:onbehalfof+info.adc+bmj.com@manuscriptcentral.com] On Behalf Of info.adc@bmj.com
Sent: Friday, April 18, 2014 11:19 PM
To: Luc Brion
Subject: Archives of Disease in Childhood - Manuscript ID fetalneonatal-2014-306057.R1

19-Apr-2014

Dear Dr. Brion,

Your revised manuscript entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" has been successfully submitted online and is presently being given full consideration for publication in Archives of Disease in Childhood.

Your manuscript ID is fetalneonatal-2014-306057.R1.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at http://mc.manuscriptcentral.com/adc and edit your user information as appropriate.

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Thank you for submitting your manuscript to Archives of Disease in Childhood.

Best wishes,

Joyce Salazar
Archives of Disease in Childhood Editorial Office

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DISEASE IN CHILDHOOD

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Journal:	*Archives of Disease in Childhood*
Manuscript ID:	fetalneonatal-2014-306057.R1
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Complete List of Authors:	LeVan, Jaclyn; Pediatrix Medical Group, Pediatrics Brion, Luc; University of Texas Southwestern Medical Center, Pediatrics Wrage, Lisa; Research Triangle Institute, Social, Statistical and Environmental Sciences Unit, RTI International, Gantz, Marie; Research Triangle Institute, Social, Statistical and Environmental Sciences Unit, RTI International, Wyckoff, Myra; University of Texas Southwestern Medical Center, Pediatrics Sanchez, Pablo; The Ohio State University - Nationwide Children's Hospital, Pediatrics Heyne, Roy; University of Texas Southwestern Medical Center, Pediatrics Jaleel, Mambarambath; University of Texas Southwestern Medical Center, Pediatrics Finer, Neil; University of California, Pediatrics Carlo, Waldemar; , University of Alabama at Birmingham, Pediatrics Das, Abhik; Research Triangle Institute, Social, Statistical and Environmental Sciences Unit, RTI International, Stoll, Barbara; 7Emory University School of Medicine, Pediatrics Higgins, Rose; Eunice Kennedy Shriver National Institute of Child, Health and Human Development,, NICHD
Keywords:	Neonatology, Respiratory, Clinical Procedures, Data Collection

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 240 words
Article length: 1,997 words
Revised 4/18/14
FetalNeonatal-2014-306057.R1

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) decreased in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA, excluding infants with syndromes or major malformations and those on comfort care only

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, p <0.0001) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusion: This study shows that DR ETI changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized controlled trial (RCT), in which preterm infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets [1,2] From 2005 through 2009, 1316 infants were enrolled in 20 centers.[1,2] The results of SUPPORT were released to NRN centers in December 2009.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1]

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI and the GA range that would be most appropriate for SUPPORT.[3]

A previous study in one NRN center that had not participated in the feasibility trial demonstrated that the proportion of DR ETI changed among eligible but nonenrolled neonates of $24^{0/7}$ to $27^{6/7}$ weeks and noneligible neonates of $28^{0/7}$ to $34^{6/7}$ weeks during SUPPORT and before release of its results.[4] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after SUPPORT in participating centers. We hypothesized that after SUPPORT there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks GA. We hypothesized that the degree of change in proportion of DR ETI in each center after SUPPORT would depend on the proportion before the trial. We also hypothesized that the change in DR ETI after SUPPORT would be less at centers that had participated in the feasibility trial than at the other centers.

METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants admitted to NRN centers) in one cohort of patients born before SUPPORT and in a second cohort born after release of the results of SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes patients born during a period preceding SUPPORT (1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Criteria were similar to those used in SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in SUPPORT. Exclusion criteria were: known malformations, and respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The last criterion was different from SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use, mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was a practice variable, DR ETI, which was defined as endotracheal intubation for ventilation (excluding intubation done for suctioning or to give surfactant and immediately removed).

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in SUPPORT), (2) the composite of severe ROP (defined as ROP surgery, retinal detachment or treatment with a drug anti-vascular endothelial growth factor) or death before discharge, and (3) death before discharge. The definitions of BPD and ROP for this study were those used in the GDB; however in SUPPORT primary outcomes also included the physiological definition of BPD, and severe ROP was determined using examinations continued until the outcome of SUPPORT was reached or resolution occurred.[1,2]

Additional outcomes are described in Tables 3 and in the Appendix, online only.

Outcome variables were selected a priori, except the proportion of babies who were never intubated (Appendix).

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT), NRN center, and pre-specified prenatal covariates shown to affect outcomes in very preterm infants[5] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted

tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[6-15] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs. post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort was higher in centers with higher proportion of DR ETI during the first period.

Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with a type I error less than 5% and a power greater than 99%.

Approvals

The IRB of each participating center has approved the GDB and SUPPORT. The protocol was approved by the NRN GDB and Steering committees.

RESULTS

Maternal and Neonatal Characteristics

The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant ($p = 0.01$). This indicates that the change in proportion of DR ETI was different in the two subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after

SUPPORT among infants from centers that had participated in the feasibility trial but decreased significantly among infants from the other centers.

Other outcomes

The adjusted risks of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). Several processes of care and outcomes changed after SUPPORT (Appendix). The proportion of babies who were never intubated increased from 5.6% before SUPPORT to 11.4% after SUPPORT (P<0.001).

DISCUSSION:

Among infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in 11 centers participating in SUPPORT, the proportion of infants with DR ETI significantly decreased after SUPPORT at centers that had not participated in the feasibility trial, but not at the 3 centers that had participated in the feasibility trial, and thus had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 2000, after prospective introduction of routine, early, bubble nasal CPAP.[16] The strengths of this study include the large sample size; the use of a prospective database of inborn patients; the use of multivariate analysis; inclusion and exclusion criteria that were similar to those in SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked serial data and data from centers that did not participate in SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study the proportion of DR ETI in one NRN center decreased in non-enrolled patients during SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.[4] In that center, DR ETI decreased by 22% during/after SUPPORT. In contrast, DR ETI decreased by only 1.6% in another large contemporaneous cohort of infants participating in the Vermont Oxford Network.[4] This study did not address how generalizable the study results might be to other centers. Centers participating in SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after SUPPORT at centers that had not previously participated in a similar trial but not at other centers. This study suggests that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

ACKNOWLEDGMENTS:

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study. The content of the publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

FUNDING

The Study Sponsor, the National Institute of Child Health and Human Development (NICHD), did not have any role in the study design; in the collection, analysis and interpretation data; in the writing of the report; and in the decision to submit the paper for publication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results.

WHAT THIS STUDY ADDS

- The proportion of delivery room intubation (a process of care) decreased after the SUPPORT trial at centers that had not participated previously in a related trial, but not at other centers.
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	**Pre-SUPPORT N=1617**	**Post-SUPPORT N=2232**	**p-value[2]**	**Adjusted RR[3] (95% CI)**	**Adjusted p-value[3]**
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1085/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval

[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial

[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.03
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.85 (0.77-0.95)	0.003
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.93 (0.81-1.1)	0.26
BPD (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.02 (0.95-1.1)	0.55
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.66 (0.53-0.82)	0.0002
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.96 (0.83-1.1)	0.59
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.83-0.97)	0.004
Days on ventilator (survivors)[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.2 (-5.7, -2.7)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted values (Post vs. Pre SUPPORT) from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Appendix. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001
Never intubated	91/1617 (5.6)	253/2222 (11.4)	<0.0001

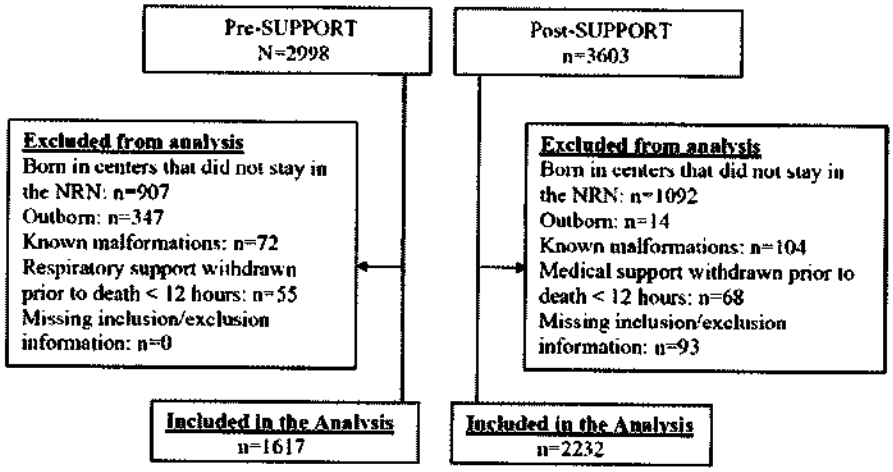
Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4]survivors to discharge or 120 days, whichever came first, max is 120 days.



Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study
64x35mm (300 x 300 DPI)

From:	Luc Brion
To:	Finer, Neil; "Gantz, Marie"; Myra Wyckoff; Mambarambath Jaleel; "Das, Abhik"; "doctorlevan@gmail.com"; Roy Heyne; "Wrage, Lisa Ann"; "Pablo.Sanchez@nationwidechildrens.org"; "Wally Carlo (WCarlo@peds.uab.edu)"; Higgins, Rosemary (NIH/NICHD) [E]; "Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)"
Subject:	RE: Updated manuscript and responses to editor and reviewers
Date:	Wednesday, April 16, 2014 5:56:55 PM
Attachments:	LeVan Pediatrics 2013 Change in Care Nonenrolled Patients.pdf

Neil:

Thanks for your email.

The data on intubation strictly for surfactant are not available in GDB. We could only extract babies who received intubation for surfactant followed by immediate extubation; this information is in the response to the reviewers.

Reviewers of the previous related manuscript from Parkland made us change "outcome variables" into "comparisons of interest" because intubation is a process of care and not an outcome (like ROP).

Luc

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
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To: Luc Brion; 'Gantz, Marie'; Myra Wyckoff; Mambarambath Jaleel; 'Das, Abhik'; 'doctorlevan@gmail.com'; Roy Heyne; 'Wrage, Lisa Ann'; 'Pablo.Sanchez@nationwidechildrens.org';

'Wally Carlo (WCarlo@peds.uab.edu)'; 'Rosemary Higgins (higginsr@mail.nih.gov)'; 'Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)'
Subject: RE: Updated manuscript and responses to editor and reviewers

Hi Luc
You have responded very well to the critiques
I am not sure I understand that ETI is a process of care- since you define it as intubation in the DR and not for surf.
However many infants who are intubated for resuscitation indications, ie persisting bradycardia or hypoxia, may receive early surf in the DR while the indication was not originally to give surf
I realize you do not have the data for that
Best of luck with this resubmission
Neil

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
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To: 'Gantz, Marie'; Myra Wyckoff; Mambarambath Jaleel; 'Das, Abhik'; 'doctorlevan@gmail.com'; Roy Heyne; 'Wrage, Lisa Ann'; 'Pablo.Sanchez@nationwidechildrens.org'; Finer, Neil; 'Wally Carlo (WCarlo@peds.uab.edu)'; 'Rosemary Higgins (higginsr@mail.nih.gov)'; 'Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)'
Subject: FW: Updated manuscript and responses to editor and reviewers

I am sending you the document with the responses to Marie.
Marie pointed out that what I sent yesterday came as a blank page.
Sorry about that
Luc

From: Luc Brion
Sent: Tuesday, April 15, 2014 10:01 PM
To: Gantz, Marie; Myra Wyckoff; Mambarambath Jaleel; Das, Abhik; doctorlevan@gmail.com; Roy Heyne; Wrage, Lisa Ann; Pablo.Sanchez@nationwidechildrens.org; nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Rosemary Higgins (higginsr@mail.nih.gov); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)
Subject: RE: Updated manuscript and responses to editor and reviewers

Marie;
Thanks a lot for your email and for great suggestions.
I have responded to all your comments in the attached version.
I also attach

1. a revised tracked version (4-15-14), which merges changes based on your comments and other recent comments from Lisa.
2. A revised response to the editor and the reviewers (4-15-14), based on your comments and Lisa's most recent comments.

Best regards,
Luc

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Subject: RE: Updated manuscript and responses to editor and reviewers

Thanks, Luc. My suggested edits and comments are attached.

Marie

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
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Subject: Updated manuscript and responses to editor and reviewers

Dear Colleagues:
Here is a revised version of the manuscript and responses to editor and reviewers.
Many thanks for Lisa's help in updating these documents.
I attach both the tracked and the clean version, as well as the submitted PDF (first version) and the text of the ADC comments.

Please edit/review within the next week so I can finalize the documents and submit to ADC next week-end.
Thanks for your collaboration and best regards,
Luc

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Change in Care Among Nonenrolled Patients During and After a Randomized Trial

Jaclyn M. LeVan, Myra H. Wyckoff, Chul Ahn, Roy Heyne, Pablo J. Sánchez, Lina Chalak, Mambarambath A. Jaleel, P. Jeannette Burchfield, Lucy Christie, Roger Soll, Gary J. Badger and Luc P. Brion

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Change in Care Among Nonenrolled Patients During and After a Randomized Trial

WHAT'S KNOWN ON THIS SUBJECT: Participating in a trial may affect processes of care by participating physicians; however, no study has assessed whether it affects processes of care for nonenrolled patients.

WHAT THIS STUDY ADDS: Participation in a trial may affect processes of care for nonenrolled patients, even when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study.

OBJECTIVE: Parkland Memorial Hospital (PMH) participated in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded controlled trial, in which preterm neonates of $24^{0/7}$ to $27^{6/7}$ weeks' gestational age (GA) were randomized in the delivery room (DR) to endotracheal intubation or nasal continuous positive airway pressure. We hypothesized that DR intubation could change in nonenrolled patients at PMH and that the change would be larger than in comparable centers not participating in the trial.

METHODS: The PMH Cohort included eligible but nonenrolled neonates of $24^{0/7}$ to $27^{6/7}$ weeks (primary) and noneligible neonates of 28 to $34^{6/7}$ weeks (confirmatory). A subset ($24^{0/7}$–$29^{6/7}$weeks) of that cohort was compared with a contemporaneous cohort born in centers participating in the Vermont Oxford Network (VON). We used a Poisson regression model to obtain adjusted relative risks (RRs) of DR intubation (during/after SUPPORT versus before SUPPORT) for PMH and for VON along with the ratio of these RRs.

RESULTS: In the PMH cohort (n = 3527), the proportion of DR intubation decreased during/after SUPPORT in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96) and the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70). Compared with the RR for DR intubation in VON, the RR at PMH was smaller in the lower (ratio of RR 0.76, 95% CI 0.65–0.87) and the upper GA group (ratio of RR 0.52, 95% CI 0.39–0.68).

CONCLUSIONS: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. *Pediatrics* 2013;132:e960–e970

AUTHORS: Jaclyn M. LeVan, DO,[a] Myra H. Wyckoff, MD,[a] Chul Ahn, PhD,[b] Roy Heyne, MD,[a] Pablo J. Sánchez, MD,[a] Lina Chalak, MD,[a] Mambarambath A. Jaleel, MD,[a] P. Jeannette Burchfield, RN,[a] Lucy Christie, RN,[a] Roger Soll, MD,[c,d] Gary J. Badger, MS,[c] and Luc P. Brion, MD[a]

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KEY WORDS

randomized controlled trial, process of care, unblinded, preterm, endotracheal intubation, birth cohort study, non-enrolled patients

ABBREVIATIONS

BW—birth weight
CI—confidence interval
CPAP—continuous positive airway pressure
DR—delivery room
GA—gestational age
NNT—number needed to treat
NRN—Neonatal Research Network
PMH—Parkland Memorial Hospital
RCT—randomized controlled trial
RD—risk difference
RR—relative risk
SUPPORT—Surfactant, Positive Pressure, and Oxygenation Randomized Trial
VON—Vermont Oxford Network

Dr LeVan conceptualized and designed the study, merged data from all Parkland Memorial Hospital (PMH) databases, participated in the interpretation of the data, drafted the first version of the manuscript, and critically reviewed the revisions; Drs Wyckoff, Heyne, Sanchez, Chalak, and Jaleel conceptualized and designed the study, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Ahn conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Ms Burchfield and Ms Christie collected and entered data into the databases and extracted the data for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Soll conceptualized and designed the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Badger conceptualized, designed, and conducted the statistical analyses for the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Brion conceptualized and designed the study, conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

(Continued on last page)

Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients.[1,2] Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.[1] Andersen et al showed that conducting a seeding trial (company-driven trial to entice doctors to prescribe a new drug being marketed by the company) changed some processes of care among participating physicians compared with nonparticipating physicians; however, processes of care for nonenrolled patients were not assessed.[3,4]

The objective of the current study was to evaluate whether a process of care of contemporaneous nonenrolled patients can change during and after recruitment to an unblinded randomized trial, when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study. We hypothesized (1) that participation of Parkland Memorial Hospital (PMH) in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded RCT comparing processes of care, could be associated with a reduction in the proportion of delivery room (DR) intubation in nonenrolled patients, and (2) that the local practice change would be larger than in comparable centers not participating in SUPPORT.

METHODS

Setting

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 × 2 factorial trial in which preterm neonates of $24^{0/7}$ to $27^{6/7}$ weeks' gestational age (GA) were randomized at birth to 2 interventions: (1) continuous positive airway pressure (CPAP) initiated in the DR and subsequent use of a protocol-driven limited ventilation strategy or DR intubation with surfactant administration, and (2) oxygen saturation targets of 85% to 89% or 91% to 95%.[5,6] The first intervention (CPAP versus DR intubation/surfactant) was unblinded, and its primary outcome was death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age.[5] PMH participated in SUPPORT from July 2005 until February 2009.

Data were compiled from 3 prospective databases, including detailed information about DR and NICU management with predetermined entry criteria and definitions: the Neonatal DR Resuscitation Registry (started in 1989), the NICU database (started in 1977), and SUPPORT registry. At PMH, all neonates <35 weeks' GA by obstetrical assessment are admitted to the NICU and included in the Resuscitation Registry and in the NICU database (unless triaged to the newborn nursery if pediatric assessment is >34 weeks' GA and the infant is otherwise well). These databases provide information on 99.8% of eligible neonates, with high interrater reliability (<1% error); most missing data points correspond to infants triaged to the newborn nursery (≤6%).

Data for an analysis cohort were abstracted by using a before–after study design during 3 consecutive epochs: (1) up to 30 months before SUPPORT initiation, (2) during SUPPORT participation, and (3) up to 15 months after trial completion. To account for secular trends in DR intubation, a subset of the PMH cohort was compared with a contemporaneous control population in the Vermont Oxford Network (VON), a voluntary collaboration of more than 900 NICUs around the world. The VON includes de-identified data by calendar year on infants with birth weight (BW) of 501 to 1500 g. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

Participants

The PMH cohort included neonates $24^{0/7}$ to $34^{6/7}$ weeks' GA born at PMH before SUPPORT (January 2003–June 2005), during SUPPORT (July 2005–February 2009), and after SUPPORT (March 2009–June 2010) until SUPPORT publication.[5,6] The study included (1) neonates $24^{0/7}$ to $27^{6/7}$ weeks' GA who were eligible for SUPPORT but not enrolled (lower GA group), and (2) noneligible neonates of $28^{0/7}$ to $34^{6/7}$ weeks' GA (upper GA group). The latter was used as a positive control for the lower GA group, in whom selection bias (due to exclusion of patients enrolled into SUPPORT) was possible.[7,8] Exclusion criteria were comfort care or major congenital anomalies known at birth, lack of patient record in the DR Resuscitation Registry or the NICU database, and enrollment in SUPPORT.

A subset of the PMH cohort, including all neonates $24^{0/7}$ to $29^{6/7}$ weeks' GA born in 2003 to 2004 (before SUPPORT) and 2006 to 2009 (during/after SUPPORT), was compared with inborn contemporaneous neonates born in level IIIb or IIIc North American centers participating in VON. The subset included (1) neonates $24^{0/7}$ to $27^{6/7}$ weeks' GA (lower GA group), and (2) neonates of $28^{0/7}$ to $29^{6/7}$ weeks' GA (upper GA group). We excluded centers participating in SUPPORT or in the VON Delivery Room Management Trial,[9] and neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies. This GA range was selected because infants in this GA range are included in the 501 to 1500 g BW range of VON. PMH was not a member of VON during the study period.

Comparisons of Interest

PMH Cohort

The primary analysis was the adjusted relative risk (RR) of DR intubation

during/after SUPPORT versus before SUPPORT in the lower GA group. The adjusted RR in the upper GA group was confirmatory and used as a positive control.

Univariate analyses in each GA group evaluated DR treatment (endotracheal intubation, positive pressure ventilation, CPAP), intubation (within the first 4 hours after admission to the NICU or during the first 24 hours of age), surfactant administration, pneumothorax, mortality to discharge from the hospital, chronic lung disease (chronic changes on chest radiograph and supplemental oxygen requirement for at least 28 days), duration of mechanical ventilation, patent ductus arteriosus, necrotizing enterocolitis (stage II or greater, modified Bell classification),[10] severe intraventricular hemorrhage (Papile grade III or IV),[11] periventricular leukomalacia, and severe retinopathy of prematurity (grade 3 or higher, international classification).[12]

Comparison With VON

The primary analysis was the comparison of RR (adjusted for baseline variables) of DR intubation (during/after SUPPORT versus before SUPPORT) in the subset of the PMH cohort in the lower GA group with the RR of DR intubation in the contemporaneous VON cohort.

The secondary analyses were (1) the adjusted ratio of RRs for DR intubation in the upper GA group and (2) the adjusted ratio of RRs for any invasive (endotracheal tube or tracheostomy) ventilation.

Statistical Analysis: PMH Cohort

Multivariate Analyses

In each GA group, the adjusted RRs for DR intubation during/after SUPPORT versus before SUPPORT were calculated using robust Poisson regression in a generalized estimating equation model adjusted for covariates that met the $P < .05$ criterion (backward selection). Candidate variables selected for modeling were characteristics preceding the decision of DR intubation and shown previously to associate with DR intubation.[13–27] To avoid collinearity with GA, BW was converted to BW *z*-score.[28] The adjusted risk difference (RD) and number needed to treat (NNT) were obtained from the adjusted RR and the proportion of DR intubation before SUPPORT. The Altman interaction test[29] was used to determine if the adjusted RRs for DR intubation were different between GA groups.

Univariate Analyses

Univariate analyses were performed by using χ^2 tests or Fisher's exact tests for categorical variables, and Student's *t* tests or analyses of variance followed by Tukey test, or Kruskal-Wallis test followed by Mann-Whitney test for continuous variables. We analyzed temporal patterns of DR intubation to determine how soon after initiating SUPPORT the proportion of DR intubation changed from baseline; we selected blocks of 15 to 16 months to limit fluctuation due to sample size.

Statistical analyses were performed by using SPSS version 19 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and SAS version 9.2 (SAS Institute, Cary, NC). Statistical significance (2-tailed) was determined based on $P < .05$, except for multiple pairwise nonparametric comparisons, for which we used the Bonferroni adjustment.

The time interval for data abstraction was set to ascertain a sufficient number of registered patients in the PMH cohort to detect changes in DR intubation in the lower GA subgroup using multivariate analysis. Given the ascertainment of data on 200 DR intubations, the analysis set was sufficient to conduct a multivariate analysis with up to 20 independent covariates tested as main effects, with a 2-sided α of 0.05. The duration of the study was set to recruit enough patients to detect changes in DR intubation in the lower GA group by univariate analysis. The effect size was selected as a 33% RR reduction in DR intubation, a conservative estimate compared with the 47% RR reduction in DR intubation in a center in which routine DR bubble CPAP was prospectively introduced in 2000.[21] A sample of 97 patients before SUPPORT and during/after SUPPORT yielded 80% power to detect a reduction in DR intubation from 60% to 40% with a 2-sided α of 0.05.

Comparison With VON

A Poisson regression model with robust variance was used for each GA group to obtain adjusted RRs (during/after SUPPORT versus before SUPPORT) for PMH and VON along with the ratio of their RRs.[30] Covariates in the model were infants' GA, gender, BW, *z*-score, and antenatal steroids. Location (PMH and VON) and epoch (before and during/after SUPPORT) were represented by a 4-level categorical variable in the model, with the appropriate linear contrasts constructed to obtain estimates of RRs and their ratio.

RESULTS

PMH Cohort

At PMH, a total of 3821 individual patient database records were reviewed, of which 3533 were eligible and 3527 (99.8%) had records in the 3 PMH databases (Fig 1). The analysis cohort comprised 3527 records. In the lower GA group, the percentage of multiple births was lower after SUPPORT (Table 1). In the upper GA group, exposure to antenatal steroids was more frequent after SUPPORT, maternal diabetes was more frequent during SUPPORT, and BW was greater during/after SUPPORT; other differences were clinically insignificant (Table 2).

During SUPPORT, patients in the lower GA group included in the current study

had a greater GA than contemporaneous patients enrolled in SUPPORT (excluded from the current study), were less likely to have been exposed to antenatal steroids, and were more likely to receive positive pressure ventilation in the DR (Appendix).

Multivariate Analysis

Among 3527 neonates, 649 (18%) were intubated in the DR. The proportion of DR intubation significantly decreased during/after SUPPORT versus before SUPPORT, in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96, $P = .02$) and in the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70, $P < .001$) (Tables 3 and 4). In the lower GA group, the proportion of DR intubation decreased from 85% before SUPPORT to 61% during/after SUPPORT (Table 5) (adjusted RD 0.21, 95% CI 0.03–0.34; NNT 5, 95% CI 3–33). In the upper GA group, the proportion decreased from 19% to 10% (Table 6) (adjusted RD 0.08, 95% CI 0.06–0.10; NNT 12, 95% CI 10–18). The decrease in DR intubation was not significantly different in the upper GA group compared with the lower GA group (adjusted ratio of RR 0.75, 95% CI 0.54–1.03).

Univariate Analyses

In the lower GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ($P = .01$) and that of CPAP increased ($P < .001$) (Table 5). Not surprisingly, the proportion of intubation in the NICU within 4 hours after admission increased over time ($P = .03$); however, intubation within 24 hours of life decreased during/after SUPPORT ($P = .002$). The proportion of surfactant administration decreased during SUPPORT ($P < .001$). The proportion of pneumothoraces increased after SUPPORT ($P = .03$). Most pneumothoraces occurred in neonates who were intubated in the DR.

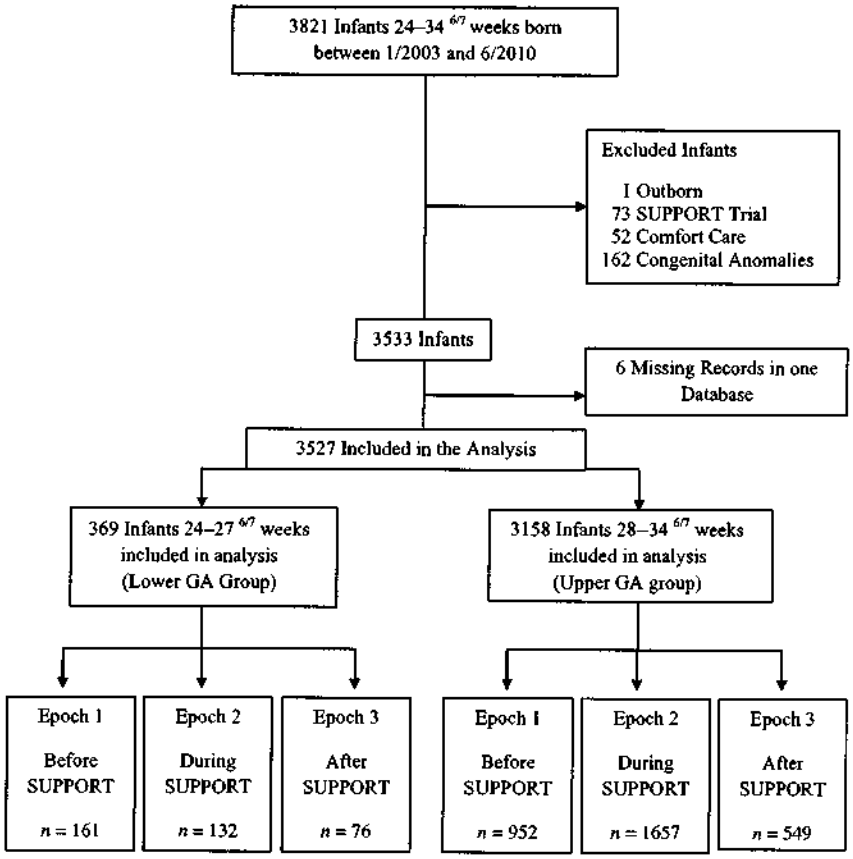

FIGURE 1
Flow diagram at PMH.

TABLE 1 Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Lower GA Group: $24^{0/7}$ to $27^{6/7}$ Weeks' Gestation

Characteristic[a]	Before SUPPORT, $n = 161$	During SUPPORT, $n = 132$	After SUPPORT, $n = 76$	*P* Value
GA, wk, mean (SD)	25.8 (1.0)	25.9 (1.1)	25.8 (1.1)	.42
BW, g, mean (SD)	858 (236)	908 (238)	874 (290)	.24
Size for age, *n* (%)				.52
Small for GA	19 (12)	14 (11)	10 (13)	
Large for GA	19 (12)	25 (19)	12 (16)	
Female, *n* (%)	74 (46)	61 (46)	36 (47)	.98
Multiple birth, *n* (%)	34 (21)	19 (14)	5 (7)*	.01
Antenatal steroids, *n* (%)	81 (50)	52 (39)	38 (50)	.14
Abruptio placentae, *n* (%)	6 (4)	11 (8)	4 (5)	.25
Placenta previa, *n* (%)	3 (2)	1 (1)	3 (4)	.25
Maternal diabetes mellitus, *n* (%)	6 (4)	10 (8)	8 (11)	.11
Gestational hypertension or preeclampsia, *n* (%)	25 (16)	28 (21)	19 (25)	.19
Clinic attendance, *n* (%)	146 (90)	113 (86)	67 (88)	.40

[a] Complete data were available for patients in the lower GA group and for GA. *P* values on the last column on the right are based on analyses of variance or χ^2 analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined using $P < .025$ and *P* values indicated as * $P < .025$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

In the upper GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ($P = .002$) (Table 6). The proportion of intubation within 24 hours of life decreased during/after SUPPORT ($P <$

TABLE 2 Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group: $28^{0/7}$ to $34^{6/7}$ Weeks' Gestation

Characteristic[a]	Before SUPPORT, $n = 952$	During SUPPORT, $n = 1657$	After SUPPORT, $n = 549$	*P* Value
GA, wk, mean (SD)	32.1 (1.8)	32.2 (1.8)	32.4 (1.8)*	.002
BW, g, mean (SD)	1824 (468)	1904 (486)*	1932 (472)*	<.001
Size for age, *n* (%)				.04
Small for GA	101 (11)	139 (9)	49 (9)	
Large for GA	103 (11)	239 (15)	64 (12)	
Female, *n* (%)	422 (46)	716 (44)	247 (46)	.64
Multiple birth, *n* (%)	182 (19)	333 (20)	122 (22)	.35
Use of antenatal steroids, *n* (%)	260 (27)	430 (26)	204 (37)**	<.001
Abruptio placentae, *n* (%)	23 (2)	41 (2)	11 (2)	.82
Placenta previa, *n* (%)	18 (2)	33 (2)	14 (3)	.66
Maternal diabetes mellitus, *n* (%)	88 (9)	216 (13)*	71 (13)	.01
Gestational hypertension or preeclampsia, *n* (%)	264 (28)	511 (30)	168 (31)	.23
Clinic attendance, *n* (%)	852 (90)	1530 (92)*	511 (93)*	.02

[a] In the upper GA group, 95% of data were available; we used the total number available as denominator. *P* values on the last column on the right are based on analyses of variance or χ^2 analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed by using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined using $P < .025$ and *P* values indicated as * $P < .025$, or ** $P < .001$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

TABLE 3 Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Lower GA Group: $24^{0/7}$ to $27^{6/7}$ Weeks' Gestation, $n = 362$

Variable	Adjusted RR[a]	*P* Value
During/after SUPPORT versus before SUPPORT[b]	0.76, 95% CI 0.59–0.96	.02
Positive pressure ventilation in the DR	3.61, 95% CI 2.02–6.45	<.001

For each categorical variable, the reference group is factor not present; for SUPPORT the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, cord pH, GA, gestational hypertension or preeclampsia, and *Z* score of BW for GA and gender.

[a] Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

[b] Primary analysis.

TABLE 4 Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Upper GA Group: $28^{0/7}$ to $34^{6/7}$ Weeks' Gestation, $n = 2742$

Variable	Adjusted RR[a]	*P* Value
During/after SUPPORT versus before SUPPORT[b]	0.57, 95% CI 0.46–0.70	<.001
Positive pressure ventilation in the DR	6.29, 95% CI 4.73–8.37	<.001
GA (per wk)	0.74, 95% CI 0.70–0.78	<.001
Gestational hypertension or preeclampsia	0.72, 95% CI 0.56–0.92	.009
Z score of BW for GA and gender	0.91, 95% CI 0.83–1.00	.046

For each categorical variable, the reference group is factor not present; for SUPPORT, the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, cord pH, GA, gestational hypertension or preeclampsia, and *Z* score of birth weight for GA and gender.

[a] Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

[b] Confirmatory analysis (positive controls).

.001). The proportion of surfactant administration decreased during SUPPORT ($P < .025$).

Most of the other outcomes except retinopathy of prematurity did not change during or after SUPPORT. The percentage of DR intubation did not change during baseline in either GA group (Fig 2). In the lower GA group, the proportion of DR intubation decreased within 15 months of SUPPORT, whereas in the upper GA group, it did not significantly change until later.

Comparison Between PMH and VON

We compared data from 576 neonates born at PMH with data from 85 118 contemporaneous neonates born in 1 of 396 North American VON centers (Table 7).

In the lower GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT at PMH (82% vs 60%; adjusted RR 0.74, 95% CI 0.64–0.86) and in VON (85% vs 84%; adjusted RR 0.98, 95% CI 0.98–0.99). The decrease was greater at PMH than in VON (adjusted ratio of RR 0.76, 95% CI 0.65–0.87). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in the VON data. The change over time was not significantly different between PMH and VON.

In the upper GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT both at PMH and in VON. The decrease was greater at PMH than in VON (adjusted ratio of RR 0.52, 95% CI 0.39–0.68). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in VON. The change over time was not significantly different between PMH and VON.

DISCUSSION

In the current study, a change in care process (proportion of DR intubation) was observed in eligible but nonenrolled patients and in noneligible more mature patients soon after SUPPORT initiation and persisted through 16 months of posttrial evaluation. This change in practice at PMH was much larger than in other comparable centers that did not participate in any trial involving random allocation to DR

TABLE 5 Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Lower GA Group: $24^{0/7}$ to $27^{6/7}$ Weeks' Gestation

Care Process or Outcome Variable[a]	Before SUPPORT, $n = 161$	During SUPPORT, $n = 132$	After SUPPORT, $n = 76$	*P* Value
Intubation in the DR, *n* (%)	136 (85)	81 (61)**	46 (61)**	<.001
Positive pressure ventilation in the DR, *n* (%)	140 (91)	106 (80)*	60 (79)*	.01
CPAP in DR, *n* (%)	48 (31)	74 (56)**	48 (63)**	<.001
Intubation in the NICU within the first 4 h after admission to the unit, *n* (%)	7 (4)[b]	14 (11)	10 (13)	.03
Intubation during the first 24 h of life, *n* (%)	141 (88)	95 (72)**	56 (73)*	.002
Surfactant, *n* (%)	121 (79)	78 (59)**	50 (66)	.001
Pneumothorax, *n* (%)	11 (7)	13 (10)	14 (18)*	.03
Death before discharge, *n* (%)	43 (27)	34 (26)	18 (24)	.91
Chronic lung disease, *n* (%)	83 (52)	61 (46)	43 (57)	.34
Total no. days intubated (endotracheal tube or tracheostomy) ($n = 338$); median (quartiles)[c]	10 (2–23)	5(1–14)	11 (2–29)	.05
Patent ductus arteriosus, *n* (%)	77 (48)	61 (46)	39 (51)	78
Necrotizing enterocolitis, stage ≥2, *n* (%)	14 (9)	10 (8)	5 (7)	.91
Intraventricular hemorrhage, grade 3 or 4, *n* (%)	25 (16)	20 (15)	18 (24)	.25
Periventricular leukomalacia, *n* (%)	9 (6)	7 (5)	5 (7)	.92
Retinopathy of prematurity, stage ≥3, *n* (%)	30 (19)	12 (9)	14 (18)	.04

P values in the last column on the right are based on χ^2 analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined by using $P < .025$, and *P* values indicated as * $P < .025$, or ** $P < .001$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

[a] Complete data were available for patients.

[b] Two patients, initially intubated in the DR, were intubated again within 4 h after admission in the NICU after a trial on CPAP.

[c] Kruskal-Wallis tests.

TABLE 6 Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group: $28^{0/7}$ to $34^{6/7}$ Weeks' Gestation

Care Process or Outcome Variable[a]	Before SUPPORT, $n = 952$	During SUPPORT, $n = 1657$	After SUPPORT, $n = 549$	*P* Value
Intubation in the DR, *n* (%)	177 (19)	162 (10)**	47 (9)**	<.001
Positive pressure ventilation in the DR, *n* (%)	332 (36)	513 (31)*	150 (28)**	.002
CPAP in the DR, *n* (%)	314 (34)	588 (36)	194 (36)	.74
Intubation in the NICU within the first 4 h after admission to the unit, *n* (%)	43 (5)	82 (5)	28 (5)	.84
Intubation during the first 24 h of life, *n* (%)	220 (23)	242 (15)**	75 (14)**	<.001
Surfactant, *n* (%)	105 (11)	131 (8)*	50 (9)	.01
Pneumothorax, *n* (%)	29 (3)	40 (2)	12 (2)	.51
Death before discharge, *n* (%)	17 (2)	19 (1)	8 (2)	.41
Chronic lung disease, *n* (%)	31 (3)	40 (2)	16 (3)	.44
Total no. days intubated (endotracheal tube or tracheostomy) ($n = 694$); median (quartiles)[b]	1 (1–3)	1 (0–4)	1 (1–6)	.097
Patent ductus arteriosus, *n* (%)	68 (7)	106 (6)	23 (4)	.07
Necrotizing enterocolitis, stage ≥2, *n* (%)	17 (2)	23 (1)	12 (2)	.42
Intraventricular hemorrhage, grade 3 or 4, *n* (%)	8 (0.8)	7 (0.4)	5 (0.9)	.22
Periventricular leukomalacia, *n* (%)	3 (0.3)	13 (0.8)	4 (0.7)	.323
Retinopathy of prematurity, stage ≥3, *n* (%)	3 (0.3)	0 (0)	3 (0.5)	.008

P values in the last column on the right are based on χ^2 analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined by using $P < .025$, and *P* values indicated as * $P < .025$, or ** $P < .001$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

[a] 95% of data were available; we used the total number available as denominator.

[b] Kruskal-Wallis tests.

intubation, suggesting that the trial participation itself influenced clinical practice well beyond the study participants.

PMH is a high-volume delivery unit with 12 000 to 15 000 deliveries per year. At PMH, the decision whether to intubate is made by resuscitation teams of practitioners who are trained in the neonatal resuscitation program. Teams for neonates with GA of 30 to 35 weeks include a nurse, a respiratory therapist, and a neonatal nurse practitioner or a senior pediatric resident. Teams for lower GA neonates also include a neonatal-perinatal fellow. Additional personnel are available for backup. The same teams provided care to all neonates, whether enrolled into SUPPORT or not. PMH did not have a policy about DR endotracheal intubation; decisions are left to team leaders according to national guidelines for neonatal resuscitation. At PMH before SUPPORT, most preterm neonates <28 weeks' GA were intubated in the DR. PMH did not participate in the NRN Feasibility Trial,[13] which preceded SUPPORT. At PMH, the only evident change in DR management was initiation of a resuscitation rotation for fellows in neonatal-perinatal medicine in 2005. The Neonatal Resuscitation Program mentioned the use of CPAP in the DR for preterm neonates in 2006, and included CPAP in the resuscitation algorithm in 2010[31,32]; however, immediate application of CPAP in the DR at PMH was not recommended for all preterm neonates <32 weeks until May 1, 2011.

The strengths of the current study include[33,34] large sample size; prospective validated databases thereby minimizing missing data, information bias, and loss to follow-up; stratified analysis yielding internal controls (upper GA group); and multivariate comparison with contemporaneous external controls (comparable VON

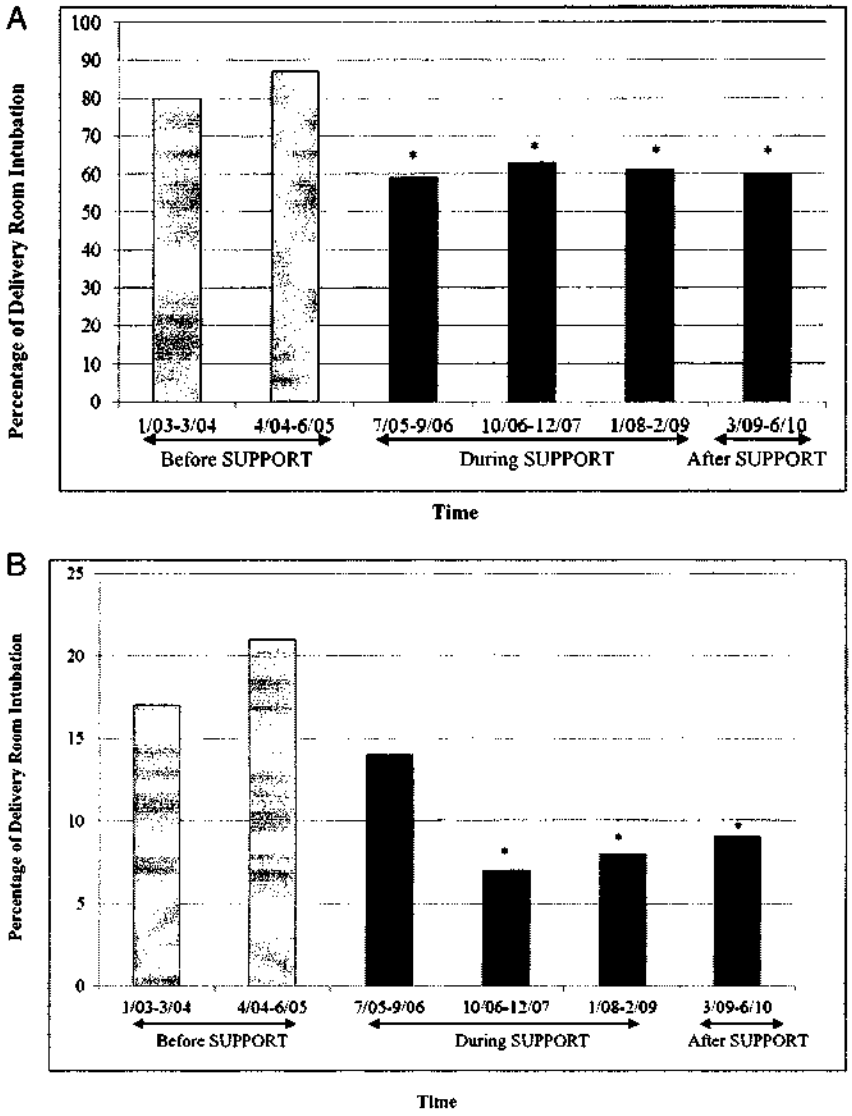

FIGURE 2

Analysis of temporal patterns in DR intubation rates by GA group at PMH. This analysis was performed using consecutive 15- to 16-month blocks. A, Lower GA group ($24^{0/7}$–$27^{6/7}$ weeks' GA infants): The percentages of DR intubation were not significantly different between blocks before SUPPORT ($P = .37$); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into the SUPPORT ($P < .001$). This change already occurred within the first 15 months of recruitment into SUPPORT. *Indicates significant (with Bonferroni adjustment, $P < .0125$) pairwise difference from baseline before starting the SUPPORT. B, Upper GA group ($28^{0/7}$–$34^{6/7}$ weeks' GA infants). The percentage of DR intubations was not significantly different between the 2 blocks before SUPPORT ($P = .10$); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into SUPPORT ($P < .001$); however, this change started to reach significance only after 15 months of recruitment into SUPPORT. *Indicates significant (with Bonferroni adjustment, $P < .0125$) pairwise difference from baseline before starting SUPPORT.

centers not participating in DR trials) with a similar baseline proportion of DR intubation. Secular trends are unlikely to explain the primary results because DR intubation at PMH decreased much more than in other comparable centers. It is unlikely that the current study affected the proportion of DR intubation because when the first data were obtained and presented at a national meeting, the change in practice had already taken place. We did not observe a regression to the mean but instead a sustained reduction in DR intubation at PMH during/after SUPPORT. A differential Hawthorne effect was ruled out because providers were not aware of an observational study of eligible, nonenrolled patients during SUPPORT.[7,8] This study was limited to a single institution rather than all NRN centers participating in SUPPORT because the generic database of the NRN includes only the most immature infants; patients in the upper GA group were important in this study as positive controls who were not eligible for SUPPORT and thus not subjected to selection bias. Selection bias at PMH in the lower GA group during SUPPORT is unlikely to explain the observed decrease in DR intubation in nonenrolled patients, because respiratory distress is associated with lower exposure to antenatal steroids,[35] and more frequent DR positive pressure ventilation (Appendix) would be expected to increase, rather than decrease, DR intubation. The lower percentage of antenatal steroids among nonenrolled patients could have resulted because of many reasons, including not enough time before delivery.[7] Rich and colleagues' study showed that a significantly larger proportion of eligible infants whose mothers were not approached for consent to SUPPORT had no prenatal steroid exposure.[7] The frequency of antenatal corticosteroid administration at PMH is low because preeclampsia and diabetes are considered contraindications.[36] Multivariate analyses showed that the RR of DR intubation decreased at PMH and decreased more at PMH than in VON, even taking into account antenatal corticosteroid administration. We were unable to analyze bronchopulmonary dysplasia, or other elements of care process examined in SUPPORT (ie, targeted ventilation strategy and oxygen saturation), which were not included in the PMH databases. In addition, target oxygen saturation values of 88% to 94%, a PMH NICU policy since May 2002,[37]

TABLE 7 Adjusted RR Estimates in Preterm Infants Born With GA 24 to $29^{6/7}$ Weeks at PMH and in Comparable North American Centers in the VON Before SUPPORT (2003–2004) and During/After SUPPORT (2006–2009)

Care Process	GA Group, wk	Location	Before SUPPORT	During/After SUPPORT	Adjusted RR[a] During/After Versus Before SUPPORT (95% CI)	Ratio of RRs PMH Versus VON (95% CI)	*P* Value
Intubated in DR	$24^{0/7}$–$27^{6/7}$	PMH	105/128 (82%)	99/164 (60%)	0.745 (0.644–0.861)	0.757 (0.654–0.875)	.0002
		VON	11 728/13726 (85.4%)	29 715/35 447 (83.8%)	0.984 (0.976–0.992)		
					n = 49 055		
	$28^{0/7}$–$29^{6/7}$	PMH	51/86 (59%)	57/198 (29.0%)	0.495 (0.375–0.652)	0.516 (0.391–0.681)	<.0001
		VON	5427/10 008 (54.2%)	13 457/25 928 (51.9%)	0.959 (0.939–0.979)		
					n = 35 851		
Received any invasive ventilation	$24^{0/7}$–$27^{6/7}$	PMH	119/128 (93.0%)	144/164 (88.0%)	0.952 (0.886–1.023)	0.965 (0.898–1.037)	.33
		VON	13 158/13 727 (95.9%)	33 469/35 453 (94.4%)	0.986 (0.982–0.991)		
					n = 49 068		
	$28^{0/7}$–$29^{6/7}$	PMH	63/86 (73.0%)	134/198 (68.0%)	0.939 (0.804–1.095)	0.988 (0.846–1.154)	.88
		VON	7599/10 008 (75.9%)	18 669/25 930 (72.0%)	0.950 (0.937–0.962)		
					n = 35 855		

[a] RR estimates are adjusted for infants' GA, gender, *z*-score for BW (computed within GA and gender), and exposure to antenatal corticosteroids by using robust Poisson regression generalized estimating equation models. Location (PMH and VON) and time period (during/after SUPPORT and before SUPPORT) were represented by a 4-level categorical variable. RRs and the ratio of RR estimates were computed based on the appropriate linear contrast of model parameters.

was used for nonenrolled patients. Because the study used databases, it was not possible to perform a propensity match, or a cluster analysis of DR team members or individual providers and to obtain their rationale for deciding whether to intubate the trachea. It is possible that the change in DR intubation was related to increased availability of T-piece devices for DR resuscitation, or to training and experience with these devices and DR CPAP.

CONCLUSIONS

A change in process of care was observed in nonenrolled patients during/after recruitment to an unblinded RCT, in the absence of changes in standard care, initiation of a protocol, or previously described trial effect. This suggests that care for patients who are not enrolled in RCTs should routinely be monitored and audited to identify changes in practice that may either be beneficial or detrimental without the evidence from a completed trial. Further studies are needed to investigate the determinants of changes in individual decisions about care process (eg, observations of short-term outcomes versus experience with novel processes of care). A trial design in which centers are randomized to participation in RCTs could further analyze the impact of changes in care process associated with unblinded RCTs.

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The first version of the PMH cohort was a poster presentation at the Pediatric Academy Society Meeting, Honolulu, HI, May 4, 2008: Brion LP, Wyckoff MH, Jaleel M, Sanchez PJ, Burchfield J, Christie L. Delivery room practice change following the initiation of the SUPPORT trial.

The final version of the PMH cohort was a platform presentation at the Pediatric Academy Society Meeting, Boston, MA, April 28, 2012: LeVan JM, Wyckoff MH, Jaleel MA, Sanchez PJ, Ahn C, Burchfield J, Christie L, Brion LP. Impact of initiating the NICHD Neonatal Research Network SUPPORT Trial on management and outcomes of gestational-age matched non-enrolled patients.

Dr LeVan was a pediatric resident at University of Texas Southwestern Medical Center and was part of the DR team during her rotations at PMH in 2006–2009. Dr Wyckoff was awarded a grant from The American Academy of Pediatrics Neonatal Resuscitation Program (2008–2009), and an Ikaria Investigator Initiated Grant (Nov 2010–Nov 2012). Dr Heyne was, during the study and remains, the follow-up principal investigator of the National Institute of Child Health and Human Development NRN at University of Texas Southwestern Medical Center. Dr Sánchez was, during the study and remains, the site principal investigator of the National Institute of Child Health and Human Development Neonatal Research Network (U10 HD40689) at University of Texas Southwestern Medical Center. Dr Chalak was awarded grant 5 KL2 RR024983–02 from the North and Central Texas Clinical and Translational Science Initiative (9/17/07–5/31/12), a North and Central Texas Clinical and Translational Science Initiative Pilot Grant Award Program (2010–2011), and a grant from the Gerber Foundation (11/17/2011–10/16/2013). Dr Jaleel is a member of the National Quality Forum Perinatal Steering Committee. Dr Brion is the alternate principal investigator of the National Institute of Child Health and Human Development NRN at University of Texas Southwestern Medical Center since April 8th, 2009. Dr Soll is the president and director of clinical trials at the VON. Nancy

A. Miller, RN, recruited patients into the SUPPORT and collected data for the study by Rich and collaborators.[7,8]

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(Continued from first page)

This trial has been registered at www.clinicaltrials.gov (identifier NCT01601886).

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APPENDIX Baseline Characteristics of Infants 24 to 27 $^{6/7}$ Weeks' Gestation Born at PMH During SUPPORT (July 2005–February 2009)

Characteristic	SUPPORT, *n* = 73, Excluded From the Current Study	NONSUPPORT, *n* = 132, Included in the Current Study	*P* Value
GA, wk, mean (SD)	25.3 (1.0)	25.9 (1.0)	<.001
BW, g, mean (SD)	878 (189)	907 (238)	.37
Size for age, *n* (%)			.03
Small for GA	1 (1)	14 (11)	
Large for GA	19 (26)	25 (19)	
Female, *n* (%)	29 (40)	61 (46)	.23
Multiple birth, *n* (%)	12 (16)	19 (14)	.69
Use of antenatal steroids, *n* (%)	49 (67)	52 (39)	<.001
Abruptio placentae, *n* (%)	3 (4)	11 (8)	.39
Placenta previa, *n* (%)	1 (1)	1 (1)	1.000
Maternal diabetes, *n* (%)	6 (8)	10 (8)	1.000
Gestational hypertension or preeclampsia, *n* (%)	15 (21)	28 (21)	1.000
Clinic attendance, *n* (%)	63 (86)	113 (86)	1.000
Positive pressure ventilation in the DR, *n* (%)	42 (58)	106 (80)	.001

Significance based on Fisher's exact tests or Student's *t* tests.

Change in Care Among Nonenrolled Patients During and After a Randomized Trial

Jaclyn M. LeVan, Myra H. Wyckoff, Chul Ahn, Roy Heyne, Pablo J. Sánchez, Lina Chalak, Mambarambath A. Jaleel, P. Jeannette Burchfield, Lucy Christie, Roger Soll, Gary J. Badger and Luc P. Brion

Pediatrics; originally published online September 16, 2013;
DOI: 10.1542/peds.2013-1595

From:	Luc Brion
To:	Gantz, Marie; Myra Wyckoff; Mambarambath Jaleel; Das, Abhik; "doctorlevan@gmail.com"; Roy Heyne; Wrage, Lisa Ann; "Pablo.Sanchez@nationwidechildrens.org"; "nfiner@ucsd.edu"; "Wally Carlo (WCarlo@peds.uab.edu)"; Higgins, Rosemary (NIH/NICHD) [E]; "Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)"
Subject:	RE: Updated manuscript and responses to editor and reviewers
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THanks for all your great suggestions!
Luc

From: Gantz, Marie [mgantz@rti.org]
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To: Luc Brion; Myra Wyckoff; Mambarambath Jaleel; Das, Abhik; 'doctorlevan@gmail.com'; Roy Heyne; Wrage, Lisa Ann; 'Pablo.Sanchez@nationwidechildrens.org'; 'nfiner@ucsd.edu'; 'Wally Carlo (WCarlo@peds.uab.edu)'; 'Rosemary Higgins (higginsr@mail.nih.gov)'; 'Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)'
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Thanks, Luc. The changes look good to me.

Marie

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I am sending you the document with the responses to Marie.
Marie pointed out that what I sent yesterday came as a blank page.
Sorry about that
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2. A revised response to the editor and the reviewers (4-15-14), based on your comments and Lisa's most recent comments.

Best regards,
Luc

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Thanks for your collaboration and best regards,

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Luc

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD,[1] Pablo J. Sánchez, MD,[1,4] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil N. Finer, MD,[5] Waldemar A. Carlo, MD,[6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

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No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 2429 words
Article length: 2,0002,49990 words
Revised 4/84/141/23/2014 rev
FetalNeonatal-2014-306057.R1

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) decreased in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA, ~~born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the NRN~~, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, p <0.0001) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

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INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized ~~2 X 2 factorial~~ controlled trial (RCT), in which preterm infants of $24^{0/7}$ ~~weeks~~ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets ~~of either 85 to 89% or 91 to 95%.~~[1,2] From ~~February~~ 2005 through ~~February~~ 2009, 1316 infants were enrolled in ~~19~~20 centers.[1,2] The results of ~~the~~ SUPPORT ~~trial~~ were released to ~~the~~ NRN centers in December 2009 ~~and published in May 2010~~.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] ~~The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.~~

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI ~~in the SUPPORT Trial~~SUPPORT and the GA range that would be most appropriate for ~~the SUPPORT Trial~~SUPPORT.[3]

Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients.[4,5] A previous study in one NRN center that had not participated in the feasibility trial demonstrated that ~~clinical practice, specifically~~ the

Comment [MG1]: Minor point, but in other papers we have called this the "surfactant" group.

Comment [I2]: Sorry about that. Since the primary outcome for this study is delivery intubation I selected DR-ETI as the abbreviation.

Comment [MG3]: This statement seems out of place here. Is there a better place for it?

Comment [I4]: I deleted that sentence.

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proportion of DR ETI, changed among non-enrolled patients during SUPPORT ~~the trial~~ and before release of its results.[64] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after ~~the SUPPORT trial~~SUPPORT in participating centers. ~~We hypothesized that that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks changed after the SUPPORT trial. compared to the period before the trial.~~ We hypothesized ~~speculated~~ that the ~~decrease~~ degree of change in proportion of DR ETI in each center after SUPPORT ~~the trial~~ would depend on the ~~baseline~~ proportion before the trial. We also hypothesized ~~speculated~~ that the ~~decrease~~ change in DR ETI after ~~the SUPPORT Trial~~SUPPORT would be less in centers that had participated in the feasibility trial than in the other centers. ~~In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.~~

Comment [MG5]: Were these infants eligible for SUPPORT?

Comment [I6]: This study included both eligible but non enrolled patients and larger noneligible patients. In entered this information in the revised version

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Comment [MG7]: I think this should be left in.

Comment [I8]: Done

METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before ~~the initiation of the~~

Comment [LW9]: Actually the inclusion criteria does not state this, either before 2008 or after 2008.

Comment [I10]: Taken from the protocol: "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 (1/1/2010-12/31/2012)."

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~~SUPPORT trial~~SUPPORT and in a second preterm cohort born after release of the results of ~~the SUPPORT trial~~SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in ~~the~~ ~~SUPPORT trial~~SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes ~~preterm~~ patients born during a ~~2-year~~ period preceding ~~the~~ ~~SUPPORT trial~~SUPPORT (~~from~~ 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT ~~Trial~~ to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

~~Eligibility and exclusion C~~eriteria were similar to those used in ~~the SUPPORT trial~~SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in ~~the SUPPORT trial~~SUPPORT, and included in the GDB during the entire study period (2003-2012).

Comment [MG11]: Already said this, above. Don't think it needs to be repeated.

Comment [J12]: Done

Exclusion criteria ~~for this analysis~~ were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The last~~tter~~ criterion was different from ~~the SUPPORT trial~~SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

~~Outcome variables were selected a priori.~~

The primary outcome variable was a practice variable, ~~i.e.,~~ DR ETI, which was defined as endotracheal intubation for ventilation (excluding intubation done for suctioning or to give surfactant and immediately removed). ~~.~~

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in ~~the SUPPORT trial~~SUPPORT), (2) the composite of severe ROP (defined as ROP surgery, ~~or~~ retinal detachment or treatment with a drug anti-vascular endothelial growth factor) or death before discharge, and (3) death before discharge. ~~Additional secondary outcomes included death by 36 weeks~~

Comment [LW13]: Or Avastin/anti VEGF drug)

~~PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors.~~ The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of ~~the SUPPORT trial~~SUPPORT, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of ~~the SUPPORT trial~~SUPPORT was reached or resolution occurred).[1,2]

Additional ~~Tertiary~~ outcomes are described in Tables 3 and ~~included practice variables~~ in the Appendix, online only. ~~such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR~~ practice, ~~Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.~~ Outcome variables were selected a priori, except the proportion of babies who were never intubated (Appendix). ~~(Appendix).~~

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student's t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to

Comment [MG14]: Both the physiologic definition and the oxygen use definition of BPD were considered primary outcomes in SUPPORT. The protocol was not clear about which definition should be used, so we used both.

Comment [I15]: Done

Comment [LW16]: Is this in a table somewhere?

Comment [LW17]: I don't think you need to say this because you say it earlier in the paragraph. Also this was not in the Appendix so I added it.

Comment [I18]: I deleted that sentence higher in the paragraph.

obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT), NRN center, and pre-specified prenatal covariates ~~(based on the literature)~~ shown to affect outcomes in very preterm infants[76] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[87-176] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi-square tests ~~and~~ also included an indicator for these subgroups and its interaction with the pre- vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered ~~as~~ exploratory. ~~A~~ Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort ~~first period (pre-SUPPORT) to the second period (post-SUPPORT)~~ was higher in centers with higher proportion of DR ETI during the first period.

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Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates. ~~in the 11 centers.~~ This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an ~~alpha~~ Type I error less than 5% and a power greater than 99%. ~~The sample size was large enough for multivariate analysis with 10 patients per covariate.~~

Approvals~~IRB~~

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and ~~the SUPPORT Trial~~SUPPORT. The protocol was approved by the NRN GDB and Steering committees.

Comment [MG19]: Can we just say "GDB?" This is confusing because GDB was already defined as the NICHD Generic Database.

Comment [I20]: Done

RESULTS

Maternal and Neonatal Characteristics

~~A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial.~~

The study population included 3,849 inborn infants~~: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group~~ (Figure 1). ~~Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants.~~

Comment [MG21]: Would include the numbers pre- and post-SUPPORT.

Comment [I22]: Done

The baseline maternal and neonatal characteristics of the pre- and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre- versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial -was significant (p = 0.01). This indicates that the change in proportion of DR ETI ~~varied across these~~was different in the two subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT among ~~in the subgroup of~~ infants from centers that had participated in the feasibility trial ~~(61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40)~~ but decreased significantly among ~~in the subgroup of~~ infants from the other centers. ~~(91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).~~

Other outcomes

Secondary outcomes~~, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven~~ were significantly lower in the post-SUPPORT group (Table 3), with the exception of BPD, death by 36 weeks and death before discharge. ~~By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.~~

~~Unadjusted comparisons of~~ Tertiary outcome variables are shown in the Appendix; online only. ~~Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).~~

Comment [LW23]: I had to add this back in because this is true using the correct table.

Comment [124]: Done

Comment [MG25]: I think a list of the significantly different variables would be more informative than a list of those that were not different.

Comment [MG26]: Removed the term "teriary" from the methods. Best to be consistent?

This is not a very informative sentence. Can we say anything about whether there were differences?

Comment [127]: Done

DISCUSSION:

~~I~~Among infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in ~~the~~ 11 centers participating in ~~the SUPPORT trial~~SUPPORT, ~~after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial~~SUPPORT. ~~The~~ the proportion of infants with DR ETI significantly decreased after SUPPORT ~~among in the subgroup of infants from~~ at centers that had not participated in the feasibility trial, but not ~~. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT among in the subgroup of infants from~~ at the 3 centers that had participated in the feasibility trial~~,~~ and thus ~~already~~ had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers,

the proportion of ETI had already decreased in 2000, after prospective introduction of ~~when neonatologists prospectively introduced~~ routine, early, bubble nasal CPAP.[187]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients~~, which limits incomplete/missing data and information bias~~; the use of multivariate analysis ~~to take into account confounding~~ variables; inclusion and exclusion criteria that were similar to those ~~used~~ in ~~the SUPPORT trial~~SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN ~~during the entire study period~~, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design~~, which prevents any cause-effect interpretation~~; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked ~~of~~ serial data and ~~lack of~~ data from centers that did not participate in ~~the SUPPORT trial~~SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study ~~we have shown that~~ the proportion of DR ETI in one NRN center ~~(which did not participate in the Feasibilty Trial)~~ decreased in non-enrolled patients ~~from baseline before the SUPPORT trial to epochs~~ during ~~the SUPPORT trial~~SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.[64] In that center, DR ETI decreased by 22% during/after ~~the SUPPORT Trial~~SUPPORT ~~(before~~

~~release of the trial results),~~ ~~but only by~~ In contrast, DR ETI decreased by only 1.6% in another large ~~large comparable~~ contemporaneous cohort ~~of infants participating in the Vermont Oxford Network~~.[64]

Comment [MG28]: Recommend keeping this information for clarity.

Comment [I29]: Done

~~Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.[18-27] We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.~~

This study did not address how generalizable the study results might be to other centers~~ that did not participate in the SUPPORT trial. It is possible that~~ Ceenters participating in ~~the SUPPORT trial~~SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~the SUPPORT trial~~SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would ~~allow to~~ test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after ~~the SUPPORT Trial~~SUPPORT ~~in the group of infants from~~at centers that had not previously participated in a similar trial ~~the feasibility trial~~ but not ~~in the group of infants from the~~at other centers.~~, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial.~~ This study ~~provides additional evidence to~~ suggests that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

FUNDING

The Study Sponsor, the National Institute of Child Health and Human Development (NICHD), did not have any role in the study design; in the collection, analysis and interpretation data; in the writing of the report; and in the decision to submit the paper for publication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. ~~It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.~~

WHAT THIS STUDY ADDS

- The proportion of delivery room intubation (a~~A change in~~ process of care) decreased after the SUPPORT trial;
- ~~This decrease was observed~~ ~~was observed only among infants born in~~ at centers that had not participated previously in a related trial, but not ~~in the~~at other centers.;
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	10856/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Comment [LW30]: Luc this one was 1085

Abbreviations: RR, relative risk; CI, confidence interval
[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial
[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adj p v
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.032
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.815 (0.773-0.9589)	<0.00301
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.9386 (0.8176-1.1098)	0.2602
BPD (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.042 (0.957-1.1)	0.5526
Severe ROP[4]	174/1294 (13.5)	181/18753 (9.7)	0.0009	-	0.663 (0.532-0.8277)	<0.
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.9688 (0.8376-1.100)	0.5906
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.834-0.97)	0.00433
Days on ventilator (survivors)[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.27 (-5.76.1, -2.73.2)		<0.0001

Comment [LW31]: This looked like the original version of the table not the latest version in which the adjusted results were updated, so I've attached that in the email

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Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted valuesRRs (Post vs. Pre SUPPORT) from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include ~~taking into account~~ gestational age, ~~GA,~~ birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD also includes ~~contained these same additional variables as well as~~ intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

~~[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).~~

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Change in Practice After
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) decreased in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA~~, born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the NRN~~, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, p <0.0001) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusion: This study shows that DR ETI ~~process of care~~ changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized ~~2 X 2 factorial~~ controlled trial (RCT), in which preterm infants of $24^{0/7}$ ~~weeks~~ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets ~~of either 85 to 89% or 91 to 95%.~~[1,2] From ~~February~~ 2005 through ~~February~~ 2009, 1316 infants were enrolled in ~~19~~20 centers.[1,2] The results of ~~the~~ SUPPORT ~~trial~~ were released to ~~the~~ NRN centers in December 2009 ~~and published in May 2010~~.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] ~~The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.~~

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI ~~in the SUPPORT Trial~~ and the GA range that would be most appropriate for ~~the SUPPORT Trial~~SUPPORT.[3]

A previous study in one NRN center that had not participated in the feasibility trial demonstrated that ~~clinical practice, specifically~~ the proportion of DR ETI, changed among ~~non-enrolled patients~~eligible but nonenrolled neonates of $24^{0/7}$ to $27^{6/7}$ weeks and

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noneligible neonates of $28^{0/7}$ to $34^{6/7}$ weeks during SUPPORT ~~the trial~~ and before release of its results.[44] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after ~~the SUPPORT trial~~SUPPORT in participating centers. We hypothesized ~~that~~ that after ~~the~~ SUPPORT ~~trial~~ there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks GA. ~~changed after the SUPPORT trial, compared to the period before the trial.~~ We hypothesized ~~speculated~~ that the degree of change ~~decrease~~ in proportion of DR ETI in each center after SUPPORT ~~the trial~~ would depend on the ~~baseline~~ proportion before the trial. We also hypothesized ~~speculated~~ that the change ~~decrease~~ in DR ETI after ~~the SUPPORT Trial~~SUPPORT would be less at~~in~~ centers that had participated in the feasibility trial than at~~in~~ the other centers. ~~In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.~~

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METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants

admitted to ~~born alive in~~ NRN centers) in one ~~birth~~ cohort of patients born before ~~the initiation of the SUPPORT trial~~SUPPORT and in a second ~~preterm~~ cohort born after release of the results of ~~the SUPPORT trial~~SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in ~~the SUPPORT trial~~SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes ~~preterm~~ patients born during a ~~2-year~~ period preceding ~~the SUPPORT trial~~SUPPORT (~~from~~ 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT ~~Trial~~ to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

~~Eligibility and exclusion~~ Ceriteria were similar to those used in ~~the SUPPORT trial~~SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in ~~the SUPPORT~~

~~trial~~SUPPORT,~~ and included in the GDB during the entire study period (2003-2012).~~

Exclusion criteria ~~for this analysis~~ were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The last~~ter~~ criterion was different from ~~the SUPPORT trial~~SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

~~Outcome variables were selected a priori.~~

The primary outcome variable was a practice variable, ~~i.e.,~~ DR ETI, which was defined as endotracheal intubation for ventilation (excluding intubation done for suctioning or to give surfactant and immediately removed). ~~.~~

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in ~~the SUPPORT trial~~SUPPORT), (2) the composite of severe ROP (defined as ROP surgery, ~~or~~ retinal detachment or treatment with a drug anti-vascular endothelial growth factor) or death before discharge, and (3)

death before discharge. ~~Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors.~~ The definitions of BPD and ROP for this study were those used in the GDB; however in SUPPORT ; ~~they were similar but not identical to those used for the primary outcomes of the SUPPORT trial~~primary outcomes also included ,~~the~~i.e., physiological definition of BPD, and severe ROP was determined using ~~(with~~ examinations continued until the outcome of ~~the SUPPORT trial~~SUPPORT was reached or resolution occurred~~)~~.[1,2]

Additional ~~Tertiary~~ outcomes are described in Tables 3 and ~~included practice variables~~ in the Appendix, online only. ~~such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.~~Outcome variables were selected a priori, except the proportion of babies who were never intubated (Appendix). ~~(Appendix).~~

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for

dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT), NRN center, and pre-specified prenatal covariates ~~(based on the literature)~~ shown to affect outcomes in very preterm infants[26] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[6,7,15,26] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs. post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort ~~first period (pre-SUPPORT) to the second period (post-SUPPORT)~~ was higher in centers with higher proportion of DR ETI during the first period.

Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates, ~~in the 11 centers.~~ This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with a type I ~~n alpha~~ error less than 5% and a power greater than 99%. ~~The sample size was large enough for multivariate analysis with 10 patients per covariate.~~

~~Approvals IRB~~

The IRB of each participating center has approved the ~~Survey of Morbidity and Mortality Among High Risk Preterm Infants (~~GDB~~)~~ and ~~the SUPPORT Trial~~SUPPORT. The protocol was approved by the NRN GDB and Steering committees.

RESULTS

Maternal and Neonatal Characteristics

~~A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial.~~

The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). ~~Three of the 11 centers~~

~~included in our study participated in the Feasibility Study, with a total n of 1321 infants.~~
The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI was different in the two ~~varied across these~~ subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT among ~~in the subgroup of~~ infants from centers that had participated in the feasibility trial ~~(61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40)~~ but decreased significantly among ~~in the subgroup of~~ infants from the other centers. ~~(91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).~~

Other outcomes

The ~~Secondary outcomes, including the~~ adjusted risks of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). ~~, with the exception of BPD, death by 36 weeks and death before discharge. By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.~~

~~Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that~~ Several processes of care and outcomes changed after SUPPORT (Appendix). T~~t~~he proportion of babies who were never intubated increased from ~~was~~ 5.6% before ~~for the Pre-~~SUPPORT to ~~group, and~~ 11.4% after ~~for the Post-~~SUPPORT ~~group~~ ($P<0.001$). ~~:~~

DISCUSSION:

Among i~~I~~nfants $24^{0/7}$ to $27^{6/7}$ weeks GA born in ~~the~~ 11 centers participating in ~~the SUPPORT trial~~SUPPORT, ~~after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial. T~~the proportion of infants with DR ETI significantly decreased after SUPPORT at ~~in the subgroup of infants from~~ centers that had not participated in the feasibility trial, but not ~~. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from~~ at the 3 centers that had participated in

the feasibility trial, and thus ~~already~~ had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 2000, after prospective introduction of ~~when neonatologists prospectively introduced~~ routine, early, bubble nasal CPAP.[167]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients~~, which limits incomplete/missing data and information bias~~; the use of multivariate analysis ~~to take into account confounding variables~~; inclusion and exclusion criteria that were similar to those ~~used~~ in ~~the SUPPORT trial~~SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN ~~during the entire study period~~, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design~~, which prevents any cause-effect interpretation~~; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked ~~of~~ serial data and ~~lack of~~ data from centers that did not participate in ~~the SUPPORT trial~~SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study ~~we have shown that~~ the proportion of DR ETI in one NRN center ~~(which did not participate in the Feasibilty Trial)~~ decreased in non-enrolled patients ~~from baseline before the SUPPORT trial to epochs~~ during ~~the SUPPORT trial~~SUPPORT and before its

publication, in the absence of any changes in DR policy or practice guidelines.[44] In that center, DR ETI decreased by 22% during/after ~~the SUPPORT Trial~~SUPPORT. ~~(before release of the trial results),~~ In contrast, DR ETI decreased by ~~but only by~~ 1.6% in another large ~~comparable~~ contemporaneous cohort of infants participating in the Vermont Oxford Network.[44]

~~Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.[18-27] We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.~~

This study did not address how generalizable the study results might be to other centers, ~~that did not participate in the SUPPORT trial. It is possible that~~ Ceenters participating in ~~the SUPPORT trial~~SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~the SUPPORT trial~~SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of

care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after ~~the SUPPORT Trial~~SUPPORT at~~in the group of infants from~~ centers that had not previously participated in a similar trial ~~the feasibility trial~~ but not at~~in the group of infants from the~~ other centers~~, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial.~~ This study ~~provides additional evidence to~~ suggests that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

FUNDING

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WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. ~~It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.~~

WHAT THIS STUDY ADDS

~~—~~The proportion of delivery room intubation (a~~A change in~~ process of care) decreased after the SUPPORT trial at :

- ~~This decrease was observed~~ was observed only among infants born in centers that had not participated previously in a related trial, but not at~~in the~~ other centers.~~:~~
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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LICENCE FOR PUBLICATION STATEMENT

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1085/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval
[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial
[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3,4]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.032
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.815 (0.773-0.9589)	<0.00301
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.9386 (0.8176-1.1098)	0.2602
BPD (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.042 (0.957-1.1)	0.5526
Severe ROP[4]	174/1294 (13.5)	181/18753 (9.7)	0.0009	-	0.663 (0.532-0.8277)	<0.00024
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.9688 (0.8376-1.100)	0.5906
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.834-0.97)	0.00433
Days on ventilator (survivors)[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.27 (-5.76-1, __-2.73-2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted valuesRRs (Post vs. Pre SUPPORT) from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include taking into account gestational age, GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD also includes contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

LIST OF CHANGES

Abstract: We have corrected the section on Setting: we entered the sentence: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN" at the beginning of this section

We have written the hypotheses as such, page 5 second paragraph lines 2-4.

We show that all outcome variables were planned except for the proportion of babies who have never been intubated (page 7, 2nd paragraph, last 2 lines).

We have shortened the manuscript by 500 words, especially in the tertiary variables and ~~the~~ discussion sections.

We have provided two revised sections (one in the background, page 4 , last paragraph and page 5, first line; and one in the discussion, page 11, second paragraph) to show the importance of ~~studying this and of analyzing~~ studying whether the phenomenon exists/does not exist.

Comment [LW1]: Hi Luc, not sure you need that extra phrase, if so I think that you should be more descriptive than just saying 'studying this'

We have tightened the "what is known" and "what this adds" section (page 16).

ITEMIZED RESPONSES TO COMMENTS

Thank you for the suggestions. Here are the itemized responses in italics.

In addition to the reviewers' comments, the editors found the paper to be long and tedious to read - please shorten by 500 words.
A: We have shortened the manuscript by 500 words.

In the abstract, what you have written as Setting is not really the setting - please state what you mean.
A: We have started this paragraph by the following statement: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN."

Please state hypotheses as such, rather than speculations.
A: On page 5 paragraph 2 we replaced the word "speculated" with "hypothesized"."

Was this a planned analysis?
A: Yes. All studies conducted at the NICHD NRN require the development of a concept proposal followed if approved by a full protocol. For this study, a protocol was submitted to the NRN GDB committee and then to the Steering Committee. The goal was to test whether the proportion of endotracheal intubation in the delivery room (DR ETI) decreased after the SUPPORT trial in other NRN centers, as had been observed in a single center (reference 4). This protocol was, after multiple revisions, approved by both NRN committees. This statement was added on page 9, paragraph 1, lines 2-~~3~~.

Please explain why all the tertiary outcome data in the Appendix would be needed.

A: These data are important to show because they describe neonatal outcomes and practice variables that might be of interest to the audience. ~~known potential confounding variables and biases that could have affected the primary and secondary outcomes.~~

Comment [LW2]: Luc, originally these were all in the secondary outcomes table. I've also seen this data described previously (in the protocol and other drafts) as secondary outcomes/ practice variables, and also as including some potential confounders. If you describe it solely as potential confouders/biases I think you could trigger questions as to why we did not adjust for more of these. You were very careful about what you chose to adjust for so you could probably handle those questions, but perhaps you could describe these more fully too??? It seems reasonable to show these in an Appendix/online as secondary outcomes/ practice variables because they might be of interest to your audience.

Discussion could be shortened.
A: We have shortened the discussion as requested.

What is known/what this adds should be tightened up and bulleted.
A: We have revised that section as requested, and have followed the guidelines to authors (page 16).

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Overall, I found this to be a good manuscript with a rigorous study design and implementation and high scientific validity within the constraints of the study design utilized.

I think the background section would benefit from inclusion of material on why it is important to study the spread of a practice within an institution when that institution participates in a randomized trial of the practice. Why is it such a big deal to study this and prove that the phenomenon exists/does not exist?
A: ~~Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients. Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.~~
A previous study in one NRN center that had not participated in the feasibility trial demonstrated that clinical practice, specifically the proportion of DR ETI, changed among non-enrolled patients during SUPPORT the trial and before release of its results, but not in a large contemporaneous cohort in the Vermont-Oxford Network (reference 6 in the revised version). Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention. This is why we conducted the present study
We have entered most of the above discussion on pages 4 (last paragraph), ~~and 5 (first paragraph).~~

Methods: It's not clear how many centers in total participated in the SUPPORT trial.
A: we entered the number in the text: 20 (page 4, introduction, line 9)

Methods, eligibility and inclusion criteria: use the word 'last criterion' instead of the 'latter criterion'
A: We changed the text as requested (page 6, Eligibility and exclusion criteria: line ~~56~~).

Methods: outcome variables. Please specify if the outcome variables were selected a priori (pre-specified) before the analysis was done (e.g. as part of a study protocol), or was there a post-hoc component to the analysis.
A: Outcome variables were selected a priori, except the proportion of babies who were never intubated (page 7, second paragraph, last line).

Analysis:

Why was there no analysis accounting for the clustering of infants within the eleven institutions? I think this is required, but this statement will need to be confirmed by a statistician.
A: All adjusted analyses controlled for NRN center by including it as a covariate in all our regression models. This is indicated in page 7, statistical analysis, line 7. The analysis by institution is presented in Figure 2.

Results: Maternal and neonatal characteristics. I think the authors can refer readers to the flow diagram in Figure 1 that shows the numbers and save some space in the text.
A: We have shortened the text as suggested (page 9).

Discussion
I think the strengths and limitations are well-described.
I think the discussion section will benefit from inclusion of material that describes the results of other studies of spread of a practice as a result of randomized trial participation, what might be the underlying mechanisms for such spread, and what the implications are for trials and for practice.
Framing this study's results in the larger context of healthcare and neonatal practice will make it more appealing and meaningful to readers.
A: We added the following statement to the end of the discussion (page 11, second paragraph): Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting on RCT.

Discussion: please correct the year where it says '200'
A: thank you for pointing this out; we have corrected the year to 2000 (page 10, discussion, first paragraph, line 67).

Reviewer: 2

Comments to the Author
This is a well executed secondary analysis of the NRN, which demonstrate that infants who are not enrolled in an RCT have improved short- and long-outcomes.

I agree with the authors that the reduction is DR ETI might have also been associated with the familiarity with the T-Piece device and their clinical observations that CPAP in the DR is possible. As mentioned by the authors a survey of other centres would not give a total picture of NICU practices in other NICUs and if SUPPORT has changes their practice too. However, this remains an interesting question as studies like SUPPORT, who demonstrated that CPAP in the DR is well tolerated by infants, should be implemented in other NICUs as well.
A: We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This has happened several times in the recent past in the NRN. Furthermore it is even more unlikely that people may remember the exact time practices changed several years ago. This is discussed on page 11, lines 41-63.
For this study we selected centers that participated in SUPPORT and remained in the NRN, because previous NRN studies have shown major interinstitution variability, and the list of NRN centers changes every 5 years. This is a strength of the study, as discussed on page 10, discussion, second paragraph, lines 43-5

Although, Table 2 demonstrates a significant reduction in DR ETI, however in Figure 2 it appears that two centres have similar DR ETI rates pre and post SUPPORT. Would INUSRE also be counted as an intubation or were these intubation only with continuous mechanical ventilation?

A: Data from the GDB do not have a specific entry for INSURE in the delivery room. The data on intubation in the delivery room (DR ETI) pertain to intubation for ventilation in the delivery room; these numbers include all patients who received surfactant and were not immediately extubated, but exclude patients who receive surfactant and were immediately extubated. The ~~GDD~~ GDB had an entry for time of surfactant administration for 941 babies in our postSUPPORT cohort who were born between Jan 2010 and March 2011, the time period we were collecting date and time of first surfactant administration. Of these, n=153 did not have surfactant administered and n=788 did. Of these 788, n=37 had missing date/time of surfactant variables, and n=14 had errors in date/time of surfactant variables. Those remaining, n=737, had surfactant administered and complete date/time information. Of these, n=206 had surfactant within 15 minutes of birth, and only ONE of these was not intubated in the DR. Thus, if one assumes that surfactant administration within 15 minutes of life took place in the delivery room, the large majority of babies who received surfactant in the DR were counted as DR ETI.

We clarified the definition of DR ETI on page 6, last paragraph.

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: RE: SUPPORT publication
Date: Tuesday, April 15, 2014 4:35:34 PM
Attachments: image001.png
image002.png

Very interesting thanks --Rose

Mona

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, April 15, 2014 2:50 PM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: SUPPORT publication

http://www.sciencedirect.com/science/article/pii/S0022347614001942

FYI - The SUPPORT Breathing outcomes paper has appeared on-line (last week).

Rose

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Subject: RE: SUPPORT publication
Date: Tuesday, April 15, 2014 2:50:16 PM

No news is good news!

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From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, April 15, 2014 2:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: RE: SUPPORT publication

Thanks, Rose.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, April 15, 2014 2:50 PM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
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To: "Shankaran, Seetha"; Abhik Das (Adas@rti.org)
Cc: (kzaterka@rti.org)
Subject: RE: SUPPORT study closure at WSU
Date: Monday, April 14, 2014 9:12:58 AM

Seetha
The SUPPORT dataset is continuing to be used for the Growth secondary (paper in progress) as well as the pulmonary outcomes at 18 months (paper just accepted). If your IRB requires that the study be kept opened for ongoing analyses, it will need to be renewed. If not, ok to close the SUPPORT and the 18-22 month FU. For the 6-7 year FU, we will be using some of the earlier collected SUPOPRT data in the analyses.

Thanks
Rose

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From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Monday, April 14, 2014 9:09 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das (Adas@rti.org)
Cc: Shankaran, Seetha
Subject: SUPPORT study closure at WSU

Rose and Abhik

I am attempting to "close out" some NICHD NRN studies otherwise we are doing Continuations every year which is a huge issue—I have to do all at my site (except TOP, HC and MILK which the respective Study PIs do) so the number is large. Looking at SUPPORT I can close out except for 2 things

1) Concurrence from the Sponsor should be obtained. The FU phase is over and Primary papers on SUPPORT and FU are completed. Can you send me an e-mail re your concurrence, Rose?
2) Data using PIH cannot be used after closure. I am assuming all analysis for the future for SUPPORT will include aggregate data without individual patient identifiers, right Abhik? PIH data can be retained at WSU so that secondary analysis of IRB approved proposals can be

performed---i.e. SUPPORT 6-7 year MRI study and Adrenal Secondary which as you know I have under review first at the institutional level (hospitals) before it can go to WSU.

Any questions let me know
Thanks
Seetha

From:	Luc Brion
To:	Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Das, Abhik (adas@rti.org); doctorlevan@gmail.com; Roy Heyne; Luc Brion; Wrage, Lisa Ann (wrage@rti.org); Pablo.Sanchez@nationwidechildrens.org; nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)
Subject:	Updated manuscript and responses to editor and reviewers
Date:	Friday, April 11, 2014 6:44:43 PM
Attachments:	Appendix 4-10-14 clean.docx Appendix 4-10-14.docx Figure 1.tif Figure 2 1200 dpi.tif Jackie LeVan Manuscript NRN 4-10-14 clean.docx Jackie LeVan Manuscript NRN 4-10-14.docx Responses to comments rev 4-10-14 clean.docx Responses to comments rev 4-10-14.docx s1-ln17211004114696332 9-1939656818Hwf-1766607715IdV752126477172110 04PDF_HI0001.pdf Comments.docx

Dear Colleagues:

Here is a revised version of the manuscript and responses to editor and reviewers.

Many thanks for Lisa's help in updating these documents.

I attach both the tracked and the clean version, as well as the submitted PDF (first version) and the text of the ADC comments.

Please edit/review within the next week so I can finalize the documents and submit to ADC next week-end.

Thanks for your collaboration and best regards,

Luc

Appendix. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001
Never intubated	91/1617 (5.6)	253/2222 (11.4)	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

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Comment [LW1]: Luc, these footnotes are not the same as you previously submitted, could you go back and find the version of footnotes that you submitted? It looks like some of them are changes you made.

Comment [I2]: I copied the footnotes from the document I submitted to ADC. These are identical.

04-Apr-2014

Manuscript ID fetalneonatal-2014-306057 entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial"

Dear Dr. Brion,

Thank you for submitting the above manuscript to Archives of Disease in Childhood. It has been considered carefully at an editorial meeting and unfortunately, we do not wish to publish it in its current form.

However, we invite you to resubmit a further version of your paper. In inviting you to resubmit, I must emphasise that there is no guarantee that your paper will be accepted but we will look at it carefully with our referees and hope that it might prove possible to eventually publish a version of it.

It is essential that you detail your response to each and every one of the reviewers' comments, including any with which you disagree so have not complied with in your revised version. The comments of the reviewer(s) are included at the bottom of this letter.

In addition to the reviewers' comments, the editors found the paper to be long and tedious to read - please shorten by 500 words. In the abstract, what you have written as Setting is not really the setting - please state what you mean. Please state hypotheses as such, rather than speculations. Was this a planned analysis? Please explain why all the tertiary outcome data in the Appendix would be needed. Discussion could be shortened. What is known/what this adds should be tightened up and bulleted.

To revise your manuscript, log into http://mc.manuscriptcentral.com/adc and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. You may also click the below link to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

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You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to Archives of Disease in Childhood, your revised manuscript should be submitted by 03-Jun-2014. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Archives of Disease in Childhood and I look forward to receiving your revision.

Sincerely,
Dr. Ann Stark
Associate Editor, Archives of Disease in Childhood

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Overall, I found this to be a good manuscript with a rigorous study design and implementation and high scientific validity within the constraints of the study design utilized.

I think the background section would benefit from inclusion of material on why it is important to study the spread of a practice within an institution when that institution participates in a randomized trial of the practice. Why is it such a big deal to study this and prove that the phenomenon exists/does not exist?

Methods: It's not clear how many centers in total participated in the SUPPORT trial.

Methods, eligibility and inclusion criteria: use the word 'last criterion' instead of the 'latter criterion'

Methods: outcome variables. Please specify if the outcome variables were selected a priori (pre-specified) before the analysis was done (e.g. as part of a study protocol), or was there a post-hoc component to the analysis.

Analysis:
Why was there no analysis accounting for the clustering of infants within the eleven institutions? I think this is required, but this statement will need to be confirmed by a statistician.

Results: Maternal and neonatal characteristics. I think the authors can refer readers to the flow diagram in Figure 1 that shows the numbers and save some space in the text.

Discussion
I think the strengths and limitations are well-described.
I think the discussion section will benefit from inclusion of material that describes the results of other studies of spread of a practice as a result of randomized trial participation, what might be the underlying mechanisms for such spread, and what the implications are for trials and for practice.
Framing this study's results in the larger context of healthcare and neonatal practice will make it more appealing and meaningful to readers.

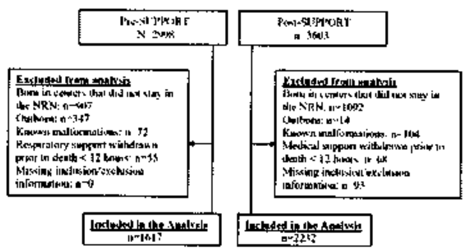
Discussion: please correct the year where it says '200'

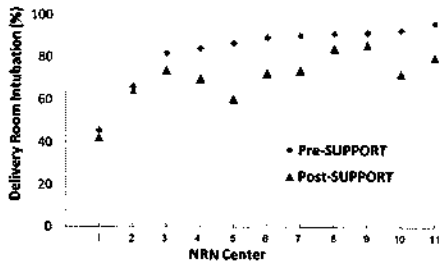
Reviewer: 2

Comments to the Author
This is a well executed secondary analysis of the NRN, which demonstrate that infants who are not enrolled in an RCT have improved short- and long-outcomes.

I agree with the authors that the reduction is DR ETI might have also been associated with the familiarity with the T-Piece device and their clinical observations that CPAP in the DR is possible. As mentioned by the authors a survey of other centres would not give a total picture of NICU practices in other NICUs and if SUPPORT has changes their practice too. However, this remains an interesting question as studies like SUPPORT, who demonstrated that CPAP in the DR is well tolerated by infants, should be implemented in other NICUs as well.

Although, Table 2 demonstrates a significant reduction in DR ETI, however in Figure 2 it appears that two centres have similar DR ETI rates pre and post SUPPORT. Would INUSRE also be counted as an intubation or were these intubation only with continuous mechanical ventilation?


Pre-SUPPORT
N=2998
Post-SUPPORT
n=3603
Excluded from analysis
Born in centers that did not stay in the NRN: n=907
Outborn: n=347
Known malformations: n=72
Respiratory support withdrawn prior to death < 12 hours: n=55
Missing inclusion/exclusion information: n=0
Excluded from analysis
Born in centers that did not stay in the NRN: n=1092
Outborn: n=14
Known malformations: n=104
Medical support withdrawn prior to death < 12 hours: n=68
Missing inclusion/exclusion information: n=93
Included in the Analysis
n=1617
Included in the Analysis
n=2232


Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD,[1] Pablo J. Sánchez, MD,[1,4] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil N. Finer, MD,[5] Waldemar A. Carlo, MD,[6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital, Columbus, OH; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

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No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 242 words
Article length: 2,000 words
Revised 4/10/14
FetalNeonatal-2014-306057.R1

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) decreased in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA, , excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, $p < 0.0001$) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, $p=0.40$).

Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized controlled trial (RCT), in which preterm infants of $24^{0/7}$ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets [1,2] From 2005 through 2009, 1316 infants were enrolled in 20 centers.[1,2] The results of SUPPORT were released to NRN centers in December 2009.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1]

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in SUPPORT and the GA range that would be most appropriate for SUPPORT.[3]

Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients.[4,5] A previous study in one NRN center that had not participated in the feasibility trial demonstrated that the proportion of DR ETI, changed among non-enrolled patients during SUPPORT and before release of its results.[6] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a

similar intervention.

The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after SUPPORT in participating centers. We hypothesized that the decrease in proportion of DR ETI in each center after SUPPORT would depend on the proportion before the trial. We also hypothesized that the decrease in DR ETI after SUPPORT would be less in centers that had participated in the feasibility trial than in the other centers.

METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before SUPPORT and in a second preterm cohort born after release of the results of SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes patients born during a period preceding SUPPORT (1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Criteria were similar to those used in SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in SUPPORT, and included in the GDB during the entire study period (2003-2012). Exclusion criteria were: known malformations, and respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The last criterion was different from SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use, mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was a practice variable, DR ETI, which was defined as endotracheal intubation for ventilation (excluding intubation done for suctioning or to give surfactant and immediately removed).

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in SUPPORT), (2) the composite of severe ROP (defined as ROP surgery, retinal detachment or treatment with a drug anti-vascular endothelial growth factor) or death before discharge, and (3) death before discharge. The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of SUPPORT, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of SUPPORT was reached or resolution occurred).[1,2]

Additional outcomes are described in Tables 3 and in the Appendix, online only.

Outcome variables were selected a priori, except the proportion of babies who were never intubated (Appendix).

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT), NRN center, and pre-specified prenatal covariates shown to affect outcomes in very preterm infants[7] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted

tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[8-17] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort was higher in centers with higher proportion of DR ETI during the first period.

Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough for multivariate analysis with 10 patients per covariate.

Approvals

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and SUPPORT. The protocol was approved by the NRN GDB and Steering committees.

RESULTS

Maternal and Neonatal Characteristics

The study population included 3,849 inborn infants (Figure 1). The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after

SUPPORT among infants from centers that had participated in the feasibility trial but decreased significantly among infants from the other centers.

Other outcomes

Secondary outcomes were significantly lower in the post-SUPPORT group (Table 3), with the exception of BPD, death by 36 weeks and death before discharge. Tertiary outcome variables are shown in the Appendix; online only.

DISCUSSION:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in SUPPORT after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before SUPPORT. The proportion of DR ETI significantly decreased among infants from centers that had not participated in the feasibility trial, but not among infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 2000, after prospective introduction of routine, early, bubble nasal CPAP.[18]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients; the use of multivariate analysis; inclusion and exclusion criteria that were similar to those in SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked serial data and data from centers that did not participate in SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study the proportion of DR ETI in one NRN center decreased in non-enrolled patients during SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.[6] In that center, DR ETI decreased by 22% during/after SUPPORT, but only by 1.6% in a large contemporaneous cohort.[6]

This study did not address how generalizable the study results might be to other centers. Centers participating in SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after SUPPORT in the group of infants from centers that had not previously participated in a similar trial but

not in the group of infants from the other centers. This study suggests that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results.

WHAT THIS STUDY ADDS

- The proportion of delivery room intubation (a process of care) decreased after the SUPPORT trial.
- This decrease was observed among infants born in centers that had not participated previously in a related trial, but not in the other centers.
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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LICENCE FOR PUBLICATION STATEMENT

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	**Pre-SUPPORT N=1617**	**Post-SUPPORT N=2232**	**p-value[2]**	**Adjusted RR[3] (95% CI)**	**Adjusted p-value[3]**
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1085/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval
[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial
[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.03
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.85 (0.77-0.95)	0.003
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.93 (0.81-1.1)	0.26
BPD (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.02 (0.95-1.1)	0.55
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.66 (0.53-0.82)	0.0002
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.96 (0.83-1.1)	0.59
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.83-0.97)	0.004
Days on ventilator (survivors)[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.2 (-5.7, -2.7)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted values (Post vs. Pre SUPPORT) from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

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Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) decreased in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA, ~~born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the NRN~~, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, $p < 0.0001$) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, $p=0.40$).

Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

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INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized ~~2 X 2 factorial~~ controlled trial (RCT), in which preterm infants of $24^{0/7}$ ~~weeks~~ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets ~~of either 85 to 89% or 91 to 95%.~~[1,2] From ~~February~~ 2005 through ~~February~~ 2009, 1316 infants were enrolled in ~~19~~20 centers.[1,2] The results of ~~the~~ SUPPORT ~~trial~~ were released to ~~the~~ NRN centers in December 2009 ~~and published in May 2010~~.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] ~~The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.~~

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in ~~the SUPPORT Trial~~SUPPORT and the GA range that would be most appropriate for ~~the SUPPORT Trial~~SUPPORT.[3]

Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients.[4,5] A previous study in one NRN center that had not participated in the feasibility trial demonstrated that ~~clinical practice, specifically~~ the

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proportion of DR ETI, changed among non-enrolled patients during SUPPORT ~~the trial~~ and before release of its results.[64] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after ~~the SUPPORT trial~~SUPPORT in participating centers. ~~We hypothesized that that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks changed after the SUPPORT trial. compared to the period before the trial.~~ We hypothesized ~~speculated~~ that the decrease in proportion of DR ETI in each center after SUPPORT ~~the trial~~ would depend on the ~~baseline~~ proportion before the trial. We also hypothesized ~~speculated~~ that the decrease in DR ETI after ~~the SUPPORT Trial~~SUPPORT would be less in centers that had participated in the feasibility trial than in the other centers. ~~In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.~~

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METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before ~~the initiation of the~~

Comment [LW1]: Actually the inclusion criteria does not state this, either before 2008 or after 2008.

Comment [I2]: Taken from the protocol: "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 (1/1/2010-12/31/2012). "

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~~SUPPORT trial~~SUPPORT and in a second preterm cohort born after release of the results of ~~the SUPPORT trial~~SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in ~~the~~ ~~SUPPORT trial~~SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes ~~preterm~~ patients born during a ~~2-year~~ period preceding ~~the~~ ~~SUPPORT trial~~SUPPORT (~~from~~ 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT ~~Trial~~ to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

~~Eligibility and exclusion C~~eriteria were similar to those used in ~~the SUPPORT trial~~SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in ~~the SUPPORT trial~~SUPPORT, and included in the GDB during the entire study period (2003-2012).

Exclusion criteria ~~for this analysis~~ were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The last~~tter~~ criterion was different from ~~the SUPPORT trial~~SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

~~Outcome variables were selected a priori.~~

The primary outcome variable was a practice variable, ~~i.e.,~~ DR ETI, which was defined as endotracheal intubation for ventilation (excluding intubation done for suctioning or to give surfactant and immediately removed). ~~.~~

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in ~~the SUPPORT trial~~SUPPORT), (2) the composite of severe ROP (defined as ROP surgery, ~~or~~ retinal detachment or treatment with a drug anti-vascular endothelial growth factor) or death before discharge, and (3) death before discharge. ~~Additional secondary outcomes included death by 36 weeks~~

Comment [LW3]: Or Avastin/anti VEGf drug)

~~PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors.~~ The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of ~~the SUPPORT trial~~SUPPORT, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of ~~the SUPPORT trial~~SUPPORT was reached or resolution occurred).[1,2]

Additional ~~Tertiary~~ outcomes are described in Tables 3 and ~~included practice variables~~ in the Appendix, online only. ~~such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.~~ Outcome variables were selected a priori, except the proportion of babies who were never intubated (Appendix). ~~(Appendix).~~

Comment [LW4]: Is this in a table somewhere?

Comment [LW5]: I don't think you need to say this because you say it earlier in the paragraph. Also this was not in the Appendix so I added it.

Comment [I6]: I deleted that sentence higher in the paragraph.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain

differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT), NRN center, and pre-specified prenatal covariates ~~(based on the literature)~~ shown to affect outcomes in very preterm infants[76] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[87-176] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort ~~first period (pre-SUPPORT) to the second period (post-SUPPORT)~~ was higher in centers with higher proportion of DR ETI during the first period.

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Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates, ~~in the 11 centers.~~ This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough for multivariate analysis with 10 patients per covariate.

Approvals~~IRB~~

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and ~~the SUPPORT Trial~~SUPPORT. The protocol was approved by the NRN GDB and Steering committees.

RESULTS

Maternal and Neonatal Characteristics

~~A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial.~~

The study population included 3,849 inborn infants~~: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group~~ (Figure 1). ~~Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants.~~

The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT among ~~in the subgroup of~~ infants from centers that had participated in the feasibility trial ~~(61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40)~~ but decreased significantly among ~~in the subgroup of~~ infants from the other centers. ~~(91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).~~

Other outcomes

Secondary outcomes~~, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven~~ were significantly lower in the post-SUPPORT group (Table 3), with the exception of BPD, death by 36 weeks and death before discharge. ~~By contrast, the adjusted risks of BPD, death before~~

Comment [LW7]: I had to add this back in because this is true using the correct table.

~~discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.~~

~~Unadjusted comparisons of T~~tertiary outcome variables are shown in the Appendix; online only. ~~Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).~~

DISCUSSION:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in ~~the SUPPORT trial~~SUPPORT after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before ~~the SUPPORT trial~~SUPPORT. The proportion of DR ETI significantly decreased among ~~in the subgroup of~~ infants from centers that had not participated in the feasibility trial, but not ~~. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT~~ among ~~in the subgroup of~~ infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 2000, after prospective introduction of ~~when neonatologists prospectively introduced~~ routine, early, bubble nasal CPAP.[18,7]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients~~, which limits incomplete/missing data and information bias~~; the use of multivariate analysis ~~to take into account confounding variables~~; inclusion and

exclusion criteria that were similar to those ~~used~~ in ~~the SUPPORT trial~~SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN ~~during the entire study period~~, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design~~, which prevents any cause-effect interpretation~~; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked ~~of~~ serial data and ~~lack of~~ data from centers that did not participate in ~~the SUPPORT trial~~SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study ~~we have shown that~~ the proportion of DR ETI in one NRN center ~~(which did not participate in the Feasibilty Trial)~~ decreased in non-enrolled patients ~~from baseline before the SUPPORT trial to epochs~~ during ~~the SUPPORT trial~~SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.[64] In that center, DR ETI decreased by 22% during/after ~~the SUPPORT Trial~~SUPPORT ~~(before release of the trial results)~~, but only by 1.6% in a large ~~large comparable~~ contemporaneous cohort ~~of infants participating in the Vermont Oxford Network~~.[64] ~~Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed~~

~~to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.[18-27] We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.~~

This study did not address how generalizable the study results might be to other centers, ~~that did not participate in the SUPPORT trial. It is possible that~~ Ceenters participating in ~~the SUPPORT trial~~SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~the SUPPORT trial~~SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after ~~the SUPPORT Trial~~SUPPORT in the group of infants from centers that had not previously participated in a similar trial ~~the feasibility trial~~ but not in the group of infants from the other centers, ~~where the proportion of ETI was already lower prior to initiation of the SUPPORT trial.~~

This study ~~provides additional evidence to~~ suggests that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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The Study Sponsor, the National Institute of Child Health and Human Development (NICHD), did not have any role in the study design; in the collection, analysis and interpretation data; in the writing of the report; and in the decision to submit the paper for publication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. ~~It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.~~

WHAT THIS STUDY ADDS

- The proportion of delivery room intubation (a~~A change in~~ process of care) decreased after the SUPPORT trial.
- This decrease was observed ~~was observed only~~ among infants born in centers that had not participated previously in a related trial, but not in the other centers.
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	10856/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Comment [LW8]: Luc this one was 1085

Abbreviations: RR, relative risk; CI, confidence interval

[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial

[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adj p v
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.032
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.815 (0.773-0.9589)	<0.00301
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.9386 (0.8176-1.1098)	0.2602
BPD (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.042 (0.957-1.1)	0.5526
Severe ROP[4]	174/1294 (13.5)	181/18753 (9.7)	0.0009	-	0.663 (0.532-0.8277)	<0.[illegible]
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.9688 (0.8376-1.100)	0.5906
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.834-0.97)	0.00433
Days on ventilator (survivors)[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.27 (-5.76-1, -2.73-2)		<0.0001

Comment [LW9]: This looked like the original version of the table not the latest version in which the adjusted results were updated, so I've attached that in the email

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Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted valuesRRs (Post vs. Pre SUPPORT) from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include ~~taking into account~~ gestational age, ~~GA,~~ birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD also includes ~~contained these same additional variables as well as~~ intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

~~[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).~~

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

LIST OF CHANGES

Abstract: We have corrected the section on Setting: we entered the sentence: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN" at the beginning of this section

We have written the hypotheses as such page 5 second paragraph lines 2-4.

We show that all outcome variables were planned except for the proportion of babies who have never been intubated (page 7, 2nd paragraph, last 2 lines).

We have shortened the manuscript by 500 words, especially the tertiary variables and the discussion.

We have provided two revised sections (one in the background,page 4 , last paragraph and page 5, first line; and one in the discussion, page 11, second paragraph) to show the importance of studying this and of analyzing whether the phenomenon exists/does not exist.

We have tightened the "what is known" and "what this adds" section (page 16).

ITEMIZED RESPONSES TO COMMENTS

Thank you for the suggestions. Here are the itemized responses in italics.

In addition to the reviewers' comments, the editors found the paper to be long and tedious to read - please shorten by 500 words.
A: We have shortened the manuscript by 500 words.

In the abstract, what you have written as Setting is not really the setting - please state what you mean.
A: We have started this paragraph by the following statement: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN."

Please state hypotheses as such, rather than speculations.
A: On page 5 paragraph 2 we replaced the word "speculated" with "hypothesized"."

Was this a planned analysis?
A: Yes. All studies conducted at the NICHD NRN require the development of a concept proposal followed if approved by a full protocol. For this study, a protocol was submitted to the NRN GDB committee and then to the Steering Committee. The goal was to test whether the proportion of endotracheal intubation in the delivery room (DR ETI) decreased after the SUPPORT trial in other NRN centers, as had been observed in a single center (reference 4). This protocol was, after multiple revisions, approved by both NRN committees. This statement was added on page 9, paragraph 1, lines 2-3.

Please explain why all the tertiary outcome data in the Appendix would be needed.
A: These data are important to show known potential confounding variables and biases that could have affected the primary and secondary outcomes.

Page 0318 of 2000

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) decreased in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85-89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the NRN, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, p <0.0001) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled.[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in the SUPPORT Trial and the GA range that would be most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the feasibility trial demonstrated that clinical practice, specifically the proportion of DR ETI, changed among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after

the SUPPORT trial in participating centers. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the trial. We speculated that the decrease in proportion of DR ETI in each center after the trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the feasibility trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.

METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT

trial and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trial, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred).[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should

be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of DR ETI during the first period.

Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough for multivariate analysis with 10 patients per covariate.

IRB

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and the SUPPORT Trial.

RESULTS

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial.

The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT in the subgroup of infants from centers that had participated in the feasibility trial (61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ($P<0.001$).

DISCUSSION:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the feasibility trial. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 200, when neonatologists prospectively introduced routine, early, bubble nasal CPAP.[17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients, which limits incomplete/missing data and information bias; the use of multivariate analysis to take into account confounding variables; inclusion and exclusion criteria that were similar to those used in the SUPPORT trial; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN during the entire study period, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions; lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study we have shown that the proportion of DR ETI in one NRN center (which did not participate in the Feasibilty Trial) decreased in non-enrolled patients from baseline before the SUPPORT trial to epochs during the SUPPORT trial and before its publication, in the absence of any changes in DR policy or practice guidelines.[4] In that center, DR ETI decreased by 22% during/after the SUPPORT Trial (before release of the trial results), but only by 1.6% in a large comparable contemporaneous cohort of infants participating in the Vermont Oxford Network .[4] Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.[18-27] We

decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.

This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after the SUPPORT Trial in the group of infants from centers that had not participated in the feasibility trial but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial. This study provides additional evidence to suggest that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.

WHAT THIS STUDY ADDS

A change in process of care after the SUPPORT trial was observed only among infants born in centers that had not participated previously in a related trial. This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval

[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial

[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
BPD	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

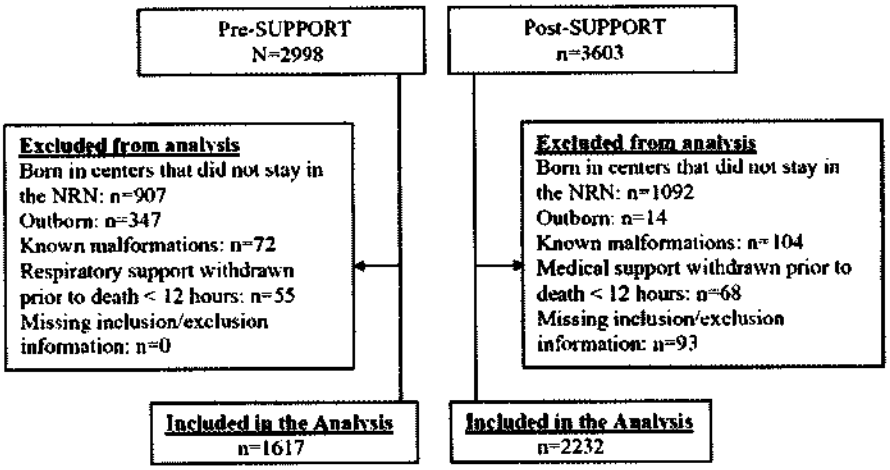
Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

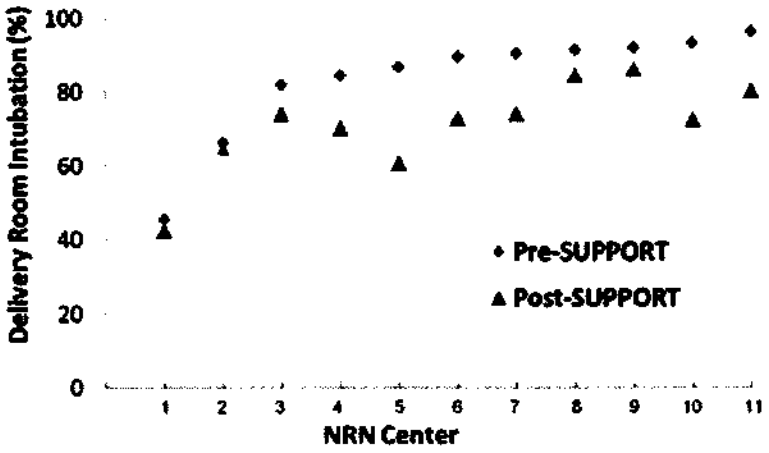
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).



Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study
64x35mm (300 x 300 DPI)



Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study
36x21mm (300 x 300 DPI)

Appendix. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

From: Luc Brion
To: Wrage, Lisa Ann
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057
Date: Monday, April 07, 2014 2:51:41 PM

Thanks a lot
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 1:49 PM
To: Luc Brion
Cc: Rosemary Higgins (higginsr@mail.nih.gov); Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc,
Thanks a lot, it sounds very reasonable, and I think we can also just state that we made that assumption since we don't have the specific question.
I'll get back to you when I have the information.
LIsa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 2:41 PM
To: Wrage, Lisa Ann
Cc: Rosemary Higgins (higginsr@mail.nih.gov); Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

I understand your question. I looked at the 2008 version of the NG03 form with Diane Vasil.

I would use a cut off of 15 minutes. Surfactant administration within 15 minutes of life would safely correspond to surfactant administration in the delivery room.

Of course, nothing is perfect.

This should exclude any administration of surfactant in the NICU in most settings (but not in Columbia, NY, where all "DR" resuscitation actually takes place in the transitional care nursery, where the baby is being moved immediately).
However, this cutoff may not capture them all (see below, CPAP arm of the VON trial):

In the VON trial: Age at intubation, median (quartile), intubation arm: 3.5 (2.0–5.0) min
INSURE: 4.0 (2.0–6.0)
CPAP: 4.5 (3.0–11.5)

Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 12:41 PM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc,

Since we don't have a specific question for DR surfactant, could you tell me what a reasonable assumption is regarding timing to first dose of surfactant and whether or not it was in the DR?
In other words within what time frame is it safe to assume that the surfactant was given in the DR.
Thanks.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 11:40 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Thanks
The two questions are:
1. How many babies received surfactant in the DR and were extubated immediately (i.e., received surfactant in the DR [NG03] but were extubated immediately (i.e, did not have an entry for intubation on NG02)?
2. What is the total number of babies for whom this information was available ?
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 10:35 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc, Thanks for the helpful information.
I will start looking at the timing of surfactant for those infants who have timing information entered. I'll get back to you when I have specific questions about what you need.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 11:23 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

I think it would be useful to respond to the reviewer, even if we do not have the data for earlier patients.
INSURE became more popular after the VON trial (see attached).

INSURE stands for "INtubate, SURfactant, Extubate".
This was one arm of the RCT run by the Vermont Oxford: CPAP, intubation + ventilation, INSURE.
Actually the VON protocol included:
"intubate-surfactant-extubate (ISX): infants were to be intubated 5 to 15 minutes after birth for the purposes of surfactant administration. Infants who required a fraction of inspired oxygen (FIO2) 0.6 without severe respiratory distress or apnea were to be extubated to nCPAP 15 to 30 minutes after surfactant instillation;"

The GDB criterion to exclude a DR INTUBATION from being entered on NG02 is much shorter intubation than that:
" Intubation?
Insertion of a tube (even if transiently) into the trachea to allow positive pressure ventilation for breathing. If intubation was done for suctioning or to give surfactant and immediately removed it should not be included here."

Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]

Sent: Monday, April 07, 2014 10:07 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

What is INSURE? Just curious.
The date/time is only on the 2008 form, not the 2002 or 2011 forms, so I would have the question on, I assume, a relatively small proportion of the later group.
But you can let me know if you think this would still be helpful.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 10:58 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Can you answer the question for the later-born babies?
INSURE has become popular lately.
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 9:55 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc, Yes that's the question we use for surfactant, but it looks like the date/time for surfactant administration was on one version of the 3 versions of the NG03 form that I used. The first version is just yes/no to surfactant administration, and the last version is just >= or < 72 hours. So, I don't at the moment see any way to determine DR intubation for surfactant on all the babies.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 10:39 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

If a patient is intubated in the DR for surfactant only, it would be entered on GDB manual on section 4.3.2.
This would come into form NGO3 B.2
See below
Luc

4.3.2 Section B - PULMONARY
1. Demonstrated clinical features of respiratory distress within the first 24 hours?
Record 'Y' if infant showed signs of grunting, flaring, retracting, paradoxical breathing, cyanosis and/or supplemental oxygen requirement within the first 24 hours.
2. Did the baby receive surfactant?
This includes any surfactant preparation used at any location (delivery room, NICU or at referring hospital).
If YES, code all that apply
a. Less than 72 hours of life?

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 9:29 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc,
I used the 'd.Intubation?' question on the NG02 which is under the 'Delivery Room resuscitation'/'Birth resuscitation/stabilization' section on the forms. It is described in each manual as intubation for PPV and it says not for suctioning (2002) /not for suctioning/surfactant (2008 & 2011). I don't see a question about intubation for surfactant in this section, could you point me to where you see that?
Thanks.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, April 04, 2014 7:23 PM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Lisa,
thanks a lot for your email.
One question: In the GDB worksheet has separate information about intubation for ventilation in the delivery and separate information about Intubation for surfactant in the delivery room.
I presume you counted intubation in the DR from the first entry only. Could you please confirm that?
Do you have or could you extract any information on intubation for surfactant in the delivery room for patients who did not remain intubated? If not, I will say that in my response to the reviewer #2.
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, April 04, 2014 11:33 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Luc Brion
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi,
It does look positive, the reviewers comments see pretty benign in terms of what they want addressed, it looks to me like reducing by 500 words might be the hardest part!
Lisa

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 04, 2014 12:15 PM
To: Das, Abhik; Luc Brion (luc.brion@utsouthwestern.edu)
Cc: Wrage, Lisa Ann
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

I agree - go for it!
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch 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, April 04, 2014 12:14 PM
To: Luc Brion (luc.brion@utsouthwestern.edu)
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Luc:

It looks to me that the changes asked for are not very radical and quite doable!

Thanks

Abhik

-----Original Message-----
From: onbehalfof+info.adc+bmj.com@manuscriptcentral.com
[mailto:onbehalfof+info.adc+bmj.com@manuscriptcentral.com] On Behalf Of info.adc@bmj.com
Sent: Friday, April 04, 2014 11:24 AM
To: luc.brion@utsouthwestern.edu
Cc: rm.beattie@btinternet.com; doctorlevan@gmail.com; luc.brion@utsouthwestern.edu; Wrage, Lisa Ann; Gantz, Marie; myra.wyckoff@utsouthwestern.edu; Pablo.Sanchez@nationwidechildrens.org; roy.heyne@utsouthwestern.edu; mambarambath.jaleel@utsouthwestern.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik; Barbara.Stoll@oz.ped.emory.edu; higginsr@mail.nih.gov
Subject: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

04-Apr-2014

Manuscript ID fetalneonatal-2014-306057 entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial"

Dear Dr. Brion,

Thank you for submitting the above manuscript to Archives of Disease in Childhood. It has been considered carefully at an editorial meeting and unfortunately, we do not wish to publish it in its current form.

However, we invite you to resubmit a further version of your paper. In inviting you to resubmit, I must emphasise that there is no guarantee that your paper will be accepted but we will look at it carefully with our referees and hope that it might prove possible to eventually publish a version of it.

It is essential that you detail your response to each and every one of the reviewers' comments, including any with which you disagree so have not complied with in your revised version. The comments of the reviewer(s) are included at the bottom of this letter.

In addition to the reviewers' comments, the editors found (b)(4),(b)(6)

(b)(4),(b)(6)

To revise your manuscript, log into http://mc.manuscriptcentral.com/adc and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. You may also click the below link to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

http://mc.manuscriptcentral.com/adc?URL_MASK=774af78a9f6b46c38fbcbc77c8a31c86

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to Archives of Disease in Childhood, your revised manuscript should be submitted by 03-Jun-2014. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Archives of Disease in Childhood and I look forward to receiving your revision.

Sincerely,
Dr. Ann Stark
Associate Editor, Archives of Disease in Childhood

Reviewer(s)' Comments to Author:

Reviewer: 1

(b)(4),(b)(6)

(b)(4),(b)(6)

Discussion: please correct the year where it says '200'

Reviewer: 2

(b)(4),(b)(6)

From:	Luc Brion
To:	Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject:	RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057
Date:	Monday, April 07, 2014 11:50:32 AM
Attachments:	Responses to comments rev 4-7-14 rev.docx Jackie LeVan Manuscript NRN 4-7-14 rev.docx

Here is a revision based on all our discussions and your suggestions.
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 10:07 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

What is INSURE? Just curious.
The date/time is only on the 2008 form, not the 2002 or 2011 forms, so I would have the question on, I assume, a relatively small proportion of the later group.
But you can let me know if you think this would still be helpful.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 10:58 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Can you answer the question for the later-born babies?
INSURE has become popular lately.
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 9:55 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc, Yes that's the question we use for surfactant, but it looks like the date/time for surfactant administration was on one version of the 3 versions of the NG03 form that I used. The first version is just yes/no to surfactant administration, and the last version is just >= or < 72 hours. So, I don't at the moment see any way to determine DR intubation for surfactant on all the babies.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 10:39 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

If a patient is intubated in the DR for surfactant only, it would be entered on GDB manual on section 4.3.2.
This would come into form NGO3 B.2
See below
Luc

4.3.2 Section B - PULMONARY

1. Demonstrated clinical features of respiratory distress within the first 24 hours?
Record 'Y' if infant showed signs of grunting, flaring, retracting, paradoxical breathing, cyanosis and/or supplemental oxygen requirement within the first 24 hours.
2. Did the baby receive surfactant?
This includes any surfactant preparation used at any location (delivery room, NICU or at referring hospital).
If YES, code all that apply
a. Less than 72 hours of life?

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 9:29 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc,
I used the 'd.Intubation?' question on the NG02 which is under the 'Delivery Room resuscitation'/'Birth resuscitation/stabilization' section on the forms. It is described in each manual as intubation for PPV and it says not for suctioning (2002) /not for suctioning/surfactant (2008 & 2011). I don't see a question about intubation for surfactant in this section, could you point me to where you see that?
Thanks.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, April 04, 2014 7:23 PM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Lisa,
thanks a lot for your email.
One question: In the GDB worksheet has separate information about intubation for ventilation in the delivery and separate information about Intubation for surfactant in the delivery room.
I presume you counted intubation in the DR from the first entry only. Could you please confirm that?
Do you have or could you extract any information on intubation for surfactant in the delivery room for patients who did not remain intubated? If not, I will say that in my response to the reviewer #2.
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, April 04, 2014 11:33 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Luc Brion
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi,
It does look positive, the reviewers comments see pretty benign in terms of what they want addressed, it looks to me like reducing by 500 words might be the hardest part!
Lisa

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 04, 2014 12:15 PM
To: Das, Abhik; Luc Brion (luc.brion@utsouthwestern.edu)
Cc: Wrage, Lisa Ann
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

I agree - go for it!

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
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-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, April 04, 2014 12:14 PM
To: Luc Brion (luc.brion@utsouthwestern.edu)
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Luc:

It looks to me that the changes asked for are not very radical and quite doable!

Thanks

Abhik

-----Original Message-----
From: onbehalfof+info.adc+bmj.com@manuscriptcentral.com [mailto:onbehalfof+info.adc+bmj.com@manuscriptcentral.com] On Behalf Of info.adc@bmj.com
Sent: Friday, April 04, 2014 11:24 AM
To: luc.brion@utsouthwestern.edu
Cc: rm.beattie@btinternet.com; doctorlevan@gmail.com; luc.brion@utsouthwestern.edu; Wrage, Lisa Ann; Gantz, Marie; myra.wyckoff@utsouthwestern.edu; Pablo.Sanchez@nationwidechildrens.org; roy.heyne@utsouthwestern.edu; mambarambath.jaleel@utsouthwestern.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik; Barbara.Stoll@oz.ped.emory.edu; higginsr@mail.nih.gov
Subject: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

04-Apr-2014

Manuscript ID fetalneonatal-2014-306057 entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial"

Dear Dr. Brion,

Thank you for submitting the above manuscript to Archives of Disease in Childhood. It has been considered carefully at an editorial meeting and unfortunately, we do not wish to publish it in its current form.

However, we invite you to resubmit a further version of your paper. In inviting you to resubmit, I must emphasise that there is no guarantee that your paper will be accepted but we will look at it carefully with our referees and hope that it might prove possible to eventually publish a version of it.

It is essential that you detail your response to each and every one of the reviewers' comments, including any with which you disagree so have not complied with in your revised version. The comments of the reviewer(s) are

included at the bottom of this letter.

In addition to the reviewers' comments, the editors found (b)(4),(b)(6)

(b)(4),(b)(6)

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Because we are trying to facilitate timely publication of manuscripts submitted to Archives of Disease in Childhood, your revised manuscript should be submitted by 03-Jun-2014. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Archives of Disease in Childhood and I look forward to receiving your revision.

Sincerely,
Dr. Ann Stark
Associate Editor, Archives of Disease in Childhood

Reviewer(s)' Comments to Author:

Reviewer: 1

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

UT Southwestern Medical Center
The future of medicine, today.

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3]
Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD,[1] Pablo J. Sánchez, MD,[1,4]
Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil N. Finer, MD,[5]
Waldemar A. Carlo, MD,[6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7]
Rosemary D. Higgins, MD,[8] on behalf of
the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital, Columbus, OH; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 2429 words
Article length: 12,49990 words
Revised 4/54/141/23/2014 rev
FetalNeonatal-2014-306057.R1

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) changed ~~decreased~~ in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA, ~~born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the NRN~~, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, p <0.0001) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

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Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized ~~2 X 2 factorial~~ controlled trial (RCT), in which preterm infants of $24^{0/7}$ ~~weeks~~ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets ~~of either 85 to 89% or 91 to 95%.~~[1,2] From ~~February~~ 2005 through ~~February~~ 2009, 1316 infants were enrolled in 19 centers.[1,2] The results of ~~the~~ SUPPORT ~~trial~~ were released to ~~the~~ NRN centers in December 2009 ~~and published in May 2010~~.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] ~~The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.~~

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in ~~the SUPPORT Trial~~SUPPORT and the GA range that would be most appropriate for ~~the SUPPORT Trial~~SUPPORT.[3] Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients. A previous study in one NRN center that had not participated in the feasibility trial demonstrated that ~~clinical practice, specifically~~ the

proportion of DR ETI, changed among non-enrolled patients during SUPPORT ~~the trial~~ and before release of its results.[4] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after ~~the SUPPORT trial~~SUPPORT in participating centers. We hypothesized that ~~that after the SUPPORT trial there would be a decrease in~~ DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks changed after ~~the SUPPORT trial~~SUPPORT. ~~compared to the period before the trial.~~ We speculated that the decrease in proportion of DR ETI in each center after SUPPORT ~~the trial~~ would depend on the ~~baseline~~ proportion before the trial. We also speculated that the decrease in DR ETI after ~~the SUPPORT Trial~~SUPPORT would be less in centers that had participated in the feasibility trial than in the other centers. ~~In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.~~

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METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of ~~the~~

~~SUPPORT trial~~SUPPORT and in a second preterm cohort born after release of the results of ~~the SUPPORT trial~~SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in ~~the~~ ~~SUPPORT trial~~SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes ~~preterm~~ patients born during a ~~2-year~~ period preceding ~~the~~ ~~SUPPORT trial~~SUPPORT (~~from~~ 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT ~~Trial to~~ NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in ~~the SUPPORT trial~~SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in ~~the SUPPORT trial~~SUPPORT, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to

death < 12 hours. The last~~ter~~ criterion was different from ~~the SUPPORT trial~~SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

~~Outcome variables were selected a priori.~~

The primary outcome variable was a practice variable, i.e., DR ETI.

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in ~~the SUPPORT trial~~SUPPORT), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge, and (3) death before discharge. ~~Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors.~~ The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of ~~the SUPPORT trial~~SUPPORT, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of ~~the SUPPORT trial~~SUPPORT was reached or resolution occurred).[1,2]

Additional ~~Tertiary~~ outcomes are described in Tables 3 and ~~included practice variables~~ in the Appendix, on line only. ~~such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.~~ Outcome variables were selected a priori, except the proportion of babies who were never intubated.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT), NRN center, and pre-specified prenatal covariates ~~(based on the literature)~~ shown to affect outcomes in very preterm infants[56] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional

variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[67-156] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort ~~first period (pre-SUPPORT) to the second period (post-SUPPORT)~~ was higher in centers with higher proportion of DR ETI during the first period.

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Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates~~, in the 11 centers.~~ This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough for multivariate analysis with 10 patients per covariate.

ApprovalsIRB

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and the SUPPORT TrialSUPPORT. The protocol was approved by the NRN GDB and Steering committees.

RESULTS

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation

coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT among ~~in the subgroup of~~ infants from centers that had participated in the feasibility trial ~~(61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40)~~ but decreased significantly among ~~in the subgroup of~~ infants from the other centers. ~~(91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).~~

Other outcomes

Secondary outcomes~~, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven~~ were significantly lower in the post-SUPPORT group (Table 3). ~~By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.~~

~~Unadjusted comparisons of T~~tertiary outcome variables are shown in the Appendix; online only. ~~Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).~~

DISCUSSION:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in ~~the SUPPORT trial~~SUPPORT after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before ~~the SUPPORT trial~~SUPPORT. The proportion of DR ETI significantly decreased among ~~in the subgroup of~~ infants from centers that had not participated in the feasibility trial, but not ~~. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT among in the subgroup of~~ infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 2000, after prospective introduction of ~~when neonatologists prospectively introduced~~ routine, early, bubble nasal CPAP.[16,17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients~~, which limits incomplete/missing data and information bias~~; the use of multivariate analysis~~ to take into account confounding variables~~; inclusion and exclusion criteria that were similar to those ~~used~~ in ~~the SUPPORT trial~~SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN ~~during the entire study period~~, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design~~, which prevents any cause-effect interpretation~~; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and

lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked ~~of~~ serial data and ~~lack of~~ data from centers that did not participate in ~~the SUPPORT trial~~SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study ~~we have shown that~~ the proportion of DR ETI in one NRN center ~~(which did not participate in the Feasibilty Trial)~~ decreased in non-enrolled patients ~~from baseline before the SUPPORT trial to epochs~~ during ~~the SUPPORT trial~~SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.[4] In that center, DR ETI decreased by 22% during/after ~~the SUPPORT Trial~~SUPPORT ~~(before release of the trial results)~~, but only by 1.6% in a large ~~large comparable~~ contemporaneous cohort ~~of infants participating in the Vermont Oxford Network~~.[4] ~~Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.~~[18-27] ~~We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.~~

This study did not address how generalizable the study results might be to other centers, ~~that did not participate in the SUPPORT trial. It is possible that C~~centers participating in ~~the SUPPORT trial~~SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~the SUPPORT trial~~SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after ~~the SUPPORT Trial~~SUPPORT in the group of infants from centers that had not participated in the feasibility trial but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of ~~the SUPPORT trial~~SUPPORT. This study provides additional evidence to suggest that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

ACKNOWLEDGMENTS:

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study. The content of the publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

FUNDING

The Study Sponsor, the National Institute of Child Health and Human Development (NICHD), did not have any role in the study design; in the collection, analysis and interpretation data; in the writing of the report; and in the decision to submit the paper for publication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. ~~It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.~~

WHAT THIS STUDY ADDS

- The proportion of delivery room intubation (a~~A change in~~ process of care) decreased after the SUPPORT trial.
- This decrease was observed ~~was observed only~~ among infants born in centers that had not participated previously in a related trial, but not in the other centers.~~.~~
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval
[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial
[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
BPD	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

LIST OF CHANGES

Abstract: We have corrected the section on Settings ~~in the abstract~~: we entered the sentence: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN" at the beginning of this section.

We have written the hypotheses as such in the Objective section of the abstract and on page 5 lines 2-3.

We show that all outcome variables were planned except for the proportion of babies who have never been intubated (page 7, 2nd paragraph, last 2 lines).

We have shortened the manuscript by 500 words, especially the tertiary variables and the discussion.

We have provided two revised sections (one in the background, page 4 , last paragraph and page 5, first line; and one in the discussion, page 11, second paragraph) to show the importance of studying this and of analyzing whether the phenomenon exists/does not exist.

We have tightened the "what is known" and "what this adds" section (page 15).

ITEMIZED RESPONSES TO COMMENTS

Thank you for the suggestions. Here are the itemized responses in italics.

In addition to the reviewers' comments, the editors found the paper to be long and tedious to read - please shorten by 500 words.
A: We have shortened the manuscript by 500 words.

In the abstract, what you have written as Setting is not really the setting - please state what you mean.
A: We have started this paragraph by the following statement: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN."

Please state hypotheses as such, rather than speculations.
A: In the abstract we replaced the word "decreased" by "changed". On page 5~~6~~ lines 2-3 we changed the text into the following statement: "We hypothesized that ~~that after the SUPPORT trial there would be a decrease in~~ DR ETI in preterm infants 240/7 to 276/7 weeks changed after ~~the~~ SUPPORT ~~trial~~."

Was this a planned analysis?
A: Yes. All studies conducted at the NICHD NRN require the development of a concept proposal followed if approved by a full protocol. For this study, a protocol was submitted to the NRN GDB committee and then to the Steering Committee. The goal was to test whether the proportion of endotracheal intubation in the delivery room (DR ETI) decreased after the SUPPORT trial in other NRN centers, as had been observed in a single center (reference 4). This protocol was, after multiple revisions, approved by both NRN committees. This statement was added on page 9, first paragraph, lines 2-3.

Please explain why all the tertiary outcome data in the Appendix would be needed.

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A: These data are important to show known potential confounding variables and biases that could have affected the primary and secondary outcomes.

Discussion could be shortened.
A: We have shortened the discussion as requested.

What is known/what this adds should be tightened up and bulleted.
A: We have revised that section as requested, and have followed the guidelines to authors. (page 15)

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Overall, I found this to be a good manuscript with a rigorous study design and implementation and high scientific validity within the constraints of the study design utilized.

I think the background section would benefit from inclusion of material on why it is important to study the spread of a practice within an institution when that institution participates in a randomized trial of the practice. Why is it such a big deal to study this and prove that the phenomenon exists/does not exist?
A: Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients. Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.
We have previously shown that a center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients. A previous study in one NRN center that had not participated in the feasibility trial demonstrated that clinical practice, specifically the proportion of DR ETI, changed among non-enrolled patients during SUPPORT the trial and before release of its results, but not in a large contemporaneous cohort in the Vermont-Oxford Network. Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.
We have entered most of the above discussion on pages 4 (last paragraph) and 5 (first paragraph).

Methods: It's not clear how many centers in total participated in the SUPPORT trial.
A: we entered the number in the text: 19 (page 3, introduction, line 9 ~~of the introduction~~)

Methods, eligibility and inclusion criteria: use the word 'last criterion' instead of the 'latter criterion'
A: We changed the text as requested (page 6, Eligibility and exclusion criteria: line 6).

Methods: outcome variables. Please specify if the outcome variables were selected a priori (pre-specified) before the analysis was done (e.g. as part of a study protocol), or was there a post-hoc component to the analysis.
A: Outcome variables were selected a priori, except the proportion of babies who were never intubated (page 7, second ~~as indicated on the last line of the~~ paragraph, last line ~~on other outcomes~~).

Analysis:
Why was there no analysis accounting for the clustering of infants within the eleven institutions? I think this is required, but this statement will need to be confirmed by a statistician.
A: All adjusted analyses controlled for NRN center by including it as a covariate in all our regression models. This is indicated in page 7, statistical analysis, line 7. ~~Analyses were all done and verified by 3 statisticians in the NRN (LAW, MGG and AD).~~ The analysis ~~with clustering~~ by institution is presented in Figure 2.

Results: Maternal and neonatal characteristics. I think the authors can refer readers to the flow diagram in Figure 1 that shows the numbers and save some space in the text.
A: We have shortened the text as suggested (page 9).

Discussion
I think the strengths and limitations are well-described.
I think the discussion section will benefit from inclusion of material that describes the results of other studies of spread of a practice as a result of randomized trial participation, what might be the underlying mechanisms for such spread, and what the implications are for trials and for practice.
Framing this study's results in the larger context of healthcare and neonatal practice will make it more appealing and meaningful to readers.
A: We added the following statement to the end of the discussion (page 11, second paragraph): Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

Discussion: please correct the year where it says '200'
A: thank you for pointing this out; we have corrected the year to 2000 (page 10, discussion, first paragraph, line 7).

Reviewer: 2

Comments to the Author
This is a well executed secondary analysis of the NRN, which demonstrate that infants who are not enrolled in an RCT have improved short- and long-outcomes.

I agree with the authors that the reduction is DR ETI might have also been associated with the familiarity with the T-Piece device and their clinical observations that CPAP in the DR is possible. As mentioned by the authors a survey of other centres would not give a total picture of NICU practices in other NICUs and if SUPPORT has changes their practice too. However, this remains an interesting question as studies like SUPPORT, who demonstrated that CPAP in the DR is well tolerated by infants, should be implemented in other NICUs as well.
A: We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This has happened several times in the recent past in the NRN. Furthermore it is even more unlikely that people may remember the exact time practices changed several years ago. This is discussed on page 11, lines 1-3.

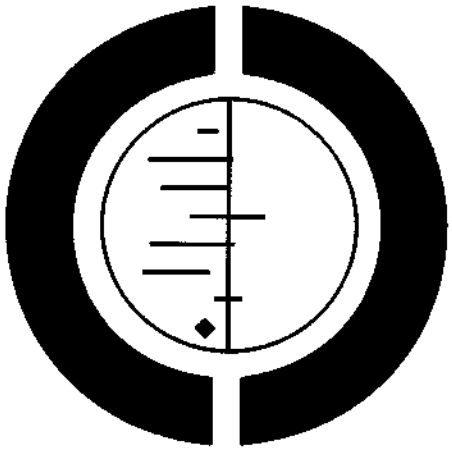
For this study we selected centers that participated in SUPPORT and remained in the NRN, because previous NRN studies have shown major interinstitution variability, and the list of NRN centers changes every 5 years. This is a strength of the study, as discussed on page 10, second paragraph, lines 3-5

Although, Table 2 demonstrates a significant reduction in DR ETI, however in Figure 2 it appears that two centres have similar DR ETI rates pre and post SUPPORT. Would INUSRE also be counted as an intubation or were these intubation only with continuous mechanical ventilation?

*A: The data on intubation pertains to intubation for ventilation in the delivery room; these numbers include patients who received surfactant and were not immediately extubated. Data from the GDB during the first period (pre-SUPPORT) do not have an entry on delivery room intubation for surfactant. The number of babies who were intubated in the delivery room for surfactant administration followed by immediate extubation is --- ~~No patient received INSURE~~ _ ~~*** Lisa: could you please verify whether this is accurate? THANKS~~*

Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome (Review)

Stevens TP, Blennow M, Myers EH, Soll R



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[Intervention Review]

Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Timothy P. Stevens[1], Mats Blennow[2], Eliza H Myers[3], Roger Soll[4]

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ABSTRACT

Background

Both prophylactic and early surfactant replacement therapy reduce mortality and pulmonary complications in ventilated infants with respiratory distress syndrome (RDS) compared with later selective surfactant administration. However, continued post-surfactant intubation and ventilation are risk factors for bronchopulmonary dysplasia (BPD). The purpose of this review was to compare outcomes between two strategies of surfactant administration in infants with RDS; prophylactic or early surfactant administration followed by prompt extubation, compared with later, selective use of surfactant followed by continued mechanical ventilation.

Objectives

To compare two treatment strategies in preterm infants with or at risk for RDS: early surfactant administration with brief mechanical ventilation (less than one hour) followed by extubation vs. later selective surfactant administration, continued mechanical ventilation, and extubation from low respiratory support. Two populations of infants receiving early surfactant were considered: spontaneously breathing infants with signs of RDS (who receive surfactant administration during evolution of RDS prior to requiring intubation for respiratory failure) and infants at high risk for RDS (who receive prophylactic surfactant administration within 15 minutes after birth).

Search methods

Searches were made of the Oxford Database of Perinatal Trials, MEDLINE (1966 - December 2006), CINAHL (1982 to December Week 2, 2006), EMBASE (1980 - December 2006), Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2006), Pediatric Research (1990 - 2006), abstracts, expert informants and hand searching. No language restrictions were applied.

Selection criteria

Randomized or quasi-randomized controlled clinical trials comparing early surfactant administration with planned brief mechanical ventilation (less than one hour) followed by extubation vs. selective surfactant administration continued mechanical ventilation, and extubation from low respiratory support.

Data collection and analysis

Data were sought regarding effects on the incidence of mechanical ventilation (ventilation continued or initiated beyond one hour after surfactant administration), incidence of bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), mortality, duration of mechanical ventilation, duration of hospitalization, duration of oxygen therapy, duration of respiratory support (including CPAP and nasal cannula), number of patients receiving surfactant, number of surfactant doses administered per patient, incidence of air leak syndromes (pulmonary interstitial emphysema, pneumothorax), patent ductus arteriosus requiring treatment, pulmonary hemorrhage, and other complications of prematurity. Stratified analysis was performed according to inspired oxygen threshold for early intubation and surfactant administration in the treatment group: inspired oxygen within lower ($FiO_2 \leq 0.45$) or higher ($FiO_2 > 0.45$) range at study entry. Treatment effect was expressed as relative risk (RR) and risk difference (RD) for categorical variables, and weighted mean difference (WMD) for continuous variables.

Main results

Six randomized controlled clinical trials met selection criteria and were included in this review. In these studies of infants with signs and symptoms of RDS, intubation and early surfactant therapy followed by extubation to nasal CPAP (NCPAP) compared with later selective surfactant administration was associated with a lower incidence of mechanical ventilation [typical RR 0.67, 95% CI 0.57, 0.79], air leak syndromes [typical RR 0.52, 95% CI 0.28, 0.96] and BPD [typical RR 0.51, 95% CI 0.26, 0.99]. A larger proportion of infants in the early surfactant group received surfactant than in the selective surfactant group [typical RR 1.62, 95% CI 1.41, 1.86]. The number of surfactant doses per patient was significantly greater among patients randomized to the early surfactant group [WMD 0.57 doses per patient, 95% CI 0.44, 0.69]. In stratified analysis by FIO_2 at study entry, a lower threshold for treatment ($FIO_2 \leq 0.45$) resulted in lower incidence of airleak [typical RR 0.46 and 95% CI 0.23, 0.93] and BPD [typical RR 0.43, 95% CI 0.20, 0.92]. A higher treatment threshold ($FIO_2 > 0.45$) at study entry was associated with a higher incidence of patent ductus arteriosus requiring treatment [typical RR 2.15, 95% CI 1.09, 4.13].

Authors' conclusions

Early surfactant replacement therapy with extubation to NCPAP compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is associated with less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes. A lower treatment threshold ($FIO_2 \leq 0.45$) confers greater advantage in reducing the incidences of airleak syndromes and BPD; moreover a higher treatment threshold (FIO_2 at study > 0.45) was associated with increased risk of PDA. These data suggest that treatment with surfactant by transient intubation using a low treatment threshold ($FIO_2 \leq 0.45$) is preferable to later, selective surfactant therapy by transient intubation using a higher threshold for study entry ($FIO_2 > 0.45$) or at the time of respiratory failure and initiation of mechanical ventilation.

PLAIN LANGUAGE SUMMARY

Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Respiratory distress syndrome (RDS) is the single most important cause of illness and death in preterm infants. Common treatments for RDS include supplemental oxygen and nasal continuous positive airway pressure (NCPAP). For severe RDS, surfactant administration during mechanical ventilation is used. Although treating RDS with surfactant improves clinical outcomes, mechanical ventilation can cause lung injury in preterm infants with RDS and contribute to the development of chronic lung disease (oxygen requirements at 36 weeks) and bronchopulmonary dysplasia (requirement for supplementary oxygen at 28 days, BPD). An important question is whether giving early surfactant with planned brief mechanical ventilation followed by prompt extubation (to NCPAP) is better than selectively giving surfactant when RDS has worsened causing respiratory insufficiency necessitating mechanical ventilation. The review authors identified six randomized trials reported between 1994 and 2006 that met the selection criteria for this review. A strategy of early surfactant administration with extubation to NCPAP was associated with significant reductions in the need for mechanical ventilation, fewer air leak syndromes (such as pneumothorax) and lower incidence of BPD compared with a strategy of later selective surfactant

administration and continued mechanical ventilation in infants with RDS. The findings suggest that a lower treatment threshold (oxygen requirement < 0.45) confers greater advantage than does a higher treatment threshold (oxygen requirement > 0.45).

An early surfactant therapy strategy results in a greater number of infants receiving surfactant and so more infants being exposed to the potential risks of intubation and surfactant administration. Although no complications of surfactant administration were reported in the studies reviewed, infants treated with an early surfactant therapy strategy tended to have a higher prevalence of patent ductus arteriosus (PDA). Two trials were terminated prior to achieving the targeted enrollment when the need for mechanical ventilation was found to be significantly different between groups at a scheduled interim analysis. Two other trials experienced slow enrollment leading to reduced numbers.

BACKGROUND

Respiratory distress syndrome (RDS) is the single most important cause of morbidity and mortality in preterm infants (Greenough 2002). Clinical trials have shown that surfactant replacement therapy in RDS decreases mortality and improves clinical outcomes of ventilated premature newborns (Soll 2002a). Trials have studied the optimal surfactant preparation, dose and time of administration. For infants at high risk for RDS, prophylactic (pre- or post-ventilation) or early (< 2 hours of age) surfactant replacement therapy compared to later selective surfactant administration of established RDS significantly improves survival and reduces the incidence of bronchopulmonary dysplasia (BPD) or death, and incidence of air leak (Gortner 1998; Yost 2002; Soll 2002b). However, despite the benefits of surfactant replacement therapy, BPD continues to be a clinically important complication of preterm birth and RDS (Yost 2002; Soll 2002a).

Previous systematic reviews of surfactant replacement therapy have evaluated trials that used a surfactant administration paradigm consisting of endotracheal intubation, surfactant administration, stabilization and intermittent positive pressure ventilation (IPPV) followed by extubation when stable on low respiratory support. IPPV for preterm infants with RDS has long been recognized to contribute to lung injury, which may lead to the development of bronchopulmonary dysplasia (BPD) (Northway 1967). Early implementation of continuous distending pressure (CDP) can avoid mechanical ventilation and prolonged intubation (Jonsson 1997; Kamper 1999) and is an effective treatment for RDS (Ho 2002). CDP has been applied as a continuous positive airway pressure (CPAP) using a nasopharyngeal tube or nasal prongs (NCPAP), or as a continuous negative pressure (CNP) applied externally to the thorax with a seal around the neck.

As early as 1971, Gregory and colleagues reported that CPAP was an effective treatment for RDS that reduced the need for mechanical ventilation (Gregory 1971). In 1987, Avery speculated that greater use of CPAP was associated with a lesser risk of BPD (Avery 1987). A recent observational study comparing the prevalence of chronic lung disease (CLD, oxygen at 36 weeks postmenstrual age) at three large NICUs identified initiation of mechanical ventilation as the major risk factor associated with an increased risk of CLD among very low birth weight infants (Van Marter 2000). Combination therapy with CPAP and surfactant replacement therapy offers potential synergy to treat RDS, avoid mechanical ventilation, and prevent lung injury that may lead to development of BPD.

This review evaluates the effect of surfactant administration via endotracheal instillation with a planned brief (< 1 hour) period of mechanical ventilation followed by extubation vs. more conventional management consisting of selective surfactant administration followed by continued mechanical ventilation and extubation from low respiratory support in previously non-intubated infants with RDS.

OBJECTIVES

To compare two treatment strategies for RDS: early surfactant administration with brief mechanical ventilation (less than one hour) followed by early extubation vs. later selective surfactant administration, continued mechanical ventilation and extubation from low respiratory support in previously non-intubated infants with RDS.

These two management strategies were compared in two populations of premature infants:

1. In spontaneously breathing infants with signs of RDS. Early intubation for surfactant administration followed by brief mechanical ventilation with planned extubation within one hour (treatment group) was compared with later intubation after progression of respiratory insufficiency, surfactant administration and continued mechanical ventilation with extubation from low respiratory support (control group). Subgroup analyses were planned according to:

i) Inspired oxygen threshold for early intubation and surfactant

administration in the treatment group: inspired oxygen within lower ($FiO_2 \leq 0.45$) or higher ($FiO_2 > 0.45$) range at study entry

ii) Method of extubation of treatment group: extubation to NCPAP or extubation to atmospheric pressure

2. In spontaneously breathing infants at risk of RDS who are < 15 minutes of age. Prophylactic intubation for surfactant administration at < 15 minutes of age followed by brief mechanical ventilation with planned extubation within one hour (treatment group) was compared with later, selective intubation after signs of RDS develop, surfactant administration and continued mechanical ventilation with extubation from low respiratory support (control group). Subgroup analyses was planned according to:

i) Inspired oxygen threshold for intubation and selective surfactant administration in the control group: inspired oxygen within lower ($FiO_2 < 0.45$) or higher ($FiO_2 > 0.45$) range

ii) Method of extubation of the treatment group: extubation to NCPAP or extubation to atmospheric pressure

METHODS

Criteria for considering studies for this review

Types of studies

Trials using random or quasi-random allocation to a treatment strategy consisting of surfactant administration via endotracheal instillation with a planned brief (< 1 hour) period of mechanical ventilation followed by extubation vs. more conventional management consisting of selective surfactant administration followed by continued mechanical ventilation and extubation from low respiratory support .

Types of participants

Infants < 37 weeks' gestation with signs of RDS (oxygen requirement, respiratory distress and consistent chest radiograph) or infants < 32 weeks gestation considered to be at high risk for RDS.

Types of interventions

Study group: Infants allocated to a strategy consisting of intubation, prophylactic or early surfactant administration, brief ventilation (< 1 hour) and planned rapid extubation.
Control group: Infants allocated to conventional treatment consisting of selective surfactant administration followed by continued mechanical ventilation and extubation from low respiratory support.

Types of outcome measures

Primary outcomes
1. Need for mechanical ventilation (incidence of ventilation continuing for one hour or more after surfactant administration in the early treatment group or initiated for respiratory insufficiency or apnea in either group)
2. Incidence of bronchopulmonary dysplasia (BPD, need for oxygen at 28 days of age)
3. Incidence of chronic lung disease (CLD, need for oxygen at 36 weeks postmenstrual age)
4. Incidence of neonatal mortality (mortality < 28 days of age)
5. Incidence of mortality prior to hospital discharge

Secondary outcomes
1. duration of mechanical ventilation (days)
2. duration of hospitalization (days)
3. duration in oxygen (days)
4. duration of any respiratory support (mechanical ventilation, CPAP and nasal cannula) (days)
5. number of patients receiving surfactant
6. number of surfactant doses per patient
7. incidence of air leak syndromes (pulmonary interstitial emphysema, pneumothorax)
8. intraventricular hemorrhage (any and severe, grade 3 - 4)
9. patent ductus arteriosus
10. necrotizing enterocolitis
11. retinopathy of prematurity (any and severe, stage 3 or greater)
12. frequency of apnea
13. time to regain birth weight (days)
14. neurodevelopmental outcome at hospital discharge and a later time point (> 1 year post-conceptional age). Neurodevelopmental impairment is defined as the presence of cerebral palsy and/or mental retardation (Bayley Scales of Infant Development Mental Developmental Index < 70) and/or legal blindness (< 20/200 visual acuity) and or deafness (aided or < 60dB on audiometric testing)
15. need for sedation/analgesia
16. parental satisfaction.

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group as outlined in the Cochrane Library was used. This included searches of the Oxford Database of Perinatal Trials, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2006), Pediatric Research, 1990 - 2006), and MEDLINE (1966 - December 2006) using MeSH headings: infant-newborn, pulmonary surfactant, CPAP, respiratory distress syndrome, clinical trial. Other databases searched included: EMBASE (1980 - December 2006), CINAHL (1982 - December 2006), reference lists of published trials and abstracts published in Pediatric Research (1990 - 2006). No language restrictions were applied.

Data collection and analysis

Standard methods of the Cochrane Collaboration and the Cochrane Neonatal Review Group were used to assess the methodologic quality of the trials. For each included study, information was collected regarding blinding of randomization, blinding of the intervention, completeness of follow-up, blinding of outcome measurements, drug intervention, stratification, and whether the trial was single or multicenter. If necessary to clarify study design or outcome data, efforts were made to directly contact the authors of the trial to complete the data set. Retrieved articles were reviewed and data extracted independently by two review authors (TS, EH). Discrepancies were resolved by discussion and consensus. The statistical methods for expressing treatment effect included relative risk (RR), risk difference (RD), number needed to treat (NNT) and mean difference (MD) when appropriate.

RESULTS

Description of studies

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

Searches of the literature identified twenty-one studies that evaluated early surfactant administration with brief ventilation and planned early extubation. Five of the reports were case series or studies having non-randomized controls (Alba 1995; Blennow 1999; Mandy 1998; Verder 1992; Victorin 1990). The trial of Dambeanu was excluded because mechanical ventilation was not available to either study group (Dambeanu 1997). The So 1994 and Tooley 2003 studies were excluded because patients received non-random administration of surfactant and were then randomized to rapid extubation or continued mechanical ventilation (So 1994; Tooley 2003). The Verder trial of infants < 30 weeks gestation was omitted because each study group had a planned brief period of mechanical ventilation (Verder 1999). The trial of Lefort (Lefort 2003, previously referred to Diniz 2002), a randomized controlled trial comparing prophylactic vs. rescue surfactant, was excluded because planned early extubation was not part of the study protocol. Sandri 2004, a large multicenter trial of prophylactic vs. rescue use of NCPAP, was excluded because surfactant administration was the primary endpoint.

Since the 2003 update of this review, four new studies evaluating early surfactant administration with brief ventilation and planned early extubation have been identified. Two of these studies (Dani 2004; Texas Research 2004) have been added to the analysis and two (Lefort 2003, Sandri 2004) were excluded as noted above. Two studies included in previous edition of this review have been updated with additional published data (Reininger 2005, previously included as D'Angio 2003) and unpublished data (NICHD 2002).

One study is awaiting assessment (Thomson 2002). Although outcomes of this study have been reported, the published version has insufficient detail to assess the quality of the study (Thomson 2002). The Thomson 2002 study was referred to as Fowlie 2002 in a previous version of this review.

Studies included in this review:

EARLY INTUBATION FOR SURFACTANT ADMINISTRATION FOLLOWED BY BRIEF MECHANICAL VENTILATION WITH PLANNED EXTUBATION WITHIN ONE HOUR IN INFANTS WITH SIGNS OF RDS.

Verder 1994: This multicenter study was performed in spontaneously breathing infants 25 - 35 weeks gestation with early RDS defined as an arterial to alveolar oxygen tension ratio < 0.22 (approximate FiO_2 < 0.55), and radiographic and clinical signs of RDS. Inclusion criteria included need for NCPAP of 6 cm of water. The treatment group consisted of early intubation for surfactant administration followed by brief mechanical ventilation with planned extubation within one hour. The control group underwent later intubation if required because of progression of respiratory insufficiency, followed by surfactant administration and continued mechanical ventilation with extubation from low respiratory support. This was a multicenter trial in Denmark and Sweden, where routine care of infants with RDS often begins with stabilization on NCPAP shortly after the onset of symptoms. This study tested the hypothesis that a single dose of porcine surfactant administered during a short period of intubation before the occurrence of serious respiratory deterioration could reduce the need for mechanical ventilation. The primary outcome was the need for mechanical ventilation (incidence of ventilation continuing for one hour or more after surfactant administration in the early treatment group or initiated for respiratory insufficiency or apnea in either group). The study was terminated early at a scheduled interim analysis, when the primary endpoint, need for mechanical ventilation, was noted to be significantly different between groups ($p < 0.01$).

NICHD 2002: This multicenter study was performed at participating NICHD Neonatal Research Network Centers in spontaneously breathing infants 1250 - 2000 grams birth weight who were < 12 hours of age with early RDS defined as an FIO_2 of 0.35 - 0.50 in an oxyhood or 0.25 - 0.50 on NCPAP, and radiographic and clinical signs of RDS. The treatment group consisted of early intubation for surfactant administration followed by brief mechanical ventilation with planned extubation as early as possible. The control group underwent later intubation if required because of progression of respiratory insufficiency followed by surfactant administration and continued mechanical ventilation with extubation from low respiratory support. The study was halted at approximately 11% of targeted study size (62 patients enrolled out of a target of 560 patients) due to slow enrollment (62 patients enrolled out of 1423 patients screened). Reasons for non-enrollment included FIO_2 outside the targeted range and chest radiograph without evidence of RDS. Unpublished methodolog-

ical details and outcome data from this trial were obtained from the NICHD Neonatal Research Network. These data reported on 62 enrolled subjects, rather than the 61 subjects included in the previous version of this review (one subject's data were included after publication of the NICHD abstract). This trial was identified as the NICHD 2001 trial in the prior version of this Cochrane review.

Vermont Oxford 2003: This multicenter study was performed at participating Vermont Oxford Network Centers in spontaneously breathing infants 1501 - 2500 grams birth weight who were 2 - 24 hours of age with early RDS defined as an FiO_2 of 0.30 - 0.60 with pCO2 < 65 mmHg in an oxyhood or on NCPAP, and radiographic signs of RDS. The treatment group consisted of early intubation for surfactant administration followed by brief mechanical ventilation with planned extubation within 15 - 30 minutes. The control group underwent later intubation if required because of progression of respiratory insufficiency followed by surfactant administration and continued mechanical ventilation with extubation from low respiratory support. Criteria for initiating mechanical ventilation for both treatment and control groups were specified as significant apnea, pCO2 > 65 mmHg, hypoxemia, or severe respiratory distress. Methodological and outcome data from this trial were obtained from the investigators and are not yet published. Data analyses and manuscript preparation are underway.

Dani 2004: This single center study was performed in 27 spontaneously breathing infants < 30 weeks gestation, who were < 6 hours of age with early RDS; the infants were randomized to receive either surfactant and initiation of mechanical ventilation (control) or surfactant and immediate extubation to NCPAP (treatment). The primary endpoint was the need for mechanical ventilation at seven days of age. The study had been designed to evaluate at least 48 infants, but an interim analysis after only 27 infants had been enrolled demonstrated statistical significance with respect to decreased incidence of mechanical ventilation in the treatment group, leading to early termination of the study.

Texas Research 2004: This multicenter study was performed in 132 spontaneously breathing infants < 36 weeks gestation and > 1250 grams, and with RDS at 4 - 24 hours of life. RDS was defined as requiring > 0.40 FiO_2 for > 1 hour and not requiring immediate intubation. Patients were randomized to receive either an early dose of surfactant followed by rapid extubation (treatment) vs. expectant management (control). This trial is unique in reporting duration of mechanical ventilation as the primary outcome. In calculating the duration of mechanical ventilation, the investigators included the time that the treatment group spent transiently intubated for surfactant administration.

Reininger 2005 (previously reported as D'Angio 2003): This single center study was performed in spontaneously breathing infants 25 0/7 - 35 6/7 weeks gestation who were < 24 hours of age with early RDS defined as respiratory distress requiring NCPAP, need for supplemental oxygen, and radiographic and clinical signs of RDS. Despite liberalizing eligibility criteria after the first 23 patients were enrolled (reducing the level of supplemental oxygen required for eligibility from an FiO_2 > 0.30 to FiO_2 > 0.21), patient accrual remained slow. Patient accrual occurred over a six year period and was eventually terminated at 50% of planned enrollment (105 patients enrolled out of a planned 206 patients). Reasons for non-enrollment included rapid progression of RDS once an FiO_2 of 0.30 was reached. The treatment group received early intubation for surfactant administration followed by brief mechanical ventilation with planned extubation within one hour. The control group underwent later intubation and surfactant replacement if required for progressive respiratory insufficiency. For both the treatment and control groups, the decision to initiate mechanical ventilation was based on the decision of the clinical care team; predetermined criteria to initiate mechanical ventilation in either the treated or control groups were not specified. As part of this trial, randomized infants underwent the study intervention behind a physical barrier at the hands of a study team not involved in the daily care of the baby. In this way, blinding the study intervention to the clinical team providing ongoing care for the baby. Although infants as young as 25 weeks gestation were potentially eligible, the average gestational age of participating infants was 32 1/2 weeks. This trial was identified as D'Angio 2003 in previous versions of this review.

EARLY INTUBATION FOR SURFACTANT ADMINISTRATION FOLLOWED BY BRIEF MECHANICAL VENTILATION WITH PLANNED EXTUBATION WITHIN ONE HOUR IN INFANTS AT RISK OF RDS.

None identified.

Risk of bias in included studies

Blinding of Randomization: In all six studies included in this review, randomization was blinded to the care team. In Verder 1994, randomization was carried out by opening sequentially numbered, sealed envelopes kept at each of the four participating hospitals. The randomization was in blocks of four to assure a similar number of babies were enrolled at each hospital. In the Vermont Oxford trial, randomization was stratified by birth weight group and age at enrollment (2 - 12 hours and 12 - 24 hours of age) (Vermont Oxford 2003). In the NICHD trial, randomization was stratified by center and birth weight group (1250 - 1500, 1501 - 1750, 1751 - 2000 grams) (NICHD 2002). In the Reininger study, sealed randomization cards were opened at the time of enrollment by study pharmacists located away from the clinical care unit. Block randomization was used without stratification (Reininger 2005). In the Texas Research Group trial, randomization was carried out through sequentially numbered, sealed, opaque envelopes at the five participating centers; randomization was stratified by center and birth weight (Texas Research Group 2004). In Dani 2004, randomization was revealed at the time of enrollment by opening sealed envelopes (Dani 2004).

Blinding of Intervention: In all but one of the six studies, no attempt was made to blind caregivers as to which randomized intervention the infant received. Blinding was generally not attempted due to the ethical problem that would be posed by a sham intubation, and the logistical difficulties of having two teams (a study team and a continuing care team) available around the clock during the course of the study. The Reininger study was unique in its attempt to blind the intervention; the intervention was blinded through use of a study team separate from the clinical care team that performed the study intervention. For all patients, the study team placed a privacy curtain around the patient's bedside. For the treatment group, the study team intubated, administered surfactant and extubated the baby to NCPAP. For control infants, no intervention was performed and the baby continued on NCPAP. The study team remained behind the privacy curtain for comparable periods of time for treatment and control infants in order to assure the clinical care team remained blinded to the intervention.
Blinding of Outcome Assessment: The primary outcome, need for mechanical ventilation, was blinded in only one of the six studies (Reininger 2005). In this study, the need for mechanical ventilation was determined by the clinical care team that was blind to the study intervention. In the other five studies (Verder 1994; NICHD 2002; Vermont Oxford 2003, Dani 2004, Texas Research Group 2004) the outcome, need for mechanical ventilation, was not determined under blinded conditions. However, the criteria for mechanical ventilation were well defined and adhered to during the studies.
Completeness of Follow-up: In the Verder study, five infants were excluded from the analysis after randomization when it was recognized that they had not met initial eligibility criteria for enrollment (two with gestational age > 36 weeks, two with oxygen-tension ratios exceeding definition of early RDS, and one with pneumonia at randomization). Sixty-eight infants were included in the final analysis. The study was terminated early when a statistically significant ($p<0.01$) difference in the primary outcome (need for mechanical ventilation) was seen at a scheduled interim analysis. At that time, 73 out of a targeted 108 patients had been enrolled. In the Reinenger study, one control subject was retrospectively determined to have a gestational age of 36 1/7 weeks and one treatment subject was found to have a congenital diaphragmatic hernia as well as RDS; these subjects were included in final analysis. In the Dani study, an interim analysis revealed a statistically significant difference in the primary endpoint, and the enrollment was stopped after enrollment of 27 infants. In the NICHD study, enrollment was ended early due to slow subject recruitment; data for one subject was compiled late, so that the abstract reports 61 patients but the data set includes 62 patients. In both the Vermont and Texas studies, enrollment was completed and all randomized patients were included in the analysis.

Effects of interventions

EARLY SURFACTANT, RAPID EXTUBATION TO NCPAP VS. SELECTIVE SURFACTANT, VENTILATION IN INFANTS WITH RDS (COMPARISON 01)

Six randomized controlled clinical trials met selection criteria and are included in this review (Verder 1994; NICHD 2002; Reininger 2005; Vermont Oxford 2003; Dani 2004; Texas Research 2004). In these six studies in infants with signs of RDS, early surfactant administration with rapid extubation to NCPAP was compared with selective surfactant administration and continued mechanical ventilation. One additional randomized trial of prophylactic administration of surfactant and planned rapid extubation vs. selective surfactant treatment among infants at risk of RDS was found (Thomson 2002). However, methodologic and detailed outcome data were not available for inclusion in this review.

Primary Outcomes

Need for Mechanical Ventilation (Outcome 01.01):
All six eligible studies reported this outcome. Early surfactant therapy followed by nasal CPAP (NCPAP) compared with later, selective surfactant administration for infants with RDS was associated with a significantly reduced need for mechanical ventilation [typical RR 0.67, 95% CI 0.57, 0.79]. In the Verder study, among infants in the early surfactant group who required mechanical ventilation, severe apnea was the most common reason (10/15, 67%) for treatment failure and initiation of mechanical ventilation. Among infants in the selective surfactant group who subsequently required mechanical ventilation, low oxygen tension ratio (a/A ratio <0.15) was the most common reason (21/28, 75%). In the Reininger study, the primary reasons for subsequent ventilation were not different between the treatment and control groups, including respiratory compromise (90% of treatment failures) and apnea (6% of treatment failure). Reasons for requiring mechanical ventilation have not been reported for the other four studies. In stratified analysis by FIO_2 at study entry, both FIO_2 sub groups ($\leq$ 0.45 and > 0.45 FIO_2) had similar benefit of early surfactant treatment.

Bronchopulmonary Dysplasia (Outcome 01.02):
BPD is defined as need for oxygen at 28 days of age. Verder 1994, Reininger 2005, NICHD 2002 and Dani 2004 reported this outcome. Early surfactant therapy followed by nasal CPAP (NCPAP) compared with later, selective surfactant administration for infants with RDS was associated with a significantly reduced incidence of BPD [typical RR 0.51, 95% CI 0.26, 0.99]. In stratified analysis by FIO_2 at study entry, the lower FIO_2 sub group ($\leq$ 0.0.45 FIO_2) had a significant reduction in the risk of BPD [typical RR 0.43 and 95% CI 0.20, 0.92]. Of the two studies with a higher FIO_2 at study entry (FIO_2 > 0.45), only the Verder study reported the incidence of BPD; this study found no difference between the treatment and control groups in the incidence of BPD.

Chronic Lung Disease
The incidence of CLD (oxygen at 36 weeks postmenstrual age)

was not reported by Verder 1994. While NICHD 2002; Reininger 2005; Vermont Oxford 2003 report no significant difference in incidence of CLD between study groups, primary data for inclusion in meta analysis are not provided on published reports.

Neonatal Mortality (Outcome 01.03):

All six included studies reported this outcome. Although there was no significant difference between groups in this outcome, the meta-analysis suggests a trend towards decreased mortality with early surfactant therapy and NCPAP compared with later selective surfactant therapy [typical RR 0.52, 95% CI 0.17, 1.56].

Mortality Prior to Hospital Discharge. Mortality prior to hospital discharge was not reported.

Secondary Outcomes

Respiratory Outcomes:

Duration of mechanical ventilation (Outcome 01.13):

Although all six studies reported duration of mechanical ventilation, meta-analysis of this outcome using a summary statistic is not possible because the outcome is reported as either mean or median values (see additional Table 1). While mean values can summarized in meta-analysis, median values cannot. Three of the six included studies reported mean duration of mechanical ventilation (Texas Research 2004; Vermont Oxford 2003; Dani 2004); the weighted mean difference between early surfactant therapy followed by nasal CPAP compared with later selective surfactant administration was not statistically different but may show a trend toward a shorter period of mechanical ventilation in the early surfactant group (WMD -0.36 days, 95% CI -0.81, 0.10). Four of the six included studies reported median duration of mechanical ventilation for treatment and control groups, as follows: Verder reported duration of mechanical ventilation as median 6 days (range 1-75) vs. median 6 days (range 1-76) for treatment and control groups, respectively; Reininger 2005 reported median values 2.3 days (range 0.8-20.8) vs. 2.6 days (range 0.6-6.3) for treatment and control groups, respectively; NICHD 2002 reported the duration of mechanical ventilation as median of 5 days for the treatment group and median of 3 days for the control group (no ranges given); Texas Research 2004 reported median 0.1 days (range 0.0-1.7) and median 0.0 days (range 0.0-1.6) for the treatment and control groups, respectively. Although early surfactant therapy followed by nasal CPAP led to fewer infants requiring mechanical ventilation, compared with later selective surfactant administration, there is no difference in length of time on mechanical ventilation.

Duration in Oxygen (Outcome 01.14):

Five studies reported this outcome, using either means or median values, which precludes full meta-analysis using a summary statistic (see additional Table 2). Verder 1994 and Reininger 2005 showed no difference in median time in oxygen. Four studies reported median time in oxygen in treated and control groups (Texas Research 2004; NICHD 2002;Verder 1994; Reininger 2005). In each study, the median time in oxygen was similar between treatment and control groups. Dani 2004 reported fewer days in oxygen for patients treated with early surfactant therapy followed by nasal CPAP (NCPAP) compared with later, selective surfactant administration [WMD -4.3 and 95% CI -7.63, -0.97].

Number of patients receiving surfactant (Outcome 01.08):

Four studies reported this outcome. Early surfactant therapy followed by NCPAP compared with later, selective surfactant administration for infants with RDS was associated with more infants being exposed to surfactant [132/132 (100%) vs. 79/130 (61%) respectively, typical RR 1.63, 95% CI 1.42, 1.88].

Number of surfactant doses per patient (Outcome 01.09):

Three studies reported this outcome. The number of surfactant doses per patient was significantly greater among patients assigned to the early surfactant group [WMD 0.57 doses per patient (95% CI 0.44, 0.69)].

Incidence of airleak syndromes (Outcome 0.10):

All six studies reported incidence of airleak syndromes. Early surfactant therapy followed by NCPAP compared with later, selective surfactant administration for infants with RDS was associated with a reduction in incidence of airleak [typical RR 0.52 (95% CI 0.28, 0.96)]. In stratified analysis by FIO_2 at study entry, the lower FIO2 sub group ($\leq$ 0.45 FIO_2) had a significant reduction in the risk of airleak [typical RR 0.46 (95% CI 0.23, 0.93)]; this advantage was not seen among studies with a higher FIO_2 at study entry (FIO_2 > 0.45).

Complications associated with prematurity.

PDA requiring treatment (Outcome 01.11):

Four studies reported this outcome. An overall trend towards a higher incidence of PDA was seen with selective surfactant and continued ventilation vs. early surfactant and rapid extubation [typical RR 1.52 (95% CI 0.90-2.57)]. In stratified analysis by FIO_2 at study entry, the higher FIO_2 sub group (FIO_2 > 0.45) had a significantly increased risk of PDA [typical RR 2.15 (95% CI 1.09, 4.23)]. In the lower FIO_2 subgroup ($FIO_2 \leq 0.45$), there was no difference between early surfactant and rapid extubation and later selective surfactant groups.

There was no evidence of effect on incidence of IVH, periventricular leukomalacia, pulmonary hemorrhage or NEC (Outcomes 01-04, 01-06, 01-07, and 01-12).

Other primary and secondary outcomes of this review were not available from the studies meeting selection criteria.

Planned subgroup analyses.

i) Individual patient data from each of the included trials will be required to perform the planned subgroup analysis according to the inspired oxygen concentration at study entry ($FiO_2 \leq 0.45$, >0.45). These results are presented above.

ii) In all studies eligible for this review, extubation in the treatment group was to NCPAP rather than to atmospheric pressure. Thus, the results presented in this review apply to the pre-specified subgroup extubated to NCPAP.

DISCUSSION

Six studies met criteria for this review. Based on the meta-analysis of these six studies, early surfactant therapy compared with later selective surfactant administration resulted in less need for mechanical ventilation, fewer airleak syndromes and lower incidence of BPD. The costs of these benefits include a greater number of infants receiving surfactant and an increased number of surfactant doses per patient. An overall trend toward greater risk of PDA occurred with later, selective surfactant treatment compared with early surfactant and was statistically significant in meta-analysis of two studies with $FIO_2 > 0.45$ at study entry. The study procedure was well tolerated and successfully accomplished in the vast majority of patients. Although early surfactant therapy compared with selective therapy resulted in more infants being exposed to the potential risks of intubation and surfactant administration, none of the studies reviewed reported complications of the intubation procedure. Early surfactant administration with extubation within 1 hour was successfully achieved in the vast majority of study subjects, except in the Texas Research Group Trial, where 53% of patients remained intubated at one hour after surfactant administration in the treatment group.

The findings in this review suggest that in spontaneously breathing preterm infants with RDS a policy of early intubation for surfactant administration followed by early extubation to NCPAP is preferable to later, selective intubation and surfactant treatment in preventing the need for mechanical ventilation, pneumothorax and BPD. The findings also suggest that lower threshold for treatment at study entry ($FIO_2 < 0.45$) confers advantage compared with a higher treatment threshold ($FIO_2 > 0.45$). Although both treatment thresholds resulted in reduced need for mechanical ventilation, the lower FIO_2 subgroup achieved the greatest reductions in incidence of airleak syndromes and BPD while the subgroup of infants with a higher FIO_2 at study entry had a significantly greater incidence of PDA requiring treatment. The PDA treatment was not characterized in any of the six studies, however, in each of these studies, the mean gestational age among enrolled infants was 28 weeks or 1250 grams or greater, a population of preterm infants for whom surgical treatment of PDA would be uncommon.

To lessen the risk of publication bias, data from both published and unpublished sources are included in this review. Four trials have been published in peer reviewed literature, while two studies included in this review have been published in abstract form only. For these two studies, information available in the abstracts has been supplemented with methodological details and outcome data obtained directly from the investigators; these materials include the full manual of procedures as well as additional analyses of clinical and safety outcomes performed for inclusion in this review. The VON trial has completed enrollment and is in data analysis and manuscript preparation. The NICHD trial terminated early, and at the time of this review, there are no plans to pursue publication of study results.

Four of the six trials reviewed here were terminated prior to achieving their targeted study size, two as a result of significant benefit in treated patients compared with controls and two due to slow accrual of study subjects. The Verder study was terminated prior to achieving the targeted enrollment when the primary outcome, need for mechanical ventilation, was found to be significantly different between groups at a scheduled interim analysis. Consequently, 68 out of a targeted 108 patients were available for the analysis. Based on power analysis, the Dani study was designed to randomize 48 infants. An interim analysis after enrolling 27 subjects found a significant reduction in need for mechanical ventilation in the treatment group, and the study was terminated early. Two studies (NICHD 2002; Reininger 2005) were terminated early due to slow accrual of potentially eligible patients. The NICHD trial (NICHD 2002) was halted at approximately 11% of planned enrollment (61 patients enrolled out of a planned 560 patients) due to slow enrollment (61 patients enrolled out of 1423 patients screened). Despite liberalizing eligibility criteria and a six year enrollment period, the Reininger 2005 trial was terminated at 50% of planned enrollment (105 patients enrolled out of a planned 206 patients). In both of these studies, reasons for non-enrollment of eligible patients included rapid progression of RDS through the range of eligible FIO_2 levels. The NICHD trial (NICHD 2002) reviewed clinical characteristics of patients not enrolled with characteristics of enrolled subjects; the two groups were similar, suggesting that non-enrolled patients may have experienced similar benefits to those enrolled. The Verder multicenter trial was conducted in Denmark and Sweden, where routine care of infants with RDS often begins with NCPAP shortly after the onset of symptoms. It is possible that patient accrual may be slower in units that have less experience and are therefore less comfortable with NCPAP. This possibility cannot be evaluated with available data.

Although the clinical approach and experience with NCPAP may have varied, each of the six randomized trials reviewed here found either a significant reduction or a strong trend towards a reduction in the need for mechanical ventilation in infants managed with early intubation for surfactant administration followed by rapid extubation to NCPAP. This suggests that generalizability of these findings may be high. However, slow accrual of eligible patients in two of the trials may mean that early surfactant followed by rapid extubation to NCPAP may be more effective or better accepted in units experienced in the use of early NCPAP.

The studies reviewed here did not address limitations on the type of patients for whom early surfactant with rapid extubation is appropriate. Although babies as premature as 25 0/7 weeks were eligible for inclusion in the Verder 1994 and Reininger 2005 trials, most enrolled infants were more than 28 weeks gestation. Further study may reveal subgroups of preterm infants, such as those < 25 weeks or < 750 grams or infants requiring intubation during resuscitation, for which more than one hour of mechanical venti-

lation is required to achieve clinical stability prior to extubation to NCPAP. Several relevant clinical outcomes were not available and other outcomes could not be definitively addressed due to a lack of power of the clinical trials meeting eligibility criteria for this systematic review. Outcomes such as incidence of chronic lung disease, total duration of respiratory support (ventilation, CPAP, nasal cannula), time to regain birth weight, need for sedation/analgesia and neurodevelopmental outcome are potentially important clinical outcomes for which data currently are not available.

AUTHORS' CONCLUSIONS

Implications for practice

Six randomized clinical trials of early surfactant administration in spontaneously breathing infants have been conducted using different thresholds for surfactant replacement. Evidence from the six studies included in this review indicates that infants with RDS treated with early surfactant replacement therapy and NCPAP are less likely to need mechanical ventilation, less likely to develop BPD and less likely to suffer from an air leak syndrome than are infants treated with NCPAP and later surfactant therapy. This review also introduces new evidence that lower FiO_2 at study entry is associated with significant reductions in incidence of air-leak syndromes and BPD; moreover studies where FIO_2 at study entry was greater than 0.45 had an increased incidence of PDA. These data suggest that among spontaneously breathing infants with early signs and symptoms of RDS, treatment with surfactant by transient intubation using a low treatment threshold (FIO2 < 0.45) is preferable to later selective therapy by transient intubation using a higher treatment threshold (FIO2 > 0.45).

Implications for research

Further research is needed to define potential limitations on the type of patients for whom early surfactant with rapid extubation is appropriate (such as very premature infants < 750 grams) and to determine the optimal severity of RDS at which to intervene with transient intubation for the purpose of surfactant administration.

Randomized controlled trials of prophylactic surfactant administration with rapid extubation compared with later, selective surfactant therapy are not available. Based on previous literature, prophylactic surfactant therapy may offer further advantage over early surfactant therapy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Dani 2004

Methods	A randomized, single center, controlled trial. Blinding of randomization: Yes Blinding of intervention: No Blinding of outcome: No Complete followup: Can't tell
Participants	Infants < 30 weeks' gestation, < 6 hours old with RDS defined as clinical signs, chest radiograph requiring CPAP and 30% oxygen or more
Interventions	Early surfactant administration with rapid extubation to NCPAP (n=13) vs NCPAP with later rescue surfactant and mechanical ventilation (n=14)
Outcomes	Need for mechanical ventilation at 7 days of age
Notes	Trial terminated early when interim analysis showed significant reduction in the need for mechanical ventilation with early surfactant use. Five participating centers. FIO2 at study entry was 0.33 (0.13) vs 0.35 (0.09) for early surfactant vs later surfactant groups, respectively. Data represent mean value and standard deviation (sd)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

NICHD 2002

Methods	A randomized, multi-center, controlled trial. Blinding of randomization: Yes Blinding of intervention: No Blinding of outcome: No Complete followup: Can't tell
Participants	Infants 1250-2000 grams birth weight less than 12 hours old with RDS defined as FIO2 of 0.35-0.5 by oxygen hood or FIO2 .25-.5 by CPAP and clinical signs and chest radiograph consistent with RDS
Interventions	Early surfactant administration with rapid extubation to NCPAP (n=32) vs NCPAP with later rescue surfactant and mechanical ventilation (n=29)
Outcomes	Need for mechanical ventilation to treat respiratory failure or apnea

NICHD 2002 *(Continued)*

Notes	Study terminated early due to slow enrollment with enrollment of 61 patients out of 1,423 screened patients. FIO2 at study entry was 0.40 (0.13) vs 0.39 (0.08) for early surfactant vs later surfactant groups, respectively. Data represent mean value and standard deviation (sd)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Reininger 2005

Methods	A randomized, single center, controlled trial. Blinding of randomization: Yes Blinding of intervention: Yes Blinding of outcome: Yes Complete followup: Can't tell
Participants	Infants 25 0/7 to 35 6/7 weeks' gestation less than 24 hours old with early RDS defined as need for NCPAP and FIO2 > .21 and clinical signs and chest radiograph consistent with RDS
Interventions	Early surfactant administration with rapid extubation to NCPAP (n=52) vs NCPAP with later rescue surfactant and mechanical ventilation (n=53). All infants in the study were begun on NCPAP prior to enrollment
Outcomes	Need for mechanical ventilation to treat respiratory failure or apnea
Notes	Intervention (intubation for administration of surfactant) was blinded to the clinical care team. Low threshold for early surfactant administration, including need for CPAP, need for any supplemental oxygen and signs and chest radiograph consistent with RDS. Despite liberalizing eligibility criteria after the first 23 patients were enrolled (reducing the level of supplemental oxygen required for eligibility from an FIO2 > 0.3 to FIO2 > 0.21), patient accrual remained slow. Patient accrual occurred over a 6 year period and was eventually terminated at 50% of planned enrollment (105 patients enrolled out of a planned 206 patients) . Reasons for non-enrollment included rapid progression of RDS once a FIO2 of 0.3 was reached. The treatment group consisted of early intubation for surfactant administration followed by brief mechanical ventilation with planned extubation within one hour. FIO2 at study entry was 0.41 (0.16) vs 0.40 (0. 19) for early surfactant vs later surfactant groups, respectively. Data represent mean value and standard deviation (sd)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Texas Research 2004

Methods	A randomized, multi-center, controlled trial. Blinding of randomization: Yes Blinding of intervention: No Blinding of outcome: No Complete followup: Can't tell
Participants	Infants with birth weight 1250 grams or more, < 36 weeks gestation, 4-24 hours old with FIO2 of 0.40 or more, with or without CPAP, and chest radiograph and clinical presentation consistent with RDS
Interventions	Early surfactant administration with rapid extubation to NCPAP (n=65) vs NCPAP with later rescue surfactant and mechanical ventilation (n=67)
Outcomes	Duration of assisted ventilation including the hand or mechanical ventilation used for surfactant administration
Notes	Five participating centers. FIO2 at study entry was 0.51(0.17) vs 0.51(0.12) for early surfactant vs later surfactant groups, respectively. Data represent mean value and standard deviation (sd)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Verder 1994

Methods	A randomized, controlled trial. Blinding of randomization: Yes Blinding of intervention: No Blinding of outcome: No Complete followup: No (5 post-randomization exclusions)
Participants	Infants 25-35 weeks' gestation with early RDS defined as an arterial to alveolar oxygen tension ratio < 0.22 in a patient with radiographic and clinical signs of RDS. Inclusion criteria included need for NCPAP of 6 cm of water
Interventions	Early surfactant administration with rapid extubation to NCPAP (n=35) vs NCPAP with later rescue surfactant and mechanical ventilation (n=33). All infants in the study were begun on NCPAP prior to enrollment
Outcomes	Need for mechanical ventilation to treat respiratory failure or apnea
Notes	Trial terminated at midpoint when interim analysis showed significant reduction in the need for mechanical ventilation with early surfactant use. FIO2 at study entry was 0.50 (0.09) vs 0.48 (0.09) for early surfactant vs later surfactant groups, respectively, assuming PaO2 = 50 and PaCO2 = 52 (study data). Data represent mean value and standard deviation (sd)

Risk of bias

Verder 1994 *(Continued)*

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Vermont Oxford 2003

Methods	A randomized, multi-center, controlled trial. Blinding of randomization: Yes Blinding of intervention: No Blinding of outcome: No Complete followup: Can't tell
Participants	Infants 1501-2500 grams birth weight 2-24 hours old with RDS defined as FIO2 of 0.3-0.6 by oxygen hood or CPAP and clinical signs and chest radiograph consistent with RDS
Interventions	Early surfactant administration with rapid extubation to NCPAP (n=138) vs NCPAP with later rescue surfactant and mechanical ventilation (n=132)
Outcomes	Need for mechanical ventilation to treat respiratory failure (pCO2 > 65, hypoxemia, severe respiratory distress) or apnea
Notes	Infants randomized by two strata, birth weight group (1501-2000 or 2001-2500) and age at randomization (< 12 hours of age or 12-24 hours of age). FIO2 at study entry was 0.40 (0.36-0.5) vs 0.40 (0.35-0.49) for early surfactant vs later surfactant groups, respectively. Data represent median value and interquartile range (IQR)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Study	Reason for exclusion
Alba 1995	The treatment group was compared with two non-randomized control groups: infants requiring immediate intubation for severe respiratory failure, and historical controls from a period before surfactant was clinically available
Blennow 1999	A case series of infants treated with early surfactant and planned rapid extubation
Dambeanu 1997	A randomized trial of prophylactic surfactant administration in Romania at a time when mechanical ventilation was not available

(*Continued*)

Lefort 2003	A randomized controlled trial comparing prophylactic versus rescue surfactant was excluded because planned early extubation was not part of the study protocol. (Lefort 2003, previously referred to Diniz 2002)
Mandy 1998	A case series of 46 premature infants with RDS treated with surfactant and endotracheal CPAP
Sandri 2004	A large multi-center trial of prophylactic versus rescue use of NCPAP in which surfactant administration was the primary endpoint
So 1994	A randomized trial of infants over 1500 grams with RDS in which infants received surfactant when the Fi02 exceeded 0.7 and were then randomized to NCPAP or continued mechanical ventilation
Tooley 2003	A randomized trial in which all infants received prophylactic surfactant with subsequent randomization to rapid extubation to NCPAP or continued mechanical ventilation until pre-determined extubation criteria were met. This study was excluded because the comparison did not meet the criteria for this systematic review. Both arms received prophylactic surfactant therapy whereas this systematic review is limited to comparisons of prophylactic or early surfactant with rapid extubation to NCPAP compared to selective surfactant therapy
Verder 1992	A case series of infants with signs of early RDS treated with early surfactant and NCPAP which served as pilot data for the Verder 1994 trial
Verder 1999	A randomized trial of infants < 30 weeks' gestation with RDS in which infants were randomized to receive early or selective surfactant. The study was excluded because both study arms (early and selective) had a planned, brief period of mechanical ventilation
Victorin 1990	A case series of 14 premature infants with RDS treated with surfactant, brief ventilation and rapid extubation to supplemental oxygen only (not CPAP). Mechanical ventilation was not available

DATA AND ANALYSES

Comparison 1. Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for mechanical ventilation.	6	664	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.57, 0.79]
1.1 FIO2 at Study Entry <=0.45	4	464	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.59, 0.87]
1.2 FIO2 at Study Entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.40, 0.77]
2 Bronchopulmonary dysplasia: need for oxygen at 28 days chronologic age.	4	262	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.26, 0.99]
2.1 FIO2 at Study Entry <=0.45	3	194	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.20, 0.92]
2.2 FIO2 at Study Entry > 0.45	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.20, 4.35]
3 Neonatal mortality: death prior to 28 days of age.	6	396	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.17, 1.56]
3.1 FIO2 at study entry <=0.45	4	196	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.15, 3.55]
3.2 FIO2 at study entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.81]
4 Intraventricular hemorrhage	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 IVH, any severity	5	517	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.39]
4.2 Serious IVH, Grades III-IV	3	358	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.15, 2.18]
5 Retinopathy of prematurity, any severity	3	109	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.63]
6 Periventricular leukomalacia	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.47]
7 Pulmonary hemorrhage	4	532	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.35, 4.07]
7.1 FIO2 at study entry < = 0.45	2	332	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.30, 27.24]
7.2 FIO2 at study entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.46]
8 Use of surfactant	4	262	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.41, 1.86]
9 Number of surfactant doses per patient	3	470	Mean Difference (IV, Fixed, 95% CI)	0.57 [0.44, 0.69]
10 Air leak syndromes, pulmonary interstitial emphysema, pneumothorax	6	664	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.96]
10.1 FIO2 at Study Entry <= 0.45	4	464	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.23, 0.93]
10.2 FIO2 at Study Entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.22, 2.89]

11 Patent ductus arteriosus requiring treatment	4	250	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.90, 2.57]
11.1 FIO2 at Study Entry <= 0.45	2	50	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.30, 1.78]
11.2 FIO2 at Study Entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.09, 4.23]
12 Necrotizing enterocolitis (NEC)	4	388	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.12, 3.25]
13 Duration of mechanical ventilation (d)	3	278	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.81, 0.10]
14 Duration in oxygen	1	27	Mean Difference (IV, Fixed, 95% CI)	-4.30 [-7.63, -0.97]

Comparison 2. Prophylactic surfactant, rapid extubation vs. selective surfactant, ventilation in babies at risk of

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No available studies.			Other data	No numeric data

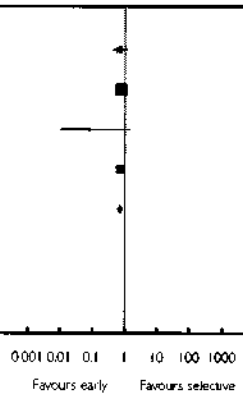
Analysis 1.1. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 1 Need for mechanical ventilation..

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 1 Need for mechanical ventilation.

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 FIO2 at Study Entry <=0.45					
NICHD 2002	13/32	18/30		10.0 %	0.68 [0.41, 1.13]
Vermont Oxford 2003	54/138	65/132		35.9 %	0.79 [0.61, 1.04]
Dani 2004	0/13	6/14		3.4 %	0.08 [0.01, 1.33]
Reininger 2005	26/52	37/53		19.8 %	0.72 [0.52, 0.99]
Subtotal (95% CI)	**235**	**229**		**69.0 %**	**0.72 [0.59, 0.87]**
Total events: 93 (Early Surfactant), 126 (Selective Surfactant)					
Heterogeneity: Chi^2 = 2.90, df = 3 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 3.31 (P = 0.00092)					



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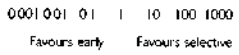
Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 FIO2 at Study Entry > 0.45					
Verder 1994	15/35	28/33		15.6 %	0.51 [0.34, 0.76]
Texas Research 2004	17/65	29/67		15.4 %	0.60 [0.37, 0.99]
Subtotal (95% CI)	**100**	**100**		**31.0 %**	**0.55 [0.40, 0.77]**
Total events: 32 (Early Surfactant), 57 (Selective Surfactant)					
Heterogeneity: Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 3.59 (P = 0.00033)					
Total (95% CI)	**335**	**329**		**100.0 %**	**0.67 [0.57, 0.79]**
Total events: 125 (Early Surfactant), 183 (Selective Surfactant)					
Heterogeneity: Chi^2 = 5.88, df = 5 (P = 0.32); I^2 =15%					
Test for overall effect: Z = 4.75 (P < 0.00001)					



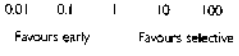
Analysis 1.2. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 2 Bronchopulmonary dysplasia: need for oxygen at 28 days chronologic age..

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 2 Bronchopulmonary dysplasia: need for oxygen at 28 days chronologic age.

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 FIO2 at Study Entry <=0.45					
Dani 2004	3/13	7/14		32.8 %	0.46 [0.15, 1.42]
Reininger 2005	0/52	2/53		12.0 %	0.20 [0.01, 4.14]
NICHD 2002	4/32	8/30		40.2 %	0.47 [0.16, 1.40]
Subtotal (95% CI)	**97**	**97**		**85.0 %**	**0.43 [0.20, 0.92]**
Total events: 7 (Early Surfactant), 17 (Selective Surfactant)					
Heterogeneity: Chi^2 = 0.28, df = 2 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.029)					
2 FIO2 at Study Entry > 0.45					
Verder 1994	3/35	3/33		15.0 %	0.94 [0.20, 4.35]



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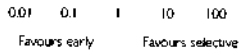
Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**35**	**33**		**15.0 %**	**0.94 [0.20, 4.35]**
Total events: 3 (Early Surfactant), 3 (Selective Surfactant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
Total (95% CI)	**132**	**130**		**100.0 %**	**0.51 [0.26, 0.99]**
Total events: 10 (Early Surfactant), 20 (Selective Surfactant)					
Heterogeneity: Chi^2 = 1.03, df = 3 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 1.99 (P = 0.047)					



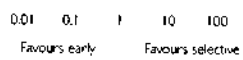
Analysis 1.3. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 3 Neonatal mortality: death prior to 28 days of age..

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS

Outcome: 3 Neonatal mortality: death prior to 28 days of age.

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 FIO2 at study entry <=0.45				
Vermont Oxford 2003	0/1	0/1		0.0 [0.0, 0.0]
Dani 2004	0/13	1/14		0.36 [0.02, 8.06]
Reininger 2005	1/52	0/53		3.06 [0.13, 73.36]
NICHD 2002	0/32	1/30		0.31 [0.01, 7.40]
Subtotal (95% CI)	**98**	**98**		**0.72 [0.15, 3.55]**
Total events: 1 (Early Surfactant), 2 (Selective Surfactant)				
Heterogeneity: Chi^2 = 1.26, df = 2 (P = 0.53); I^2 =0.0%				
Test for overall effect: Z = 0.40 (P = 0.69)				
2 FIO2 at study entry > 0.45				
Texas Research 2004	0/65	0/67		0.0 [0.0, 0.0]
Verder 1994	2/35	5/33		0.38 [0.08, 1.81]



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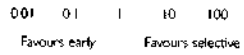
Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**100**	**100**		**0.38 [0.08, 1.81]**
Total events: 2 (Early Surfactant), 5 (Selective Surfactant)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.22 (P = 0.22)				
Total (95% CI)	**198**	**198**		**0.52 [0.17, 1.56]**
Total events: 3 (Early Surfactant), 7 (Selective Surfactant)				
Heterogeneity: Chi^2 = 1.51, df = 3 (P = 0.68); I^2 =0.0%				
Test for overall effect: Z = 1.17 (P = 0.24)				



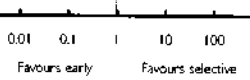
Analysis 1.4. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 4 Intraventricular hemorrhage.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 4 Intraventricular hemorrhage

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 IVH, any severity				
Verder 1994	8/35	8/33		0.94 [0.40, 2.22]
Vermont Oxford 2003	6/138	8/132		0.72 [0.26, 2.01]
Dani 2004	1/13	1/14		1.08 [0.07, 15.50]
Texas Research 2004	0/65	1/67		0.34 [0.01, 8.28]
NICHD 2002	0/12	1/8		0.23 [0.01, 5.05]
Subtotal (95% CI)	**263**	**254**		**0.76 [0.41, 1.39]**
Total events: 15 (Early Surfactant), 19 (Selective Surfactant)				
Heterogeneity: Chi^2 = 1.14, df = 4 (P = 0.89); I^2 =0.0%				
Test for overall effect: Z = 0.90 (P = 0.37)				
2 Serious IVH, Grades III-IV				
Verder 1994	3/35	5/33		0.57 [0.15, 2.18]



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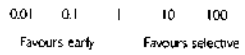
Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Vermont Oxford 2003	0/138	0/132		0.0 [0.0, 0.0]
NICHD 2002	0/12	0/8		0.0 [0.0, 0.0]
Subtotal (95% CI)	**185**	**173**		**0.57 [0.15, 2.18]**
Total events: 3 (Early Surfactant), 5 (Selective Surfactant)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.83 (P = 0.41)				



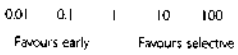
Analysis 1.5. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 5 Retinopathy of prematurity, any severity.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 5 Retinopathy of prematurity, any severity

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dani 2004	1/13	3/14		0.36 [0.04, 3.03]
NICHD 2002	0/8	0/6		0.0 [0.0, 0.0]
Verder 1994	1/35	1/33		0.94 [0.06, 14.47]
Total (95% CI)	**56**	**53**		**0.51 [0.10, 2.63]**
Total events: 2 (Early Surfactant), 4 (Selective Surfactant)				
Heterogeneity: Chi^2 = 0.30, df = 1 (P = 0.58); I^2 =0.0%				
Test for overall effect: Z = 0.80 (P = 0.42)				



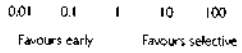
Analysis 1.6. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 6 Periventricular leukomalacia.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 6 Periventricular leukomalacia

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Verder 1994	0/35	1/33		100.0 %	0.31 [0.01, 7.47]
Total (95% CI)	**35**	**33**		**100.0 %**	**0.31 [0.01, 7.47]**
Total events: 0 (Early Surfactant), 1 (Selective Surfactant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					



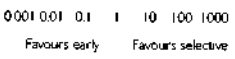
Analysis 1.7. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 7 Pulmonary hemorrhage.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 7 Pulmonary hemorrhage

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 FIO2 at study entry < = 0.45				
Vermont Oxford 2003	3/138	1/132		2.87 [0.30, 27.24]
NICHD 2002	0/32	0/30		0.0 [0.0, 0.0]
Subtotal (95% CI)	**170**	**162**		**2.87 [0.30, 27.24]**
Total events: 3 (Early Surfactant), 1 (Selective Surfactant)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.92 (P = 0.36)				
2 FIO2 at study entry > 0.45				
Verder 1994	0/35	2/33		0.19 [0.01, 3.79]
Texas Research 2004	2/65	1/67		2.06 [0.19, 22.19]
Subtotal (95% CI)	**100**	**100**		**0.71 [0.14, 3.46]**
Total events: 2 (Early Surfactant), 3 (Selective Surfactant)				
Heterogeneity: Chi^2 = 1.52, df = 1 (P = 0.22); I^2 =34%				
Test for overall effect: Z = 0.43 (P = 0.67)				
Total (95% CI)	**270**	**262**		**1.19 [0.35, 4.07]**
Total events: 5 (Early Surfactant), 4 (Selective Surfactant)				
Heterogeneity: Chi^2 = 2.24, df = 2 (P = 0.33); I^2 =11%				
Test for overall effect: Z = 0.28 (P = 0.78)				



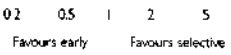
Analysis 1.8. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 8 Use of surfactant.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 8 Use of surfactant

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Verder 1994	35/35	19/33		24.7 %	1.72 [1.28, 2.30]
Dani 2004	13/13	7/14		8.9 %	1.93 [1.15, 3.23]
Reininger 2005	52/52	35/53		43.4 %	1.51 [1.24, 1.83]
NICHD 2002	31/32	18/30		22.9 %	1.61 [1.20, 2.18]
Total (95% CI)	**132**	**130**		**100.0 %**	**1.62 [1.41, 1.86]**
Total events: 131 (Early Surfactant), 79 (Selective Surfactant)					
Heterogeneity: Chi^2 = 1.14, df = 3 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 6.81 (P < 0.00001)					



Analysis 1.9. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 9 Number of surfactant doses per patient.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

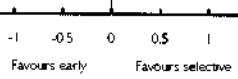
Outcome: 9 Number of surfactant doses per patient

Study or subgroup	Early Surfactant N	Mean(SD)	Selective Surfactant N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Verder 1994	35	1.09 (0.28)	33	0.58 (0.5)		41.3 %	0.51 [0.32, 0.70]
Vermont Oxford 2003	138	1.3 (0.7)	132	0.8 (1.1)		31.9 %	0.50 [0.28, 0.72]
Texas Research 2004	65	1.28 (0.6)	67	0.55 (0.8)		26.9 %	0.73 [0.49, 0.97]
Total (95% CI)	**238**		**232**			**100.0 %**	**0.57 [0.44, 0.69]**

Heterogeneity: Chi^2 = 2.44, df = 2 (P = 0.29); I^2 = 18%

Test for overall effect: Z = 8.89 (P < 0.00001)

Test for subgroup differences: Not applicable



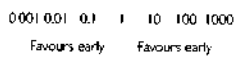
Analysis 1.10. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 10 Air leak syndromes, pulmonary interstitial emphysema, pneumothorax.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 10 Air leak syndromes, pulmonary interstitial emphysema, pneumothorax

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 FIO2 at Study Entry <= 0.45					
Vermont Oxford 2003	8/138	15/132		54.1 %	0.51 [0.22, 1.16]
Dani 2004	0/13	1/14		5.1 %	0.36 [0.02, 8.06]
Reininger 2005	0/52	4/53		15.7 %	0.11 [0.01, 2.05]
NICHD 2002	2/32	2/30		7.3 %	0.94 [0.14, 6.24]
Subtotal (95% CI)	**235**	**229**		**82.3 %**	**0.46 [0.23, 0.93]**
Total events: 10 (Early Surfactant), 22 (Selective Surfactant)					
Heterogeneity: Chi^2 = 1.52, df = 3 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 2.17 (P = 0.030)					
2 FIO2 at Study Entry > 0.45					
Verder 1994	1/35	2/33		7.3 %	0.47 [0.04, 4.96]
Texas Research 2004	3/65	3/67		10.4 %	1.03 [0.22, 4.92]
Subtotal (95% CI)	**100**	**100**		**17.7 %**	**0.80 [0.22, 2.89]**
Total events: 4 (Early Surfactant), 5 (Selective Surfactant)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.34 (P = 0.73)					
Total (95% CI)	**335**	**329**		**100.0 %**	**0.52 [0.28, 0.96]**
Total events: 14 (Early Surfactant), 27 (Selective Surfactant)					
Heterogeneity: Chi^2 = 2.23, df = 5 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 2.09 (P = 0.036)					



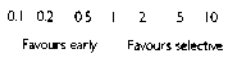
Analysis 1.11. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 11 Patent ductus arteriosus requiring treatment.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 11 Patent ductus arteriosus requiring treatment

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 FIO2 at Study Entry <= 0.45					
Dani 2004	4/13	6/14		31.8 %	0.72 [0.26, 1.98]
NICHD 2002	2/13	2/10		12.5 %	0.77 [0.13, 4.55]
Subtotal (95% CI)	**26**	**24**		**44.3 %**	**0.73 [0.30, 1.78]**
Total events: 6 (Early Surfactant), 8 (Selective Surfactant)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 FIO2 at Study Entry > 0.45					
Verder 1994	13/35	6/33		34.0 %	2.04 [0.88, 4.74]
Texas Research 2004	9/65	4/67		21.7 %	2.32 [0.75, 7.16]
Subtotal (95% CI)	**100**	**100**		**55.7 %**	**2.15 [1.09, 4.23]**
Total events: 22 (Early Surfactant), 10 (Selective Surfactant)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 2.21 (P = 0.027)					
Total (95% CI)	**126**	**124**		**100.0 %**	**1.52 [0.90, 2.57]**
Total events: 28 (Early Surfactant), 18 (Selective Surfactant)					
Heterogeneity: Chi^2 = 3.68, df = 3 (P = 0.30); I^2 =18%					
Test for overall effect: Z = 1.57 (P = 0.12)					



Analysis 1.12. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 12 Necrotizing enterocolitis (NEC).

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs selective surfactant, ventilation in babies with RDS.

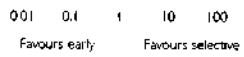
Outcome: 12 Necrotizing enterocolitis (NEC)

Study or subgroup	Early Surfactant n/N	Selective Surfactant n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Verder 1994	0/35	0/33		0.0 [0.0, 0.0]
Vermont Oxford 2003	1/138	3/132		0.32 [0.03, 3.03]
Dani 2004	0/13	0/14		0.0 [0.0, 0.0]
NICHD 2002	1/13	0/10		2.36 [0.11, 52.41]
Total (95% CI)	**199**	**189**		**0.63 [0.12, 3.25]**

Total events: 2 (Early Surfactant), 3 (Selective Surfactant)

Heterogeneity: Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =4%

Test for overall effect: Z = 0.55 (P = 0.58)



Analysis 1.13. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 13 Duration of mechanical ventilation (d).

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

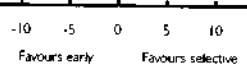
Outcome: 13 Duration of mechanical ventilation (d)

Study or subgroup	Early surfactant N	Mean(SD)	Selective surfactant N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Vermont Oxford 2003	54	1.7 (1.6)	65	1.9 (1.4)		70.1 %	-0.20 [-0.75, 0.35]
Dani 2004	13	2 (1.4)	14	5.6 (3.1)		6.5 %	-3.60 [-5.39, -1.81]
Texas Research 2004	65	1.37 (2.6)	67	1.3 (2.93)		23.4 %	0.07 [-0.87, 1.01]
Total (95% CI)	**132**		**146**			**100.0 %**	**-0.36 [-0.81, 0.10]**

Heterogeneity: Chi^2 = 13.67, df = 2 (P = 0.001); I^2 =85%

Test for overall effect: Z = 1.53 (P = 0.13)

Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 14 Duration in oxygen.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

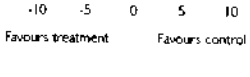
Outcome: 14 Duration in oxygen

Study or subgroup	Early Surfactant N	Mean(SD)	Selective Surfactant N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dani 2004	13	7 (2.9)	14	11.3 (5.6)		100.0 %	-4.30 [-7.63, -0.97]
Total (95% CI)	**13**		**14**			**100.0 %**	**-4.30 [-7.63, -0.97]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.53 (P = 0.011)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Time in oxygen (median in days, range unless otherwise stated)

Study	Early Surfactant	Selective Surfactant
Verder 1994	6 (1 - 75) n = 35	6 (1 - 76) n = 33
NICHD 2002	5 n = 32	6 n = 30
Dani 2004	mean = 7.0 (standard deviation = 1.4) n = 13	mean = 11.3 (standard deviation = 5.6) n = 14
Texas Research Group 2004	4.3 (2.3 - 6.1) n = 65	4.7 (3.3 - 6.5) n = 67
Reininger 2005	4 (1 - 40) n = 52	4 (1 - 78) n = 53

Table 2. Duration mechanical ventilation (median in days, range unless otherwise stated)

Study	Early Surfactant	Selective Surfactant
Verder 1994	2.5 (range not available) n = 35	2.5 (range not available) n = 33
NICHD 2002	5 n = 32	3 n = 30
Vermont Oxford 2003	stated no difference between groups	stated no difference between groups
Dani 2004	mean = 2.0 (standard deviation = 1.4) n = 13	mean = 5.6 (standard deviation = 3.1) n = 14
Texas Research Group 2004	0.1 (0.0 - 1.7) n = 65	0.0 (0.0 - 1.6) n = 67
Reininger 2005	2.3 (0.8 - 20.8) n = 52	2.6 (0.6 - 6.3) n = 53

WHAT'S NEW

Last assessed as up-to-date: 19 June 2007.

Date	Event	Description
27 February 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 2, 2002

Date	Event	Description
20 June 2007	New search has been performed	This review updates the existing version of "Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for RDS" that was first published in The Cochrane Library, Issue 2, 2002 (Stevens 2002). Since the last update, published and unpublished data have become available from studies identified in the previous version of this review of early surfactant administration with rapid extubation vs. selective surfactant and continued mechanical ventilation. Extensive searches of various databases did not identify additional randomized controlled trials of this therapeutic strategy. This update includes complete data from three studies published in 2004 or after [Dani 2004, Texas Research Group, and Reininger 2005 (previously included as D'Angio 2003)] as well as methodological details and outcome data of the NICHD 2002 trial that was obtained from the investigators [NICHD 2002 (formerly Habermann 2002)]. One study is currently awaiting assessment; the Thomson 2002 trial is published in outline form without sufficient detail to assess the quality of the study and important clinical outcomes (Thomson 2002). Six randomized controlled trials of early surfactant administration with rapid extubation vs. selective surfactant and continued mechanical ventilation have been completed. Review of these six trials suggests that early surfactant replacement therapy with extubation to NCPAP compared with later, selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is associated with less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes. In a subgroup comparison examining treatment threshold, a lower treatment threshold (FIO2 <= 0.45) confers greater advantage in reducing the incidences of airleak syndromes and BPD; moreover a higher treatment threshold (FIO2 at study > 0. 45) had an increased incidence of PDA. These data suggest that treatment with surfactant by transient intubation using a low treatment threshold (FIO2 < 0.45) is preferable to later selective surfactant therapy by transient intubation using a

(Continued)

		higher threshold for study entry (FIO2 > 0.45) or at the time of respiratory failure and initiation of mechanical ventilation
20 June 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

TP Stevens, EW Harrington and RF Soll updated the search strategy.

TP Stevens and EW Harrington excerpted data from studies and drafted the revised review.

M Blennow and RF Soll checked data from identified studies and reviewed the update.

TP Stevens, M Blennow and RF Soll wrote the original review.

DECLARATIONS OF INTEREST

Dr. R. Soll is the principal investigator for several trials of pulmonary surfactant and has acted as a paid consultant for several of the pharmaceutical companies that manufacture surfactant products (Abbott Laboratories, Dey Laboratories, Ross Laboratories).

INDEX TERMS

Medical Subject Headings (MeSH)

*Respiration, Artificial; Infant, Newborn; Infant, Premature; Pulmonary Surfactants [*therapeutic use]; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn [drug therapy; *therapy]; Risk

MeSH check words

Humans

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Randomized Trial Comparing 3 Approaches to the Initial Respiratory Management of Preterm Neonates

Michael S. Dunn, Joseph Kaempf, Alan de Klerk, Rose de Klerk, Maureen Reilly, Diantha Howard, Karla Ferrelli, Jeanette O'Conor, Roger F. Soll and for the Vermont Oxford Network DRM Study Group

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Randomized Trial Comparing 3 Approaches to the Initial Respiratory Management of Preterm Neonates

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KEY WORDS
premature, resuscitation, surfactant, CPAP, randomized controlled trial

ABBREVIATIONS
RDS—respiratory distress syndrome
BPD—bronchopulmonary dysplasia
nCPAP—nasal continuous positive airway pressure
PS—prophylactic surfactant
ISX—intubate-surfactant-extubate
FIO_2—fraction of inspired oxygen
CI—confidence interval
COIN—Continuous Positive Airway Pressure or Intubation at Birth

This trial has been registered at www.clinicaltrials.gov (identifier NCT00244101).

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

WHAT'S KNOWN ON THIS SUBJECT: Intubation with prophylactic surfactant administration protects preterm infants from the complications of respiratory distress syndrome. From recent studies it was suggested that initial respiratory support with continuous positive airway pressure and later selective surfactant treatment might be an acceptable alternative.

WHAT THIS STUDY ADDS: Preterm neonates managed with early nasal CPAP or prophylactic surfactant with rapid extubation to nasal CPAP had outcomes similar to those treated with prophylactic surfactant followed by mechanical ventilation. Early CPAP might obviate the need for mechanical ventilation and/or surfactant.

OBJECTIVE: We designed a multicenter randomized trial to compare 3 approaches to the initial respiratory management of preterm neonates: prophylactic surfactant followed by a period of mechanical ventilation (prophylactic surfactant [PS]); prophylactic surfactant with rapid extubation to bubble nasal continuous positive airway pressure (intubate-surfactant-extubate [ISX]) or initial management with bubble continuous positive airway pressure and selective surfactant treatment (nCPAP).

DESIGN/METHODS: Neonates born at 26⅞ to 29⅞ weeks' gestation were enrolled at participating Vermont Oxford Network centers and randomly assigned to PS, ISX, or nCPAP groups before delivery. Primary outcome was the incidence of death or bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age.

RESULTS: 648 infants enrolled at 27 centers. The study was halted before the desired sample size was reached because of declining enrollment. 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% confidence interval: 0.64–1.09) for the nCPAP group. There were no statistically significant differences in mortality or other complications of prematurity. In the nCPAP group, 48% were managed without intubation and ventilation, and 54% without surfactant treatment.

CONCLUSIONS: Preterm neonates were initially managed with either nCPAP or PS with rapid extubation to nCPAP had similar clinical outcomes to those treated with PS followed by a period of mechanical ventilation. An approach that uses early nCPAP leads to a reduction in the number of infants who are intubated and given surfactant. *Pediatrics* 2011;128:e1069–e1076

The majority of neonates born at <30 weeks' gestation require respiratory support after birth to facilitate transition and ensure adequate gas exchange.[1] The best approach to the initial respiratory management of these infants is uncertain.

Endotracheal administration of exogenous surfactant decreases complications of respiratory distress syndrome (RDS) in premature infants.[2] Both prophylactic treatment, in which surfactant is administered shortly after birth to infants at high risk of developing RDS,[3] or selective therapy, in which surfactant is administered to infants only after they have exhibited evidence of significant RDS,[4] have been proven to be effective. Meta-analysis of 8 trials to compare these approaches revealed that prophylactic surfactant led to reduced rates of pneumothorax, neonatal mortality and the combined outcome of death or bronchopulmonary dysplasia (BPD).[5] However, several aspects of these trials deserve closer examination to determine their relevance to current clinical practice. Infants enrolled in these studies had low rates of exposure to antenatal steroids. If randomly assigned to receive prophylactic surfactant, infants were generally ventilated for a significant period of time after treatment and most infants in the selective treatment groups were on mechanical ventilation before surfactant treatment.

In 1987, Avery et al[6] reported that the application of early nasal continuous positive airway pressure (nCPAP) was associated with reduced rates of BPD. Over the past decade, many trials have demonstrated the feasibility and apparent benefits of providing early nCPAP,[7–11] and studies have also revealed that surfactant can be effectively administered to many infants initially managed with nCPAP with a brief period of endotracheal intubation followed by rapid extubation back to nCPAP.[12] Our trial was designed to compare the effect of 3 distinct approaches to the initial respiratory management of very preterm infants on the incidence of death or BPD.

METHODS

Study Design

The Delivery Room Management Trial was a multicenter randomized trial conducted at participating Vermont Oxford Network centers. To participate, study centers must have demonstrated competency in the use of bubble nCPAP by successfully completing a Web-based educational program and effectively using it in at least 20 infants. Each center obtained approval to conduct the study from their institutional review boards. Expectant parents were approached for informed consent if considered at high risk of having a preterm delivery at 26⅐ – 29⅐ weeks' gestation. Women who were carrying a fetus with a potentially life-threatening anomaly or condition were excluded. Random assignment took place when it was deemed that delivery was imminent. Infants could be excluded after randomization only if found to be stillborn or to have a previously unrecognized life-threatening congenital anomaly. Investigators randomly allocated infants to 1 of the 3 treatment arms by drawing a card contained within a sealed envelope. Stratification and block randomization was according to center and according to gestational age. Infants from multiple gestation pregnancies were randomly assigned as individual subjects.

Study Interventions

Infants were randomly allocated to 1 of 3 groups:

1. prophylactic surfactant (PS): infants were to be intubated 5 to 15 minutes after birth for the purposes of surfactant administration, then stabilized on mechanical ventilation for a minimum of 6 hours after which time they could be extubated to nCPAP;
2. intubate-surfactant-extubate (ISX): infants were to be intubated 5 to 15 minutes after birth for the purposes of surfactant administration. Infants who required a fraction of inspired oxygen (F_{IO_2}) < 0.6 without severe respiratory distress or apnea were to be extubated to nCPAP 15 to 30 minutes after surfactant instillation; or
3. nCPAP: infants were to be supported with nCPAP within 15 minutes after birth and intubated only if meeting 1 or more of the following criteria: (*a*) >12 episodes of apnea that required stimulation or more than 1 episode that required bagging in a 6-hour period; (*b*) P_{CO_2} > 65 mm Hg on arterial or capillary blood gas; or (*c*) requirement for F_{IO_2} of >0.4 to maintain oxygen saturation of 86% to 94%. Intubation was discretionary if F_{IO_2} was 0.4 to 0.6 and mandatory if F_{IO_2} > 0.6. After intubation, infants requiring supplemental oxygen were to be treated with surfactant.

Decisions regarding subsequent management with ongoing mechanical ventilation or extubation to nCPAP were at the discretion of the clinical team. All infants who required mechanical ventilation and F_{IO_2} of >0.30 for >6 hours after receiving surfactant were eligible for retreatment.

Patients who received nCPAP were initially supported with a pressure of 5 cm H_2O, which could be increased to a maximum of 7 cm H_2O. Short, binasal prongs were used as the interface. CPAP was generated by continuous gas flow delivered through a heated, humidified circuit with the end submerged to an appropriate depth in a water-filled bottle. We attempted to maintain infants on bubble nCPAP for

at least 72 hours after extubation and until 1 week of age if requiring supplemental oxygen. After the first week, the degree and method of respiratory support were determined by the clinicians caring for the infant.

Extubation was attempted when an infant on mechanical ventilation remained stable for a 6 hour period with a mean airway pressure of ≤ 7 cm H_2O and an F_{IO_2} of ≤ 0.30. Clinicians could extubate from higher ventilator settings if deemed appropriate. Use of methylxanthines before extubation was encouraged but not mandated.

Primary and Secondary Outcomes

The primary outcome was death or moderate to severe BPD at 36 weeks' postmenstrual age.[13] An infant was deemed to have BPD if on mechanical ventilation, CPAP, or required supplemental oxygen to maintain an arterial oxygen saturation of $\geq 88\%$.[14] Infants who required <30% oxygen via head box or 250 mL/minute of oxygen via nasal cannula were subjected to a oxygen saturation test to confirm the need for supplemental oxygen. Secondary outcomes included the number of infants who received surfactant, number of surfactant doses, use of postnatal steroids, growth, days on assisted ventilation, days on nCPAP, and days on supplemental oxygen. Other outcomes included the incidence of common complications of prematurity and mortality.[15]

Long-term outcomes including health and neurodevelopmental status as determined by questionnaire at 2 years' corrected age will form the basis of a future report.

Statistical Analysis

The primary analysis was performed by comparing each of the 2 "experimental" groups (ISX and nCPAP) to the "standard management" group (PS). Analysis was performed on an intention to treat basis. χ^2 test for categorical variables and analysis of variance for continuous variables were used. Relative risks and 95% confidence intervals (CIs) were calculated to compare outcomes of ISX and nCPAP groups to the PS group. Logistic regression was used to assess the effect of study group on the primary outcome, adjusting for gender, birth weight, antenatal steroid administration, mode of delivery, multiple birth, and chorioamnionitis.

Planned sample size was based on a 30% reduction in the number of infants with BPD per death from 36% to 25% ($\alpha = 0.05$; $\beta = 0.2$). Baseline incidence of BPD/death for infants born at 26⅐ to 29⅐ weeks' gestation was determined from the Vermont Oxford Network database. A total of 876 infants were to be enrolled with 292 in each arm of the study.

RESULTS

Three interim analyses for efficacy and safety were performed at scheduled intervals and revealed no safety concerns or significant differences between groups in the primary outcome. An additional analysis was requested in January 2009 to assess the effect of declining enrollment on study viability. The Data Safety Monitoring Committee recommended to the steering committee that recruitment be halted in March 2009 before the desired sample size was reached.

A total of 648 infants from 27 Vermont Oxford Network centers were enrolled between September 2003 and March 2009. During this time frame, 3335 infants within the eligible gestational age range were born at participating centers. Centers enrolled a median of 8 patients (range: 2–167). 55% of the infants were recruited from the top 3 enrolling centers. There were 301 infants of 26⅐ to 27⅐ and 347 of 28⅐ to 29⅐ weeks' gestation. Eight infants who were randomly assigned were not subsequently enrolled (Fig 1). Enrolled infants had a mean birth weight of 1053 g and mean gestational age of 28⅐ weeks. There were no significant differences in demographics or population characteristics between groups other than fewer male infants in the nCPAP group ($P < .05$, PS versus nCPAP group) (Table 1).

Adherence to assigned treatment protocol was assessed by examining support provided to study infants in the first hour after birth (Table 2). More than 98% of infants in both the PS and ISX groups were intubated and given surfactant. Of infants in the ISX group, 83.3% were successfully extubated, and 82.1% of infants in the nCPAP group were managed without intubation during this interval.

The rates of the primary outcome are shown in Table 3. There were no statistically significant differences between groups in the combined outcome of BPD or death at 36 weeks' postmenstrual age. The relative risk of BPD or death was 0.78 (95% CI: 0.59–1.03) for the ISX group and 0.83 (95% CI: 0.64–1.09) for the nCPAP group compared with the PS group. Adjustment of the rates using logistic regression analysis failed to alter the conclusion (death or BPD: ISX versus PS, OR: 0.68 [95% CI: 0.43–1.08]; nCPAP versus PS, OR: 0.82 [95% CI: 0.52–1.29]). Results were similar when the analysis was performed, excluding 21 infants in whom status using physiologic criteria for BPD was not clearly coded. Mortality and rates of death or BPD analyzed according to gestational age strata did not differ between groups.

Within the first week after birth, 100 of 222 (45.1%) of the infants in the nCPAP group were intubated, and all of them received surfactant. Number of surfactant doses received by infants in each group is shown in Fig 2. Of the infants in the ISX group, 111 of 216 (51.4%) had

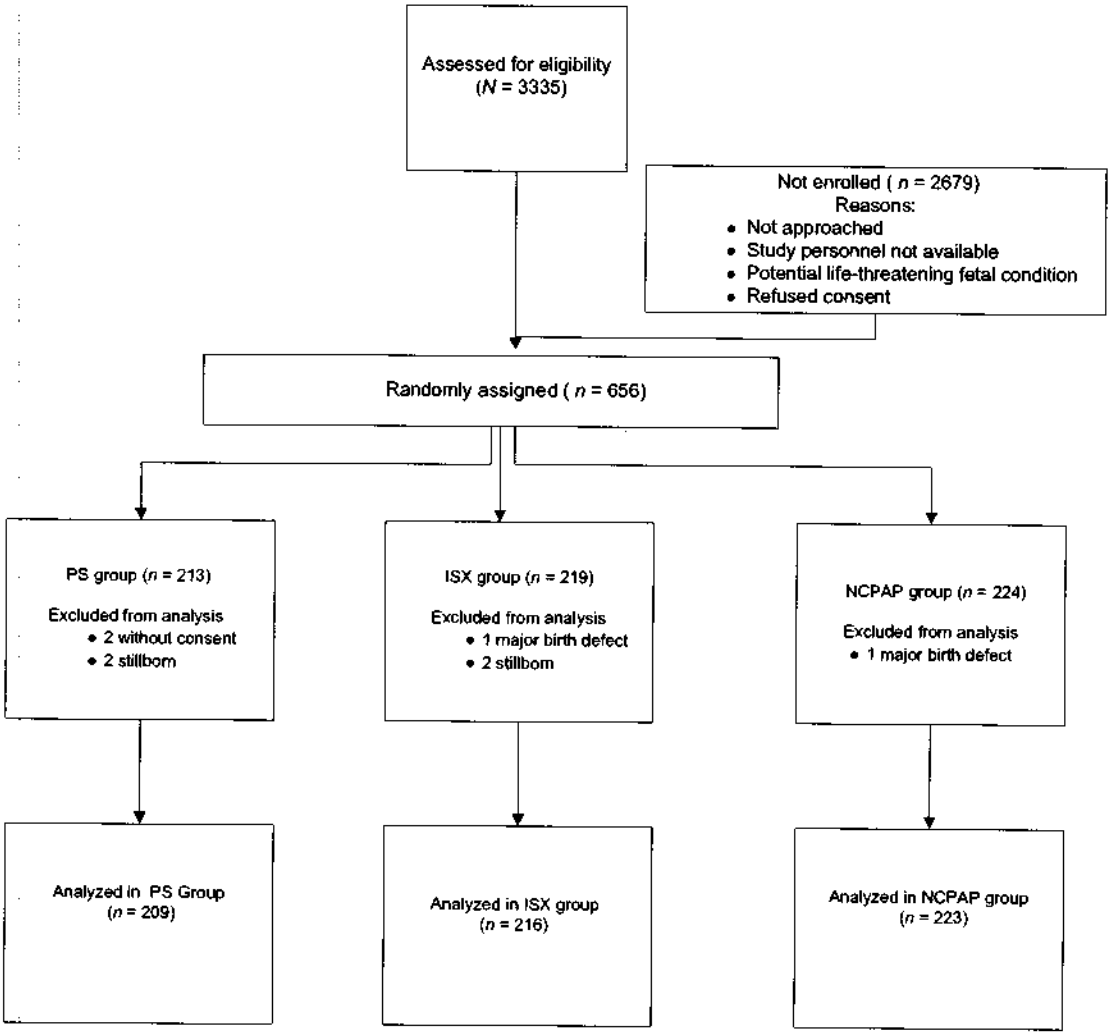

FIGURE 1
Consort diagram.

TABLE 1 Baseline Group Characteristics

	PS (n = 209)	ISX (n = 216)	nCPAP (n = 223)
Maternal characteristics, *n/N* (%)			
Prenatal care	206/209 (98.6)	214/216 (99.1)	221/223 (99.1)
Any antenatal steroids	206/209 (98.6)	213/216 (98.6)	220/223 (98.7)
Vaginal delivery	57/209 (27.3)	70/216 (32.4)	61/223 (27.4)
ROM >24 h	48/208 (23.1)	49/216 (22.7)	52/223 (23.3)
Clinical chorioamnionitis	14/209 (6.7)	24/216 (11.1)	24/222 (10.8)
Neonatal characteristics			
Birth weight, mean ± SD, kg	1040 ± 244	1066 ± 270	1053 ± 252
Gestational age, mean ± SD, wk	28.0 ± 1.1	28.1 ± 1.3	28.1 ± 1.1
Male, *n/N* (%)	118/209 (56.5)	115/216 (53.2)	99/223 (44.4)
White race, *n/N* (%)	154/206 (74.8)	164/213 (77.0)	151/218 (74.8)
Maternal education less than high school, *n/N* (%)	26/205 (12.7)	32/211 (15.2)	29/213 (13.6)
Multiple birth, *n/N* (%)	77/209 (36.8)	63/216 (29.2)	76/223 (34.1)
Median Apgar score			
At 1 min	6	6	7
At 5 min	8	8	8

an endotracheal tube at some point within the first week after birth but after the first hour. Of those that had been successfully extubated in the first hour, 75 of 180 (41.7%) required reintubation. Overall, 128 of 216 (59.3%) of the infants in this group received mechanical ventilation at some point during their hospitalization. The corresponding number for the nCPAP group was 116 of 222 (52.3%), which indicates that almost half of the infants managed with nCPAP initially were able to completely avoid endotracheal intubation. Other than differences in the rates of mechanical ventilation, there were no significant differences

TABLE 2 Respiratory Support in First Hour of Life

Intervention	PS (n = 209)	ISX (n = 216)	nCPAP (n = 223)
NCPAP, *n/N* (%)	11/209 (5.3)	167/216 (77.3)	203/223 (91.0)
Intubated, *n/N* (%)	207/209 (99.0)	213/216 (98.6)	40/223 (17.9)
Age at intubation, median (quartile), min	3.5 (2.0–5.0)	4.0 (2.0–6.0)	4.5 (3.0–11.5)
Surfactant administration, *n/N* (%)	206/209 (98.6)	212/216 (98.2)	33/223 (14.8)
Extubation, *n/N* (%)	1/209 (0.5)	180/216 (83.3)	5/223 (2.2)

TABLE 3 Status at 36 Weeks' Postmenstrual Age

	PS	ISX	RR (95% CI)	NCPAP	RR (95% CI)
All, *N*	209	216	—	223	—
Death, %	7.2	7.0	0.97 (0.49–1.94)	4.1	0.57 (0.25–1.27)
Death or BPD, %	36.5	28.5	0.78 (0.59–1.03)	30.5	0.83 (0.64–1.09)
Gestational age 26–27⅐ wk, *N*	98	101	—	102	—
Death, %	11.2	10.1	0.90 (0.40–2.02)	5.9	0.53 (0.20–1.38)
Death or BPD, %	53.1	43.4	0.82 (0.61–1.10)	40.6	0.77 (0.57–1.03)
Gestational age 28–29⅐ wk, *N*	111	115	—	121	—
Death, %	3.6	4.4	1.20 (0.33–4.34)	2.5	0.69 (0.16–3.03)
Death or BPD, %	21.8	15.7	0.72 (0.41–1.25)	21.9	1.00 (0.61–1.64)

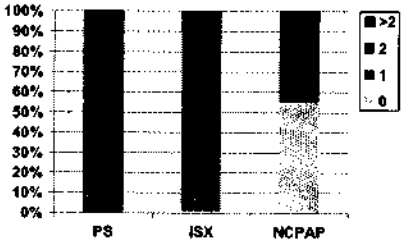

FIGURE 2
Surfactant dosing.

in type or duration of various forms of respiratory support provided to infants in the 3 groups (Table 4).

Other secondary outcomes are detailed in Table 5. There were no statistically significant differences between the groups except in the incidence of PDA. Although PDA was less common in the ISX group, the rates of surgical ligation were not different. Of note, the incidence of pneumothorax was similar between groups. There were also no differences in rates of weight gain or time to full feeds between groups (data not shown).

DISCUSSION

In this study, infants born at 26⅐ to 29⅐ weeks' gestation whom investigators attempted to initially support with nCPAP or those given prophylactic surfactant followed by rapid extubation to nCPAP seemed to have similar clinical outcomes to those treated with prophylactic surfactant followed by mechanical ventilation. The study was stopped after recruitment reached 74% of the projected sample size because of difficulties with enrollment. It is possible that statistically significant differences in outcome might have been demonstrated if the full sample size had been attained.

Early application of nCPAP in very preterm infants at high-risk of RDS seems to be safe and might lead to improved outcomes compared with elective intubation and ventilation. Even if considered equivalent, many would advocate using this approach as a means of providing a less invasive method of support. A significant number of infants stabilized with nCPAP shortly after birth can avoid intubation, ventilation, and surfactant treatment altogether. In this study, 48% of the infants in the nCPAP group were ultimately managed without intubation, and 54% were managed without the use of surfactant.

It is interesting to compare our study with the other recently reported randomized trials examining initial respiratory management of very preterm infants. The COIN trial (Continuous Positive Airway Pressure or Intubation at Birth) compared routine intubation to management with early nCPAP in spontaneously breathing preterm infants born between 25 and 28 weeks' gestation.[16] Results were equivocal, which suggests that clinicians should be comfortable using either approach and should expect comparable outcomes. In the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) trial, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network examined a similar question.[17] They found that the outcomes of infants managed with either early nCPAP or intubation and prophylactic surfactant were similar. In the subgroup of infants born at 24 to 25 weeks' gestation, outcomes seemed to be improved if initial management with nCPAP was attempted. The European CURPAP study compared initial

TABLE 4 Respiratory Support

	PS (n = 209)	ISX (n = 216)	NCPAP (n = 223)
Time on O_2[a], mean ± SD, d	30.3 ± 26.5	26.0 ± 24.7	29.2 ± 28.3
Received nCPAP, *n/N* (%)	202/209 (96.7)	212/216 (98.2)	219/222 (98.7)
Time on nCPAP, mean ± SD, d[a]	17.0 ± 14.3	15.2 ± 13.0	16.1 ± 14.7
Received any mode of ventilation, *n/N* (%)	200/209 (95.7)	128/216 (59.3)	116/222 (52.3)
Time on any mode of ventilation, mean ± SD, d[a]	7.7 ± 12.4	9.2 ± 13.8	12.5 ± 14.1
Received HFV, *n/N* (%)	41/209 (19.6)	30/216 (13.9)	34/222 (15.3)
Time on HFV, mean ± SD, d[a]	7.7 ± 9.7	7.1 ± 10.3	9.3 ± 11.1
Nasal cannula >1 L/min, *n/N* (%)	51/175 (29.1)	45/178 (25.3)	55/181 (30.4)
Time on nasal cannula >1 L/min, mean ± SD, d[a]	13.0 ± 9.7	16.3 ± 11.5	11.7 ± 9.1

HFV indicates high-frequency ventilation.
[a] After first hour, only for infants who received the intervention.

TABLE 5 Complications of Prematurity

	PS, *n/N* (%)	ISX, *n/N* (%)	RR vs PS (95% CI)	NCPAP, *n/N* (%)	RR vs PS (95% CI)
Pneumothorax	10/209 (4.8)	7/216 (3.2)	0.68 (0.26–1.75)	12/222 (5.4)	1.13 (0.50–2.56)
Pulmonary hemorrhage	6/209 (2.9)	7/216 (3.2)	1.13 (0.39–3.30)	3/222 (1.4)	0.47 (0.12–1.86)
PDA	92/208 (44.2)	74/216 (34.3)	0.77 (0.61–0.98)	101/222 (45.5)	1.03 (0.83–1.27)
NEC	14/209 (6.7)	16/216 (7.4)	1.11 (0.55–2.21)	18/222 (8.1)	1.21 (0.69–2.54)
NEC surgery	9/209 (4.3)	7/215 (3.3)	0.75 (0.29–1.98)	12/222 (5.4)	1.25 (0.54–2.90)
Gastrointestinal perforation	10/209 (4.8)	6/216 (2.8)	0.58 (0.21–1.57)	7/221 (3.2)	0.66 (0.26–1.71)
Sepsis					
Late-onset bacterial infection[a]	27/205 (13.2)	25/214 (11.7)	0.89 (0.53–1.48)	17/220 (7.7)	0.59 (0.33–1.04)
Coagulase-negative staphylococcus	18/205 (8.8)	17/214 (7.9)	0.90 (0.48–1.71)	16/221 (7.2)	0.82 (0.43–1.57)
Late-onset fungal infection	3/205 (1.5)	3/214 (1.4)	0.96 (0.20–4.69)	1/221 (0.5)	0.31 (0.03–2.95)
Received cranial ultrasound	203/209 (97.1)	207/216 (95.8)	0.99 (0.95–1.02)	218/222 (98.2)	1.01 (0.98–1.04)
With any IVH, %	46/203 (22.7)	43/206 (20.9)	0.92 (0.64–1.33)	47/218 (21.6)	0.95 (0.66–1.36)
With severe IVH, %	12/203 (5.9)	8/206 (3.9)	0.66 (0.27–1.57)	6/218 (2.8)	0.47 (0.18–1.22)
PVL	2/190 (1.1)	6/204 (2.9)	2.79 (0.57–13.68)	3/206 (1.5)	1.38 (0.23–8.19)
Any ROP	65/183 (35.5)	61/180 (33.9)	0.95 (0.72–1.27)	85/192 (44.3)	1.25 (0.97–1.60)
Severe ROP	7/183 (3.8)	4/180 (2.2)	0.58 (0.17–1.95)	13/192 (6.8)	1.77 (0.72–4.34)

PDA indicates patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.
[a] All bacterial pathogens, including coagulase-negative staphylococcus.

management with nCPAP to prophylactic surfactant followed by rapid extubation to nCPAP in infants born at 25 to 28 weeks' gestation.[18] The investigators found similar outcomes between these groups and concluded that early application of nCPAP shortly after birth followed by selective surfactant treatment should be the preferred management strategy because many infants will be able to avoid intubation and surfactant treatment.

The COIN trial, SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial), and our study compared infants managed with elective intubation and ventilation versus early application of nCPAP. The findings from these 3 studies are remarkably consistent. Although entry criteria and indications for intubation and surfactant administration were different and no single trial was able to demonstrate a statistically significant difference, each study showed a lower relative risk of death or BPD when infants were managed initially with nCPAP.

Our study included a third treatment arm in which infants were intubated, given surfactant, and rapidly extubated to nCPAP. In theory, this might be the best approach because it allows the established benefit of prophylactic surfactant while avoiding exposing infants to ventilator induced lung injury. The Colombian Neonatal Research Network studied infants born at 27 to 31 weeks' gestation with signs of RDS at less than 1 hour of age who were randomly assigned to treatment approaches similar to our nCPAP and ISX groups.[19] Rates of mechanical ventilation and pneumothorax were reduced with very early surfactant administration without mandatory ventilation. However, there were no differences in rates of mechanical ventilation or BPD in their lower gestational age stratum of 27 to 29 weeks, consistent with the findings of our trial.

The 2 arms in the CURPAP study are also similar to the nCPAP and ISX groups of our study. Although there are some differences in entry criteria and study protocol, results are similar. Neither trial found a statistically significant advantage to either approach with respect to clinical outcomes. In both studies, approximately half of the infants placed electively on nCPAP shortly after birth were able to avoid intubation and surfactant treatment.

There are risks inherent to prophylactic surfactant administration. Even a short period of endotracheal intubation with positive pressure ventilation can lead to lung injury.[20] Furthermore, surfactant is not an inexpensive therapy, and some infants will deteriorate during the instillation process.[21] Prophylactic treatment results in a significant number of infants receiving treatment who seem to be able to do just as well without it, particularly those exposed to antenatal steroids.[22] However, attempts to provide initial respiratory support with nCPAP should not result in infants with significant RDS being disadvantaged by having surfactant withheld or administration delayed.

Several systematic reviews have been performed to examine timing of surfactant treatment in preterm infants with or at risk for RDS. Although studies included in these reviews did not generally include infants managed with nCPAP from shortly after birth, the reviews consistently conclude that outcomes are improved if surfactant is given earlier rather than later.[5,12,23] The increased rate of pneumothorax seen in the nCPAP group of the COIN trial might be in part because of the low percentage of these very preterm infants being given surfactant expeditiously. In the COIN study, the oxygenation criterion for intubation was a requirement for F_{IO_2} of >0.60 and, even with intubation, surfactant treat-

ment was not mandated. Verder et al[24] found that, when evaluating the INSURE approach (Intubation, Surfactant, Extubation) to surfactant treatment in preterm infants initially managed with nCPAP, those who were treated earlier with less severe disease had better outcomes than those treated only after requiring higher levels of supplemental oxygen. In the systematic review by Stevens et al,[12] infants selectively treated with surfactant at a lower F_{IO_2} threshold (<0.45) had fewer complications than those treated at a higher F_{IO_2}. We chose an oxygen requirement of >0.4 to prompt clinicians to strongly consider intubation and surfactant treatment. Using this criterion, only 45% of the nCPAP group was treated with surfactant, and there was no increase in rate of pneumothorax. The CURPAP study used similar criteria for selective surfactant treatment in the nCPAP group and did not demonstrate an increase in pneumothorax. If nCPAP is to be used to stabilize very preterm infants after birth, it is likely to be optimal if selective surfactant treatment is provided early in their course, as soon as infants have clear evidence of respiratory distress syndrome.

Because this study could not be blinded, there was a possibility of bias influencing the outcomes if providers managing the infants did not follow strict guidelines. However, the assigned treatment strategy was successfully applied in the majority of randomly assigned infants. Fewer than 20% of the infants in the ISX and nCPAP groups were unable to be managed as intended. Clinicians choosing to adopt either approach can expect successful application in most cases when managing infants born at 26 to 29 weeks.

CONCLUSIONS

We have shown that preterm neonates born at 26⅐ to 29⅐ weeks' gestation who are initially managed with either nCPAP or prophylactic surfactant with rapid extubation to nCPAP seem to have similar clinical outcomes to those treated with prophylactic surfactant followed by a period of mechanical ventilation. An approach that uses early nCPAP leads to a reduction in the number of infants who are intubated and receive surfactant. Because there seems to be no negative effect to applying an elective early nCPAP approach to these infants, it may be recommended as a less invasive and potentially less expensive method of management.

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Randomized Trial Comparing 3 Approaches to the Initial Respiratory Management of Preterm Neonates

Michael S. Dunn, Joseph Kaempf, Alan de Klerk, Rose de Klerk, Maureen Reilly, Diantha Howard, Karla Ferrelli, Jeanette O'Conor, Roger F. Soll and for the Vermont Oxford Network DRM Study Group

Pediatrics; originally published online October 24, 2011;
DOI: 10.1542/peds.2010-3848

From:	Luc Brion
To:	Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject:	RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057
Date:	Monday, April 07, 2014 11:28:25 AM
Attachments:	Pediatrics-2011-Dunn-VON.peds.2010-3848.pdf INSURE vs surfactant IMV Stevens, CD003063.pdf

I think it would be useful to respond to the reviewer, even if we do not have the data for earlier patients.
INSURE became more popular after the VON trial (see attached).

INSURE stands for "INtubate, SURfactant, Extubate".
This was one arm of the RCT run by the Vermont Oxford: CPAP, intubation + ventilation, INSURE.
Actually the VON protocol included:
"intubate-surfactant-extubate (ISX): infants were to be intubated 5 to 15 minutes after birth for the purposes of surfactant administration. Infants who required a fraction of inspired oxygen (FIO2) 0.6 without severe respiratory distress or apnea were to be extubated to nCPAP 15 to 30 minutes after surfactant instillation;"

The GDB criterion to exclude a DR INTUBATION from being entered on NG02 is much shorter intubation than that:
" Intubation?
Insertion of a tube (even if transiently) into the trachea to allow positive pressure ventilation for breathing. If intubation was done for suctioning or to give surfactant and immediately removed it
should not be included here."

Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 10:07 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

What is INSURE? Just curious.
The date/time is only on the 2008 form, not the 2002 or 2011 forms, so I would have the question on, I assume, a relatively small proportion of the later group.
But you can let me know if you think this would still be helpful.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 10:58 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Can you answer the question for the later-born babies?
INSURE has become popular lately.
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 9:55 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc, Yes that's the question we use for surfactant, but it looks like the date/time for surfactant administration was

on one version of the 3 versions of the NG03 form that I used. The first version is just yes/no to surfactant administration, and the last version is just >= or < 72 hours. So, I don't at the moment see any way to determine DR intubation for surfactant on all the babies.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, April 07, 2014 10:39 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

If a patient is intubated in the DR for surfactant only, it would be entered on GDB manual on section 4.3.2.
This would come into form NGO3 B.2
See below
Luc

4.3.2 Section B - PULMONARY
1. Demonstrated clinical features of respiratory distress within the first 24 hours?
Record 'Y' if infant showed signs of grunting, flaring, retracting, paradoxical breathing, cyanosis and/or supplemental oxygen requirement within the first 24 hours.
2. Did the baby receive surfactant?
This includes any surfactant preparation used at any location (delivery room, NICU or at referring hospital).
If YES, code all that apply
a. Less than 72 hours of life?

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, April 07, 2014 9:29 AM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi Luc,
I used the 'd.Intubation?' question on the NG02 which is under the 'Delivery Room resuscitation'/'Birth resuscitation/stabilization' section on the forms. It is described in each manual as intubation for PPV and it says not for suctioning (2002) /not for suctioning/surfactant (2008 & 2011). I don't see a question about intubation for surfactant in this section, could you point me to where you see that?
Thanks.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, April 04, 2014 7:23 PM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Lisa,
thanks a lot for your email.
One question: In the GDB worksheet has separate information about intubation for ventilation in the delivery and separate information about Intubation for surfactant in the delivery room.
I presume you counted intubation in the DR from the first entry only. Could you please confirm that?
Do you have or could you extract any information on intubation for surfactant in the delivery room for patients who did not remain intubated? If not, I will say that in my response to the reviewer #2.
Luc

-----Original Message-----
From: Wrage, Lisa Ann [mailto:wrage@rti.org]

Sent: Friday, April 04, 2014 11:33 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Luc Brion
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Hi,
It does look positive, the reviewers comments see pretty benign in terms of what they want addressed, it looks to me like reducing by 500 words might be the hardest part!
Lisa

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 04, 2014 12:15 PM
To: Das, Abhik; Luc Brion (luc.brion@utsouthwestern.edu)
Cc: Wrage, Lisa Ann
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

I agree - go for it!
Thanks
Rose

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-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, April 04, 2014 12:14 PM
To: Luc Brion (luc.brion@utsouthwestern.edu)
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

Luc:

It looks to me that the changes asked for are not very radical and quite doable!

Thanks

Abhik

-----Original Message-----
From: onbehalfof+info.adc+bmj.com@manuscriptcentral.com
[mailto:onbehalfof+info.adc+bmj.com@manuscriptcentral.com] On Behalf Of info.adc@bmj.com
Sent: Friday, April 04, 2014 11:24 AM
To: luc.brion@utsouthwestern.edu
Cc: rm.beattie@btinternet.com; (b)(6) @gmail.com; luc.brion@utsouthwestern.edu; Wrage, Lisa Ann; Gantz, Marie; myra.wyckoff@utsouthwestern.edu; Pablo.Sanchez@nationwidechildrens.org; roy.heyne@utsouthwestern.edu; mambarambath.jaleel@utsouthwestern.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik; Barbara.Stoll@oz.ped.emory.edu; higginsr@mail.nih.gov
Subject: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

04-Apr-2014

Manuscript ID fetalneonatal-2014-306057 entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial"

Dear Dr. Brion,

Thank you for submitting the above manuscript to Archives of Disease in Childhood. It has been considered carefully at an editorial meeting and unfortunately, we do not wish to publish it in its current form.

However, we invite you to resubmit a further version of your paper. In inviting you to resubmit, I must emphasise that there is no guarantee that your paper will be accepted but we will look at it carefully with our referees and hope that it might prove possible to eventually publish a version of it.

It is essential that you detail your response to each and every one of the reviewers' comments, including any with which you disagree so have not complied with in your revised version. The comments of the reviewer(s) are included at the bottom of this letter.

In addition to the reviewers' comments, the editors found the (b)(4),(b)(6)
(b)(4),(b)(6)

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Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

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IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to Archives of Disease in Childhood, your revised manuscript should be submitted by 03-Jun-2014. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Archives of Disease in Childhood and I look forward to receiving your revision.

Sincerely,
Dr. Ann Stark

Associate Editor, Archives of Disease in Childhood

Reviewer(s)' Comments to Author:

Reviewer: 1

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD,[1] Pablo J. Sánchez, MD,[1,4] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil N. Finer, MD,[5] Waldemar A. Carlo, MD,[6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

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No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 2429 words
Article length: 12,4990 words
Revised 4/54/141/23/2014 rev
FetalNeonatal-2014-306057.R1

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) changed ~~decreased~~ in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA, ~~born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the NRN~~, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, $p < 0.0001$) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, $p=0.40$).

Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized ~~2 X 2 factorial~~ controlled trial (RCT), in which preterm infants of $24^{0/7}$ ~~weeks~~ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets ~~of either 85 to 89% or 91 to 95%.~~[1,2] From ~~February~~ 2005 through ~~February~~ 2009, 1316 infants were enrolled in 19 centers.[1,2] The results of ~~the~~ SUPPORT ~~trial~~ were released to ~~the~~ NRN centers in December 2009 ~~and published in May 2010~~.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] ~~The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.~~

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in ~~the SUPPORT Trial~~SUPPORT and the GA range that would be most appropriate for ~~the SUPPORT Trial~~SUPPORT.[3] Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients. A previous study in one NRN center that had not participated in the feasibility trial demonstrated that ~~clinical practice, specifically~~ the

proportion of DR ETI, changed among non-enrolled patients during SUPPORT ~~the trial~~ and before release of its results.[4] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

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The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after ~~the SUPPORT trial~~SUPPORT in participating centers. We hypothesized that ~~that after the SUPPORT trial there would be a decrease in~~ DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks changed after ~~the SUPPORT trial~~SUPPORT, ~~compared to the period before the trial.~~ We speculated that the decrease in proportion of DR ETI in each center after SUPPORT ~~the trial~~ would depend on the ~~baseline~~ proportion before the trial. We also speculated that the decrease in DR ETI after ~~the SUPPORT Trial~~SUPPORT would be less in centers that had participated in the feasibility trial than in the other centers. ~~In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.~~

METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of ~~the~~

~~SUPPORT trial~~SUPPORT and in a second preterm cohort born after release of the results of ~~the SUPPORT trial~~SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in ~~the~~ ~~SUPPORT trial~~SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes ~~preterm~~ patients born during a ~~2-year~~ period preceding ~~the~~ ~~SUPPORT trial~~SUPPORT (~~from~~ 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT ~~Trial~~ to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in ~~the SUPPORT trial~~SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in ~~the SUPPORT trial~~SUPPORT, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to

death < 12 hours. The lastter criterion was different from the SUPPORT trialSUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

Outcome variables were selected a priori.

The primary outcome variable was a practice variable, i.e., DR ETI.

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trialSUPPORT), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trialSUPPORT, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of the SUPPORT trialSUPPORT was reached or resolution occurred).[1,2]

Additional ~~Tertiary~~ outcomes are described in Tables 3 and ~~included practice variables~~ in the Appendix, on line only. ~~such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.~~ Outcome variables were selected a priori, except the proportion of babies who were never intubated.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT) and pre-specified prenatal covariates ~~(based on the literature)~~ shown to affect outcomes in very preterm infants[56] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that

preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[67-156] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort ~~first period (pre-SUPPORT) to the second period (post-SUPPORT)~~ was higher in centers with higher proportion of DR ETI during the first period.

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Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough for multivariate analysis with 10 patients per covariate.

IRB

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and ~~the SUPPORT Trial~~SUPPORT.

RESULTS

Maternal and Neonatal Characteristics

~~A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial.~~ The study population included 3,849 inborn infants~~: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group~~ (Figure 1). ~~Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants.~~ The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT among ~~in the subgroup of~~ infants from centers that had participated in the feasibility trial ~~(61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40)~~ but decreased significantly among ~~in the subgroup of~~ infants from the other centers. ~~(91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).~~

Other outcomes

Secondary outcomes~~, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven~~ were significantly lower in the post-SUPPORT group (Table 3). ~~By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.~~

~~Unadjusted comparisons of~~ Ttertiary outcome variables are shown in the Appendix; online only. ~~Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).~~

DISCUSSION:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in ~~the SUPPORT trial~~SUPPORT after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before ~~the SUPPORT trial~~SUPPORT. The proportion of DR ETI significantly decreased among ~~in the subgroup of~~ infants from centers that had not participated in the feasibility trial, but not. ~~In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT~~ among ~~in the subgroup of~~ infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 2000, after prospective introduction of ~~when neonatologists prospectively introduced~~ routine, early, bubble nasal CPAP.[16,17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients~~, which limits incomplete/missing data and information bias~~; the use of multivariate analysis ~~to take into account confounding variables~~; inclusion and exclusion criteria that were similar to those ~~used~~ in ~~the SUPPORT trial~~SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN ~~during the entire study period~~, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design~~, which prevents any cause-effect interpretation~~; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually

obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked ~~of~~ serial data and ~~lack of~~ data from centers that did not participate in ~~the SUPPORT trial~~SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study ~~we have shown that~~ the proportion of DR ETI in one NRN center ~~(which did not participate in the Feasibility Trial)~~ decreased in non-enrolled patients ~~from baseline before the SUPPORT trial to epochs~~ during ~~the SUPPORT trial~~SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.[4] In that center, DR ETI decreased by 22% during/after ~~the SUPPORT Trial~~SUPPORT ~~(before release of the trial results)~~, but only by 1.6% in a large ~~large comparable~~ contemporaneous cohort ~~of infants participating in the Vermont Oxford Network~~.[4] ~~Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.[18-27] We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.~~

This study did not address how generalizable the study results might be to other centers, ~~that did not participate in the SUPPORT trial. It is possible that~~ Ceenters participating in

~~the SUPPORT trial~~SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~the SUPPORT trial~~SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after ~~the SUPPORT Trial~~SUPPORT in the group of infants from centers that had not participated in the feasibility trial but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of ~~the SUPPORT trial~~SUPPORT. This study provides additional evidence to suggest that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. ~~It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.~~

WHAT THIS STUDY ADDS

- The proportion of delivery room intubation (a~~A change in~~ process of care) decreased after the SUPPORT trial.
- This decrease was observed ~~was observed only~~ among infants born in centers that had not participated previously in a related trial, but not in the other centers.
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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LICENCE FOR PUBLICATION STATEMENT

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval
[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial
[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
BPD	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

LIST OF CHANGES

We have corrected the section on Settings in the abstract.

We have written the hypotheses as such.

We show that all outcome variables were planned except for the proportion of babies who have never been intubated.

We have shortened the manuscript by 500 words, especially the tertiary variables and the discussion.

We have provided two revised sections (one in the background, one in the discussion) to show the importance of studying this and of analyzing whether the phenomenon exists/does not exist.

We have tightened the "what is known" and "what this adds" section.

ITEMIZED RESPONSES TO COMMENTS

Thank you for the suggestions. Here are the itemized responses in italics.

In addition to the reviewers' comments, the editors found the paper to be long and tedious to read - please shorten by 500 words.
A: We have shortened the manuscript by 500 words.

In the abstract, what you have written as Setting is not really the setting - please state what you mean.
A: We have started this paragraph by the following statement: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN."

Please state hypotheses as such, rather than speculations.
A: In the abstract we replaced the word "decreased" by "changed". On page 6 we changed the text into the following statement: "We hypothesized that that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants 240/7 to 276/7 weeks changed after the SUPPORT trial."

Was this a planned analysis?
A: Yes. All studies conducted at the NICHD NRN require the development of a concept proposal followed if approved by a full protocol. For this study, a protocol was submitted to the NRN GDB committee and then to the Steering Committee. The goal was to test whether the proportion of endotracheal intubation in the delivery room (DR ETI) decreased after the SUPPORT trial in other NRN centers, as had been observed in a single center (reference 4). This protocol was, after multiple revisions, approved by both NRN committees.

Please explain why all the tertiary outcome data in the Appendix would be needed.
A: These data are important to show known potential confounding variables and biases that could have affected the primary and secondary outcomes.

Discussion could be shortened.
A: We have shortened the discussion as requested.

What is known/what this adds should be tightened up and bulleted.
A: We have revised that section as requested, and have followed the guidelines to authors.

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Overall, I found this to be a good manuscript with a rigorous study design and implementation and high scientific validity within the constraints of the study design utilized.

I think the background section would benefit from inclusion of material on why it is important to study the spread of a practice within an institution when that institution participates in a randomized trial of the practice. Why is it such a big deal to study this and prove that the phenomenon exists/does not exist?
A: Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients. Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.
We have previously shown that a center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients. A previous study in one NRN center that had not participated in the feasibility trial demonstrated that clinical practice, specifically the proportion of DR ETI, changed among non-enrolled patients during SUPPORT the trial and before release of its results, but not in a large contemporaneous cohort in the Vermont-Oxford Network. Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.
We have entered most of the above discussion on pages 4 (last paragraph) and 5 (first paragraph).

Methods: It's not clear how many centers in total participated in the SUPPORT trial.
A: we entered the number in the text: 19 (line 9 of the introduction)

Methods, eligibility and inclusion criteria: use the word 'last criterion' instead of the 'latter criterion'
A: We changed the text as requested.

Methods: outcome variables. Please specify if the outcome variables were selected a priori (pre-specified) before the analysis was done (e.g. as part of a study protocol), or was there a post-hoc component to the analysis.
A: Outcome variables were selected a priori, except the proportion of babies who were never intubated (as indicated on the last line of the paragraph on other outcomes.

Analysis:
Why was there no analysis accounting for the clustering of infants within the eleven institutions? I think this is required, but this statement will need to be confirmed by a statistician.

A: Analyses were all done and verified by 3 statisticians in the NRN (LAW, MGG and AD). The analysis with clustering by institution is presented in Figure 2.

Results: Maternal and neonatal characteristics. I think the authors can refer readers to the flow diagram in Figure 1 that shows the numbers and save some space in the text.
A: We have shortened the text as suggested.

Discussion
I think the strengths and limitations are well-described.
I think the discussion section will benefit from inclusion of material that describes the results of other studies of spread of a practice as a result of randomized trial participation, what might be the underlying mechanisms for such spread, and what the implications are for trials and for practice.
Framing this study's results in the larger context of healthcare and neonatal practice will make it more appealing and meaningful to readers.
A: We added the following statement to the end of the discussion:
Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

Discussion: please correct the year where it says '200'
A: thank you for pointing this out; we have corrected the year to 2000.

Reviewer: 2

Comments to the Author
This is a well executed secondary analysis of the NRN, which demonstrate that infants who are not enrolled in an RCT have improved short- and long-outcomes.

I agree with the authors that the reduction is DR ETI might have also been associated with the familiarity with the T-Piece device and their clinical observations that CPAP in the DR is possible. As mentioned by the authors a survey of other centres would not give a total picture of NICU practices in other NICUs and if SUPPORT has changes their practice too. However, this remains an interesting question as studies like SUPPORT, who demonstrated that CPAP in the DR is well tolerated by infants, should be implemented in other NICUs as well.
A: We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This has happened several times in the recent past in the NRN. Furthermore it is even more unlikely that people may remember the exact time practices changed several years ago.

Although, Table 2 demonstrates a significant reduction in DR ETI, however in Figure 2 it appears that two centres have similar DR ETI rates pre and post SUPPORT. Would INUSRE also be counted as an intubation or were these intubation only with continuous mechanical ventilation?
*A: The data on intubation pertains to intubation for ventilation in the delivery room. No patient received INSURE _*** Lisa: could you please verify whether this is accurate? THANKS*

From: Luc Brion
To: (b)(6)@gmail.com; Luc Brion; wrage@rti.org; mgantz@rti.org; Myra Wyckoff; Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Mambarambath Jaleel; nfiner@ucsd.edu; wcarlo@peds.uab.edu; adas@rti.org; Barbara.Stoll@oz.ped.emory.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057
Date: Monday, April 07, 2014 9:17:59 AM
Attachments: Jackie LeVan Manuscript NRN 4-5-14.docx
Responses to comments.docx

Here is a first draft of list of changes, itemize responses and revised manuscript.
Please review and comment
Thanks
Luc

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Cc: rm.beattie@btinternet.com; (b)(6)@gmail.com; Luc Brion; wrage@rti.org; mgantz@rti.org; Myra Wyckoff; Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Mambarambath Jaleel; nfiner@ucsd.edu; wcarlo@peds.uab.edu; adas@rti.org; Barbara.Stoll@oz.ped.emory.edu; higginsr@mail.nih.gov
Subject: Archives of Disease in Childhood - Decision on Manuscript ID fetalneonatal-2014-306057

04-Apr-2014

Manuscript ID fetalneonatal-2014-306057 entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial"

Dear Dr. Brion,

Thank you for submitting the above manuscript to Archives of Disease in Childhood. It has been considered carefully at an editorial meeting and unfortunately, we do not wish to publish it in its current form.

However, we invite you to resubmit a further version of your paper. In inviting you to resubmit, I must emphasise that there is no guarantee that your paper will be accepted but we will look at it carefully with our referees and hope that it might prove possible to eventually publish a version of it.

It is essential that you detail your response to each and every one of the reviewers' comments, including any with which you disagree so have not complied with in your revised version. The comments of the reviewer(s) are included at the bottom of this letter.

In addition to the reviewers' comments, the editors found (b)(4),(b)(6)

(b)(4),(b)(6)

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Because we are trying to facilitate timely publication of manuscripts submitted to Archives of Disease in Childhood, your revised manuscript should be submitted by 03-Jun-2014. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Archives of Disease in Childhood and I look forward to receiving your revision.

Sincerely,
Dr. Ann Stark
Associate Editor, Archives of Disease in Childhood

Reviewer(s)' Comments to Author:

Reviewer: 1

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 2429 words
Article length: 12,4990 words
Revised 4/54/141/23/2014 rev
FetalNeonatal-2014-306057.R1

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) changed ~~decreased~~ in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Eleven centers that participated in the SUPPORT trial and remained part of the NRN. Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85- 89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA, ~~born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the~~ NRN, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, $p < 0.0001$) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, $p=0.40$).

Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized ~~2 X 2 factorial~~ controlled trial (RCT), in which preterm infants of $24^{0/7}$ ~~weeks~~ to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) one of two oxygen saturation targets ~~of either 85 to 89% or 91 to 95%~~.[1,2] From ~~February~~ 2005 through ~~February~~ 2009, 1316 infants were enrolled in 19 centers.[1,2] The results of ~~the~~ SUPPORT ~~trial~~ were released to ~~the~~ NRN centers in December 2009 ~~and published in May 2010~~.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] ~~The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.~~

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in ~~the SUPPORT Trial~~SUPPORT and the GA range that would be most appropriate for ~~the SUPPORT Trial~~SUPPORT.[3] Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients. A previous study in one NRN center that had not participated in the feasibility trial demonstrated that ~~clinical practice, specifically~~ the

proportion of DR ETI, changed among non-enrolled patients during SUPPORT ~~the trial~~ and before release of its results.[4] Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.

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The objective of this study was to determine if the proportion of DR ETI (a process of care) decreased after ~~the SUPPORT trial~~SUPPORT in participating centers. We hypothesized that ~~that after the SUPPORT trial there would be a decrease in~~ DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks changed after ~~the SUPPORT trial~~SUPPORT, ~~compared to the period before the trial.~~ We speculated that the decrease in proportion of DR ETI in each center after SUPPORT ~~the trial~~ would depend on the ~~baseline~~ proportion before the trial. We also speculated that the decrease in DR ETI after ~~the SUPPORT Trial~~SUPPORT would be less in centers that had participated in the feasibility trial than in the other centers. ~~In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.~~

METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of ~~the~~

~~SUPPORT trial~~SUPPORT and in a second preterm cohort born after release of the results of ~~the SUPPORT trial~~SUPPORT to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in ~~the~~ ~~SUPPORT trial~~SUPPORT and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes ~~preterm~~ patients born during a ~~2-year~~ period preceding ~~the~~ ~~SUPPORT trial~~SUPPORT (~~from~~ 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT ~~Trial~~ to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in ~~the SUPPORT trial~~SUPPORT.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in ~~the SUPPORT trial~~SUPPORT, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to

death < 12 hours. The last~~ter~~ criterion was different from ~~the SUPPORT trial~~SUPPORT, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

~~Outcome variables were selected a priori.~~

The primary outcome variable was a practice variable, i.e., DR ETI.

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in ~~the SUPPORT trial~~SUPPORT), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge, and (3) death before discharge. ~~Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors.~~ The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of ~~the SUPPORT trial~~SUPPORT, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of ~~the SUPPORT trial~~SUPPORT was reached or resolution occurred).[1,2]

Additional ~~Tertiary~~ outcomes are described in Tables 3 and ~~included practice variables~~ in the Appendix, on line only. ~~such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.~~ Outcome variables were selected a priori, except the proportion of babies who were never intubated.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT) and pre-specified prenatal covariates ~~(based on the literature)~~ shown to affect outcomes in very preterm infants[26] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that

preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[67-156] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the 1st cohort to the 2nd cohort ~~first period (pre-SUPPORT) to the second period (post-SUPPORT)~~ was higher in centers with higher proportion of DR ETI during the first period.

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Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough for multivariate analysis with 10 patients per covariate.

IRB

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and ~~the SUPPORT Trial~~SUPPORT.

RESULTS

Maternal and Neonatal Characteristics

~~A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial.~~

The study population included 3,849 inborn infants~~: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group~~ (Figure 1). ~~Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants.~~

The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT among ~~in the subgroup of~~ infants from centers that had participated in the feasibility trial ~~(61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40)~~ but decreased significantly among ~~in the subgroup of~~ infants from the other centers. ~~(91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).~~

Other outcomes

Secondary outcomes~~, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven~~ were significantly lower in the post-SUPPORT group (Table 3). ~~By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The~~ average ~~number of ventilator days among survivors decreased after the SUPPORT trial.~~

~~Unadjusted comparisons of T~~tertiary outcome variables are shown in the Appendix; online only. ~~Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).~~

DISCUSSION:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in ~~the SUPPORT trial~~SUPPORT after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before ~~the SUPPORT trial~~SUPPORT. The proportion of DR ETI significantly decreased among ~~in the subgroup of~~ infants from centers that had not participated in the feasibility trial, but not ~~. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT~~ among ~~in the subgroup of~~ infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 2000, after prospective introduction of ~~when neonatologists prospectively introduced~~ routine, early, bubble nasal CPAP.[16,17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients~~, which limits incomplete/missing data and information bias~~; the use of multivariate analysis ~~to take into account confounding variables~~; inclusion and exclusion criteria that were similar to those ~~used~~ in ~~the SUPPORT trial~~SUPPORT; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN ~~during the entire study period~~, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design~~, which prevents any cause-effect interpretation~~; the high percentage of exclusions; lack of information on DR CPAP, oxygen saturation and individual decisions about DR ETI; and lack of information on policies and practice guidelines in NRN centers. We decided against conducting a survey of clinical practices because information in queries is usually

obtained from an single individual and may not be reflective of all practitioners at individual sites. The study lacked ~~of~~ serial data and ~~lack of~~ data from centers that did not participate in ~~the SUPPORT trial~~SUPPORT, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study ~~we have shown that~~ the proportion of DR ETI in one NRN center ~~(which did not participate in the Feasibilty Trial)~~ decreased in non-enrolled patients ~~from baseline before the SUPPORT trial to epochs~~ during ~~the SUPPORT trial~~SUPPORT and before its publication, in the absence of any changes in DR policy or practice guidelines.[4] In that center, DR ETI decreased by 22% during/after ~~the SUPPORT Trial~~SUPPORT ~~(before release of the trial results)~~, but only by 1.6% in a large ~~large comparable~~ contemporaneous cohort ~~of infants participating in the Vermont Oxford Network~~.[4]

~~Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.[18-27] We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.~~

This study did not address how generalizable the study results might be to other centers. ~~that did not participate in the SUPPORT trial. It is possible that~~ Ceenters participating in

~~the SUPPORT trial~~SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~the SUPPORT trial~~SUPPORT. Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after ~~the SUPPORT Trial~~SUPPORT in the group of infants from centers that had not participated in the feasibility trial but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of ~~the SUPPORT trial~~SUPPORT. This study provides additional evidence to suggest that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

ACKNOWLEDGMENTS:

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study. The content of the publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

FUNDING

The Study Sponsor, the National Institute of Child Health and Human Development (NICHD), did not have any role in the study design; in the collection, analysis and interpretation data; in the writing of the report; and in the decision to submit the paper for publication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. ~~It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.~~

WHAT THIS STUDY ADDS

- The proportion of delivery room intubation (a~~A change in~~ process of care) decreased after the SUPPORT trial.
- This decrease was observed ~~was observed only~~ among infants born in centers that had not participated previously in a related trial, but not in the other centers.
- This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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LICENCE FOR PUBLICATION STATEMENT

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Group and co-owners or contracting owning societies (where published by the BMJ Group on their behalf), and its Licensees to permit this article (if accepted) to be published in Archives of Disease in Childhood and any other BMJ Group products and to exploit all subsidiary rights, as set out in our licence.

FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the Generic Database during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval
[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial
[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
BPD	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

LIST OF CHANGES

We have corrected the section on Settings in the abstract.

We have written the hypotheses as such.

We show that all outcome variables were planned except for the proportion of babies who have never been intubated.

We have shortened the manuscript by 500 words, especially the tertiary variables and the discussion.

We have provided two revised sections (one in the background, one in the discussion) to show the importance of studying this and of analyzing whether the phenomenon exists/does not exist.

We have tightened the "what is known" and "what this adds" section.

ITEMIZED RESPONSES TO COMMENTS

Thank you for the suggestions. Here are the itemized responses in italics.

In addition to the reviewers' comments, the editors found the paper to be long and tedious to read - please shorten by 500 words.
A: We have shortened the manuscript by 500 words.

In the abstract, what you have written as Setting is not really the setting - please state what you mean.
A: We have started this paragraph by the following statement: "Eleven centers that participated in the SUPPORT trial and remained part of the NRN."

Please state hypotheses as such, rather than speculations.
A: In the abstract we replaced the word "decreased" by "changed". On page 6 we changed the text into the following statement: "We hypothesized that that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants 240/7 to 276/7 weeks changed after the SUPPORT trial."

Was this a planned analysis?
A: Yes. All studies conducted at the NICHD NRN require the development of a concept proposal followed if approved by a full protocol. For this study, a protocol was submitted to the NRN GDB committee and then to the Steering Committee. The goal was to test whether the proportion of endotracheal intubation in the delivery room (DR ETI) decreased after the SUPPORT trial in other NRN centers, as had been observed in a single center (reference 4). This protocol was, after multiple revisions, approved by both NRN committees.

Please explain why all the tertiary outcome data in the Appendix would be needed.
A: These data are important to show known potential confounding variables and biases that could have affected the primary and secondary outcomes.

Discussion could be shortened.
A: We have shortened the discussion as requested.

What is known/what this adds should be tightened up and bulleted.
A: We have revised that section as requested, and have followed the guidelines to authors.

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Overall, I found this to be a good manuscript with a rigorous study design and implementation and high scientific validity within the constraints of the study design utilized.

I think the background section would benefit from inclusion of material on why it is important to study the spread of a practice within an institution when that institution participates in a randomized trial of the practice. Why is it such a big deal to study this and prove that the phenomenon exists/does not exist?
A: Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients. Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.
We have previously shown that a center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. Outcomes in control patients enrolled in RCTs may be better than contemporaneous, eligible but nonenrolled patients. A previous study in one NRN center that had not participated in the feasibility trial demonstrated that clinical practice, specifically the proportion of DR ETI, changed among non-enrolled patients during SUPPORT the trial and before release of its results, but not in a large contemporaneous cohort in the Vermont-Oxford Network. Thus, a center's participation in an unblinded RCT may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether prior exposure of a center to an RCT might affect the change in process of care associated with the conduct of an unblinded RCT involving a similar intervention.
We have entered most of the above discussion on pages 4 (last paragraph) and 5 (first paragraph).

Methods: It's not clear how many centers in total participated in the SUPPORT trial.
A: we entered the number in the text: 19 (line 9 of the introduction)

Methods, eligibility and inclusion criteria: use the word 'last criterion' instead of the 'latter criterion'
A: We changed the text as requested.

Methods: outcome variables. Please specify if the outcome variables were selected a priori (pre-specified) before the analysis was done (e.g. as part of a study protocol), or was there a post-hoc component to the analysis.
A: Outcome variables were selected a priori, except the proportion of babies who were never intubated (as indicated on the last line of the paragraph on other outcomes.

Analysis:
Why was there no analysis accounting for the clustering of infants within the eleven institutions? I think this is required, but this statement will need to be confirmed by a statistician.

A: Analyses were all done and verified by 3 statisticians in the NRN (LAW, MGG and AD). The analysis with clustering by institution is presented in Figure 2.

Results: Maternal and neonatal characteristics. I think the authors can refer readers to the flow diagram in Figure 1 that shows the numbers and save some space in the text.
A: We have shortened the text as suggested.

Discussion
I think the strengths and limitations are well-described.
I think the discussion section will benefit from inclusion of material that describes the results of other studies of spread of a practice as a result of randomized trial participation, what might be the underlying mechanisms for such spread, and what the implications are for trials and for practice.
Framing this study's results in the larger context of healthcare and neonatal practice will make it more appealing and meaningful to readers.
A: We added the following statement to the end of the discussion:
Further studies are needed to investigate how participating in an RCT might affect individual decisions about process of care. A trial in which centers are randomly allocated to participation in an unblinded RCT would allow to test whether such participation may affect process of care and outcomes in enrolled and non-enrolled patients during and after conducting an RCT.

Discussion: please correct the year where it says '200'
A: thank you for pointing this out; we have corrected the year to 2000.

Reviewer: 2

Comments to the Author
This is a well executed secondary analysis of the NRN, which demonstrate that infants who are not enrolled in an RCT have improved short- and long-outcomes.

I agree with the authors that the reduction is DR ETI might have also been associated with the familiarity with the T-Piece device and their clinical observations that CPAP in the DR is possible. As mentioned by the authors a survey of other centres would not give a total picture of NICU practices in other NICUs and if SUPPORT has changes their practice too. However, this remains an interesting question as studies like SUPPORT, who demonstrated that CPAP in the DR is well tolerated by infants, should be implemented in other NICUs as well.
A: We decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This has happened several times in the recent past in the NRN. Furthermore it is even more unlikely that people may remember the exact time practices changed several years ago.

Although, Table 2 demonstrates a significant reduction in DR ETI, however in Figure 2 it appears that two centres have similar DR ETI rates pre and post SUPPORT. Would INUSRE also be counted as an intubation or were these intubation only with continuous mechanical ventilation?
*A: The data on intubation pertains to intubation for ventilation in the delivery room. No patient received INSURE _*** Lisa: could you please verify whether this is accurate? THANKS*

From: Childress, Kerri (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Upcoming SUPPORT publication
Date: Wednesday, April 02, 2014 5:03:19 PM

Much appreciated. Thanks Rose.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 02, 2014 5:02 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: Re: Upcoming SUPPORT publication

As I originally said, (b)(5)
(b)(5) - not much to say other than to refer them to the nejm2013 publication by Drs. Hudson, Guttmacher and Collins

Thanks
Rose

Sent from my iPhone

On Apr 2, 2014, at 4:52 PM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

> Hi Rose. Please see the inquiry we got from NHLBI, below.
>
> I'm inclined to think that (b)(5)
> (b)(5)
>
> (b)(5)
>
> Anything I might be missing, Rose?
>
> **From:** Striar, Diane (NIH/NHLBI) [E]
> **Sent:** Wednesday, April 02, 2014 3:27 PM
> **To:** Childress, Kerri (NIH/NICHD) [E]
> **Cc:** Johnson, Lenora (NIH/NHLBI) [E]; Ferrier, Robin (NIH/NHLBI) [E]; Zagorski, Nicholas (NIH/NHLBI) [E]; Bock, Robert (NIH/NICHD) [E]
> **Subject:** FW: Upcoming SUPPORT publication
>
> Hi Kerri,
>
> We understand you're (b)(5)
> (b)(5)
> Also, do you know if the journal will issue a release?

Thanks,

Diane
Diane Striar
Chief
Public Affairs Branch
Office of Communications
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, MD 20892-2480
Phone: 301 496 4236
E-mail: striard@nhlbi.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, March 27, 2014 10:59 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: Upcoming SUPPORT publication

Hi
Attached is an upcoming publication related to the SUPPORT trial. We do not yet have a publication date. This is an FYI – I don't think (b)(5) This is the largest study of pul0mary outcomes at 18-22 months in ELBW infants at risk for chronic lung disease. The good news is (b)(5)
(b)(5)
(b)(5) Let me know what you think

Thanks
Rose

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

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blansfield, Earl (NIH/NICHD) [E]
Subject: FW: Sign-in Sheet: Informational meeting: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
Date: Tuesday, April 01, 2014 1:41:33 PM
Attachments: Info session 7.29.13 sign-in sheet..higgins.doc

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

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: Brown, Tiffany (NIH/OD) [E]
Sent: Monday, July 29, 2013 2:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Stein, Meredith (NIH/OD) [E]; Hereford, Russell W (OIG/OEI); Buck, Andrea C (OIG/OEI) (Andrea.Buck@oig.hhs.gov); Searcy, Talisha M (OIG/OEI); Galvin, Chris P (OIG/OEI)
Cc: Yates, Kim A (OIG/OEI)
Subject: Sign-in Sheet: Informational meeting: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

Thank you for your participation in today's meeting!

TIFFANY BROWN

NIH/OD/OMA

(301) 496-2464 - DIRECT

(301) 402-0169 - FAX

-----Original Appointment-----
From: Brown, Tiffany (NIH/OD) [E]
Sent: Wednesday, July 24, 2013 11:39 AM
To: Brown, Tiffany (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Stein, Meredith (NIH/OD) [E]; Hereford, Russell W (OIG/OEI); Buck, Andrea C (OIG/OEI) (Andrea.Buck@oig.hhs.gov); Searcy, Talisha M (OIG/OEI); Galvin, Chris P (OIG/OEI)
Cc: Yates, Kim A (OIG/OEI)
Subject: Informational meeting: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
When: Monday, July 29, 2013 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Teleconference - (Dial-in #: (b)(6) Passcode: (b)(6)

NIH Participants:

Rosemary Higgins, Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Network, Pregnancy and Perinatology Branch, NICHD

Stephanie Devaney, Health Scientist Policy Analyst, OD

OIG Participants:

Russell Hereford, Deputy Regional Inspector General (Boston)

Andrea Buck, Assistant Inspector General for Evaluations

Talisha Searcy, Supervisory Program Analyst

Chris Galvin, Program Analyst

Kim Yates, Program Analyst

OIG-NIH INFORMATOINAL MEETING:
PARTICIPANT LIST
Office of Human Research Protections Oversight of the SUPPORT Clinical Trial
(OEI-01-13-00420)
July 29, 2013 (1:00PM – 2:00PM)

NAME	*ORGANIZATION*	*EMAIL*	*PHONE#*
Rosemary Higgins	NIH/NICHD/DER/PPB National Institutes of Health, National Institute of Child Health and Human Development, Division of Extramural Research, Pregnancy and Perinatology Branch, Program Scientist	higginsr@mail.nih.gov	(301) 435-7909
Stephanie Devaney	NIH/OD Health Scientist Policy Analyst, Office of the Director	devaneysa@mail.nih.gov	(301) 402-1994
Meredith Stein	NIH/OD/OMA Office of Management Assessment Director, Division of Outside Review & Liaison and Division of Quality Management	steinme@mail.nih.gov	(301) 402-8482
Tiffany Brown	NIH/OD/OMA Management Analyst *Point of Contact for all NIH participants*	Browntyl@mail.nih.gov	(301) 496-2464
Joyce Greenleaf	OIG/OEI Office of Inspector General Office of Evaluations and Inspections Regional Inspector General (boston)	Joyce.greenleaf@oig.hhs.gov	(617) 565-1057
Russell Hereford	OIG/OEI Deputy Regional Director (Boston)	Russell.hereford@oig.hhs.gov	(617) 565-1054
Andrea Buck	OIG/OEI Assistant Inspector General for Evaluations	Andrea.buck@oig.hhs.gov	--
Talisha Searcy	OIG/OEI Supervisory Program Analyst *Analyst-in-Charge*	Talisha.searcy@oig.hhs.gov	(202) 619-3409
Chris Galvin	GAO/OEI Program Analyst	Chris.galvin@oig.hhs.gov	(305) 557-1192
Kim Yates	GAO/OEI Program Analyst	Kim.yates@oig.hhs.gov	(617) 565-2911

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 02, 2014 4:51 PM
To: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: Upcoming SUPPORT publication

We do not. I wrote Rose an earlier e-mail asking her about it. Off the top of my head, I'm (b)(5) (b)(5) but I wanted to check with her first.

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Wednesday, April 02, 2014 4:50 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: Upcoming SUPPORT publication

Do we have a statement Bob? And could you check to see if the journal will be doing a release (b)(5)

From: Striar, Diane (NIH/NHLBI) [E]
Sent: Wednesday, April 02, 2014 3:27 PM
To: Childress, Kerri (NIH/NICHD) [E]
Cc: Johnson, Lenora (NIH/NHLBI) [E]; Ferrier, Robin (NIH/NHLBI) [E]; Zagorski, Nicholas (NIH/NHLBI) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: FW: Upcoming SUPPORT publication

Hi Kerri,

We understand you're (b)(5) (b)(5)

Also, do you know if the journal will issue a release?

Thanks,

Diane
Diane Striar
Chief
Public Affairs Branch
Office of Communications
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, MD 20892-2480
Phone: 301 496 4236
E-mail: striard@nhlbi.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, March 27, 2014 10:59 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: Upcoming SUPPORT publication

Hi

Attached is an upcoming publication related to the SUPPORT trial. We do not yet have a publication date. This is an FYI – I don't think (b)(5) This is the largest study of pul0mary outcomes at 18-22 months in ELBW infants at risk for chronic lung disease. (b)(5)

(b)(5) Let me know what you think

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: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Upcoming SUPPORT publication
Date: Monday, March 31, 2014 11:20:44 AM
Attachments: image001.png

Thanks Rose.
How are you doing? Seems you remain very busy—hope all is well,

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
NIH National Heart, Lung, and Blood Institute

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, March 29, 2014 11:32 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: Re: Upcoming SUPPORT publication

We do not yet have a publication date

Sent from my iPhone

On Mar 29, 2014, at 10:17 AM, "Blaisdell, Carol (NIH/NHLBI) [E]" <blaisdellcj@nhlbi.nih.gov> wrote:

> Hi rose
> When is this due to be published?
> Hope you are doing well
> Carol
>
> **From**: Higgins, Rosemary (NIH/NICHD) [E]
> **Sent**: Thursday, March 27, 2014 10:59 AM Eastern Standard Time
> **To**: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
> **Cc**: Raju, Tonse (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
> **Subject**: Upcoming SUPPORT publication
>
> Hi
> Attached is an upcoming publication related to the SUPPORT trial. We do not yet have a publication date. This is an FYI – I don't think (b)(5) This is the largest study of pul0mary outcomes at 18-22 months in ELBW infants at risk for chronic lung disease. (b)(5)

(b)(5)

(b)(5) Let me know what you think

Thanks

Rose

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Poe, Grace (NIH/NICHD) [E]
To: Whatley, Alan (NIH/OD) [E]; Stocks, Nkenge (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Jackson, Bonnie J. (NIH/NICHD) [E]
Subject: RE: 5 U10 HD 040461 PI: FINER, NEIL Norman
Date: Friday, March 28, 2014 4:22:45 PM

Thank you very much!
Grace

From: Whatley, Alan (NIH/OD) [E]
Sent: Friday, March 28, 2014 4:22 PM
To: Poe, Grace (NIH/NICHD) [E]; Stocks, Nkenge (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Jackson, Bonnie J. (NIH/NICHD) [E]
Subject: RE: 5 U10 HD 040461 PI: FINER, NEIL Norman

This FFR has now been accepted.

Alan Whatley
National Institutes of Health
Office of Financial Management
Lead Accountant, Government Accounting Branch
(301)451-9210

From: Poe, Grace (NIH/NICHD) [E]
Sent: Wednesday, March 26, 2014 4:17 PM
To: Stocks, Nkenge (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Whatley, Alan (NIH/OD) [E]; Jackson, Bonnie J. (NIH/NICHD) [E]
Subject: RE: 5 U10 HD 040461 PI: FINER, NEIL Norman

Hi Nkenge,

Just a reminder.....

~Grace

From: Poe, Grace (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:00 AM
To: Stocks, Nkenge (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: 5 U10 HD 040461 PI: FINER, NEIL Norman

Good Morning Nkenge,

Would you please review the year 07's FFR of the above referenced grant? This grant is start at 4/1/2014. Thanks.

~ *Grace*
Grace D. Poe
Grants Management Specialist
Eunice Kennedy Shriver National Institute
of Child Health and Human Development

National Institutes of Health
6100 Executive Blvd.
Room 8A17J, MSC 7510
Bethesda Maryland 20892 (For Fed Ex/UPS Use 20852)
Phone: 301-435-7011
FAX: 301-451-5510
poeq@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Thursday, March 27, 2014 1:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Upcoming SUPPORT publication

Hi Rose,
Yes, received this breathing outcomes pub—congrats!
Not sure why my email is "no longer valid"—did it bounce back to you?
I understand (b)(5)
(b)(5)

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
NIH National Heart, Lung, and Blood Institute

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, March 27, 2014 10:59 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: Upcoming SUPPORT publication

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(b)(5) Let me know what you think
Thanks
Rose

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

From: Poe, Grace (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: 5 U10 HD 040461 PI: FINER, NEIL Norman
Date: Thursday, March 27, 2014 12:19:57 PM

They did submitted FFR, but OFM has not accepted yet. that is why I checked with Nkenge.

From: Poe, Grace (NIH/NICHD) [E]
Sent: Wednesday, March 26, 2014 4:16 PM
To: Stocks, Nkenge (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Whatley, Alan (NIH/OD) [E]; Jackson, Bonnie J. (NIH/NICHD) [E]
Subject: RE: 5 U10 HD 040461 PI: FINER, NEIL Norman

Hi Nkenge,

Just a reminder.....

~Grace

From: Poe, Grace (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:00 AM
To: Stocks, Nkenge (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: 5 U10 HD 040461 PI: FINER, NEIL Norman

Good Morning Nkenge,

Would you please review the year 07's FFR of the above referenced grant? This grant is start at 4/1/2014. Thanks.

~ *Grace*
Grace D. Poe
Grants Management Specialist
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of Child Health and Human Development
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Phone: 301-435-7011
FAX: 301-451-5510
poeg@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, March 27, 2014 11:01 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: Upcoming SUPPORT publication

So better outcomes – that is good

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: Thursday, March 27, 2014 10:59 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: FW: Upcoming SUPPORT publication
Date: Thursday, March 27, 2014 11:01:15 AM
Attachments: Stevens - breathing outcomes from SUPPORT Trial.pdf

Please confirm receipt – I am being told the email is np longer valid

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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(b)(5)
(b)(5) Let me know what you think
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ELSEVIER

INSTRUCTIONS ON THE ANNOTATION OF PDF FILES

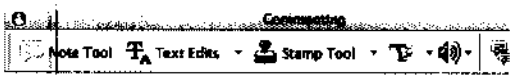
To view, print and annotate your article you will need Adobe Reader version 9 (or higher). This program is freely available for a whole series of platforms that include PC, Mac, and UNIX and can be downloaded from http://get.adobe.com/reader/. The exact system requirements are given at the Adobe site: http://www.adobe.com/products/reader/tech-specs.html.

Note: If you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file.

PDF ANNOTATIONS

Adobe Reader version 9

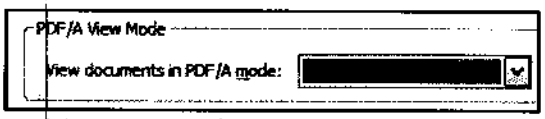
When you open the PDF file using Adobe Reader, the Commenting tool bar should be displayed automatically; if not, click on 'Tools', select 'Comment & Markup', then click on 'Show Comment & Markup tool bar' (or 'Show Commenting bar' on the Mac). If these options are not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than 9 or the PDF has not been prepared properly.



(Mac)

PDF ANNOTATIONS (Adobe Reader version 9)

The default for the Commenting tool bar is set to 'off' in version 9. To change this setting select 'Edit | Preferences', then 'Documents' (at left under 'Categories'), then select the option 'Never' for 'PDF/A View Mode'.

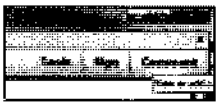


(Changing the default setting, Adobe version 9)

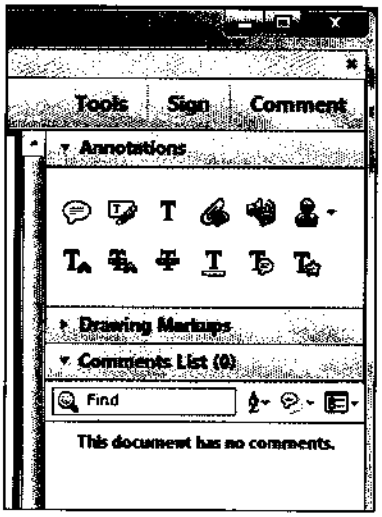
Adobe Reader version X and XI

To make annotations in the PDF file, open the PDF file using Adobe Reader XI, click on 'Comment'.

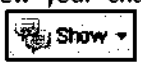
If this option is not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than XI or the PDF has not been prepared properly.



This opens a task pane and, below that, a list of all Comments in the text. These comments initially show all the changes made by our copyeditor to your file.



HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Insert text	Click the 'Text Edits' button  on the Commenting tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner.	Click the 'Insert Text' icon  on the Comment tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on '_'  in the top right-hand corner.
Replace text	Click the 'Text Edits' button  on the Commenting tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).	Click the 'Replace (Ins)' icon  on the Comment tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).
Remove text	Click the 'Text Edits' button  on the Commenting tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.	Click the 'Strikethrough (Del)' icon  on the Comment tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.
Highlight text/ make a comment	Click on the 'Highlight' button  on the Commenting tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.	Click on the 'Highlight Text' icon  on the Comment tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.
Attach a file	Click on the 'Attach a File' button  on the Commenting tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. To make a comment, go to 'General' in the 'Properties' window, and then 'Description'. A graphic will appear in the PDF file indicating the insertion of a file.	Click on the 'Attach File' icon  on the Comment tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. A graphic will appear indicating the insertion of a file.
Leave a note/ comment	Click on the 'Note Tool' button  on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.	Click on the 'Add Sticky Note' icon  on the Comment tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.

HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial

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Objective ~~To explore the early childhood pulmonary outcomes of infants who participated in the National Institute of Child Health and Human Development's Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial, using a factorial design that randomized extremely preterm infants to lower vs higher oxygen saturation targets and delivery room continuous positive airway pressure (CPAP) vs intubation/surfactant.~~

Study design The Breathing Outcomes Study, a prospective study ~~secondary~~ to the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial ~~study~~, assessed respiratory morbidity at 6-month intervals from hospital discharge to 18-22 months corrected age (CA). Two prespecified primary outcomes—wheezing more than twice per week during the worst 2-week period and cough longer than 3 days without a cold—were compared for each randomized intervention.

Results One or more interviews were completed for 918 of ~~the~~ 922 eligible infants. The incidence of wheezing ~~was 47.9% and that of cough was 31.0%, and these did~~ not differ between the study arms of either randomized intervention. Infants randomized to lower vs higher oxygen saturation targets had a similar risk of death or respiratory morbidity (except for croup and treatment with oxygen or diuretics at home). Infants randomized to CPAP vs intubation/surfactant had fewer episodes of wheezing without a cold (28.9% vs 36.5%; $P < .05$), respiratory illnesses diagnosed by a doctor (47.7% vs 55.2%; $P < .05$), and physician or emergency room visits for breathing problems (68.0% vs 72.9%; $P < .05$) by 18-22 months CA.

Conclusion Treatment with early CPAP rather than intubation/surfactant is associated with less respiratory morbidity by 18-22 months CA. Longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions for neonates. *(J Pediatr 2014;■:■-■).*

See editorial and related article, p •••

Extremely preterm infants are at greater risk for respiratory morbidity and the need for pulmonary care in early childhood compared with later preterm and term infants[1-7] and contribute substantially to the US public

BPD	Bronchopulmonary dysplasia
CA	Corrected age
CPAP	Continuous positive airway pressure
SUPPORT	Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial

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health burden of childhood respiratory disease.[8] Lung injury, which may result from mechanical ventilation and supplemental oxygen exposure in the early neonatal period, has been identified as a risk factor for development of bronchopulmonary dysplasia (BPD) and pulmonary morbidity in infancy, childhood, and beyond.[1,2,9,10] Although infants with BPD are at greater risk for poor pulmonary outcomes, neonates without BPD also are at risk for airway dysfunction and pulmonary morbidity during infancy.[4,11]

The Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network studied infants of 24 0/7 to 27 6/7 weeks gestational age treated with each of 2 respiratory strategies designed to minimize mechanical ventilation and supplemental oxygen exposure: lower (85%-89%) vs higher (91%-95%) oxygen saturation targets and early noninvasive continuous positive airway pressure (CPAP) vs early intubation and surfactant administration (intubation/surfactant). Our network previously reported SUPPORT ~~results~~ demonstrating no significant differences in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants randomized to ~~2~~ respiratory interventions.[12-14] It is important to note that although the composite incidence of death or BPD was similar ~~in the 2 groups~~, infants randomized to lower rather than higher oxygen saturation targets had a significantly lower incidence of retinopathy of prematurity but significantly higher mortality at discharge.

Here we report on the Breathing Outcomes Study, a ~~sub~~study ~~of the~~ SUPPORT ~~study~~, which compared respiratory morbidities in extremely preterm infants treated with the SUPPORT interventions as neonates. It was hypothesized that infants randomized to lower rather than higher oxygen saturation targets or to CPAP rather than intubation/surfactant would have a lower incidence of wheezing more than twice per week during their worst 2-week period, a lower incidence of cough lasting more than 3 days without a cold, and, as a secondary outcome, less need for outpatient pulmonary care between discharge and 18-22 months corrected age (CA; age in months after the expected date of full-term delivery).

Methods

Infants eligible for the Breathing Outcomes Study were infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. A total of 1316 infants from 20 centers across the US were enrolled into SUPPORT between February 2005 and February 2009 and seen at follow-up between 2006 and 2011. As a ~~substudy of~~ SUPPORT, the Breathing Outcomes Study gained approval and began recruitment after SUPPORT began enrollment. As a result, not all SUPPORT participants were successfully recruited into the Breathing Outcomes Study. Written informed consent to participate in the Breathing Outcomes Study was obtained either at the time of enrollment into SUPPORT or separately for those patients already enrolled in SUPPORT but not yet discharged from the hospital. The study was approved by the Institutional Review Boards at all participating network centers.[12,13]

Interventions of the SUPPORT Trial

Infants enrolled in SUPPORT were randomly assigned before delivery to receive CPAP after birth, followed by a limited ventilation strategy if intubation was required (CPAP group), or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of life (intubation/surfactant group). Using a 2 × 2 factorial design, SUPPORT subjects were also randomly assigned to treatment with an oxygen saturation target of either 85%-89% (lower saturation group) or 91%-95% (higher saturation group). The methodology for study enrollment, interventions, data collection, and primary analysis has been reported previously.[13] Primary outcomes of SUPPORT included the incidence of death or meeting criteria for the physiological definition of BPD, along with death or meeting criteria for traditional BPD, defined as receipt of supplemental oxygen at 36 weeks postmenstrual age.[15]

Assessments of the Breathing Outcomes Study

For each subject enrolled in the Breathing Outcomes Study, a parent or primary caregiver was interviewed by research staff either in person or by telephone using structured questionnaires and interview scripts at each of 4 time points: at or near the time of hospital discharge and at or near 6, 12, and 18-22 months CA. 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 review the operations manual, which included a written interview script. Interview trainees then interviewed a standardized patient simulated by the project trainers. With the aid of the operations manual, 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, New York). Interviews were conducted in either English or Spanish as appropriate.

To minimize loss of recall over time, 4 interviews were conducted at approximately 6-month intervals beginning at the time of hospital discharge.[16] 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 on discharge from the hospital. Based on the preference of each participating center, the 6-, 12-, and 18- to 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

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each of the 6-, 12-, and 18- to 22-month interviews, the parent or caregiver was asked to base his or her responses on the 6-month interval since the last interview. If an interview at one time point was not completed, the respondent was asked to base his or her responses during the next interview on the interval since the last completed interview.

The 4-questionnaire series was designed to provide a complete respiratory history over the first 18-22 months CA. In addition to reporting interview responses during the first 18-22 months CA (defined as the combined responses to the 6-, 12-, and 18- to 22-month interviews and listed as 6-22 months), we report responses from the 6-month interview, because preterm infants are at especially high risk for respiratory morbidity during the first 6 months of age.[17]

Respiratory Questionnaires

Questionnaires that had been developed, validated, and used with permission of the Tucson Children's Respiratory Study, a large prospective birth cohort study of term infants, were administered to elicit the frequency and characteristics of respiratory signs, including wheezing and cough; incidence of physician-diagnosed asthma or allergy; presence of pets in home; siblings; reactive airway disease; incidence of bronchiolitis, bronchitis, pneumonia, or 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.[18,19]

Outcomes

Primary Outcomes. Because preterm infants with or without BPD are at risk for altered airway function and at greater risk for wheezing in infancy and later childhood,[20-24] we chose to assess respiratory symptoms as a measure of pulmonary morbidity in infancy. Some authors have used the incidence of recurrent wheezing as a primary measure of pulmonary morbidity,[8,23,25] and others have used a combined outcome with either recurrent wheezing or chronic cough as a measure of occult wheezing in preterm infants.[1,2,26] To best capture overt and occult wheezing, 2 primary outcomes were assessed by parental report: the incidence of wheezing more than twice per week during the worst 2-week period and the incidence of cough lasting for more than 3 days without a cold.

The incidence of wheezing was ascertained with the primary question used and validated in the Tucson study: "Has his/her chest sounded wheezy or whistling?"[18] The outcome for wheezing more than twice per week during the worst 2-week period was considered positive if the parent selected "more than 2 times a week" in response to the question: "During the worst 2-week period, how often has your child's chest sounded wheezy or whistling?" The incidence of cough lasting more than 3 days without a cold was ascertained using the Tucson study question: "Has your child had a cough for 3 days or more when he/she did not have a cold?"[18]

Secondary Outcomes and Covariates. Secondary outcomes included the incidence of any wheezing and incidence of the combined outcome, wheezing more than twice per week during the worst 2-week period or cough lasting more than 3 days without a cold. Also assessed were parental report of respiratory signs, physician-diagnosed respiratory diseases, medication use, health services use, and impact on the family. To ensure that follow up cohorts were comparable, questions not validated before this study were added to the Tucson study questionnaires to more fully elicit data on the use of preventive therapies, including palivizumab and influenza immunization; attendance at daycare; frequency of BPD exacerbation or flare-ups; impact on the family, including whether the parent or caregiver needed to change plans due to their child's breathing; parental report of at least some breast milk intake on any of the 6-, 12-, or

Table I. Demographic and neonatal characteristics of follow-up cohorts

	Low oxygen saturation (n = 439)	High oxygen saturation (n = 479)	CPAP (n = 474)	Intubation/surfactant (n = 444)
Birth weight, g, mean ± SD	858 ± 186	844 ± 190	850 ± 184	851 ± 193
Gestational age, w, mean ± SD	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0
Gestational age 24 wk 0 d to 25 wk 6 d, n (%)	158 (35.5)	184 (37.5)	183 (37.7)	159 (35.3)
Gestational age 25 wk 0 d to 27 wk 6 d, n (%)	287 (64.5)	307 (62.5)	303 (62.4)	291 (64.7)
Male sex, n (%)	222 (49.7)	264 (53.8)	238 (49.0)	248 (54.9)
Race/ethnicity, n (%)				
Non-Hispanic black	168 (37.6)	157 (32.0)	173 (35.6)	152 (33.6)
Non-Hispanic white	176 (39.4)*	226 (46.0)	196 (40.3)	206 (45.6)
Hispanic	88 (19.7)	91 (18.5)	98 (20.2)	81 (17.9)
Other/unknown	15 (3.4)	17 (3.5)	19 (3.9)	13 (2.9)
Length of hospitalization, d, median (range)	90 (39-365)	93 (46-366)	91 (44-366)	93 (39-365)
BPD (traditional definition), n (%)	160 (36.3)†	221 (45.8)	187 (39.1)	194 (43.5)
BPD (physiological definition), n (%)	165 (37.4)	193 (40.0)	183 (38.3)	175 (39.2)
Discharged home on oxygen, n (%)	105 (24.0)	111 (23.2)	108 (22.8)	108 (24.4)
Discharged home on respiratory medications, n (%)	101 (27.3)	106 (27.1)	110 (27.8)	97 (26.6)
Discharged home October-March, n (%)	232 (52.9)	227 (47.5)	232 (48.8)	227 (51.4)

*Low oxygen saturation vs high oxygen saturation, $P < .05$.
†Low oxygen saturation vs high oxygen saturation, $P < .01$.

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Table IV. Respiratory outcomes in lower vs higher oxygen saturation target gups and early CPAP vs intubation/surfactant groups at the 6-mo interview and for the first 18-22 mo CA (combined responses to the 6-, 12-, and 18- to 22-mo interviews)

Outcome	Low oxygen saturation, n (%)	High oxygen saturation, n (%)	ARR (95% CI)	*P* value	CPAP	Intubation/surfactant	ARR (95% CI)	*P* value
Primary outcomes								
Has your child's chest sounded wheezy or whistling more than twice in 1 wk?								
6 months	94 (22.0)	129 (27.7)	0.73 (0.53-1.01)	.06	107 (23.2)	116 (26.9)	0.79 (0.58-1.09)	.16
6-22 months	203 (46.7)	233 (49.1)	0.92 (0.70-1.22)	.57	224 (47.7)	212 (48.2)	0.90 (0.68-1.19)	.47
Has your child had a cough for more than 3 days without a cold?								
6 months	63 (16.9)	76 (19.3)	0.84 (0.57-1.22)	.35	63 (16.2)	76 (20.2)	0.77 (0.53-1.12)	.17
6-22 months	127 (30.8)	141 (31.1)	1.01 (0.75-1.37)	.93	127 (28.4)	141 (33.7)	0.81 (0.60-1.10)	.18
Secondary outcomes								
Symptoms								
Wheezing/whistling more than twice in 1 wk or cough for more than 3 d								
6 months*	162 (43.5)	195 (49.5)	0.78 (0.58-1.05)	.10	178 (45.8)	179 (47.5)	0.95 (0.70-1.28)	.72
6-22 months	276 (66.8)	316 (69.5)	0.87 (0.65-1.18)	.37	303 (67.8)	289 (68.7)	0.95 (0.70-1.29)	.74
Has your child's chest sounded wheezy or whistling?								
6 months	135 (36.3)	171 (43.4)	0.73 (0.54-1.00)	<.05	151 (38.8)	155 (41.1)	0.89 (0.66-1.21)	.47
6-22 months	245 (59.3)	286 (62.9)	0.85 (0.64-1.13)	.27	269 (60.2)	262 (62.2)	0.86 (0.64-1.15)	.31
Has your baby's chest sounded wheezy or whistling apart from colds?								
6 months	61 (16.4)	84 (21.3)	0.73 (0.50-1.06)	.10	66 (17.0)	79 (21.0)	0.77 (0.53-1.11)	.16
6-22 months	117 (28.4)	165 (36.3)	0.67 (0.49-0.91)	.01	129 (28.9)	153 (36.5)	0.68 (0.50-0.92)	.01
Illnesses								
Has your child had asthma, reactive airway disease, or BPD exacerbation or flare-up diagnosed by a doctor?								
6 months*	51 (13.7)	62 (15.7)	0.84 (0.56-1.27)	.41	48 (12.3)	65 (17.2)	0.66 (0.44-1.00)	<.05
6-22 months*	140 (33.9)	158 (35.0)	1.01 (0.75-1.37)	.93	144 (32.2)	154 (36.8)	0.81 (0.60-1.09)	.16
Has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?								
6 months	72 (19.4)	78 (19.8)	0.98 (0.67-1.41)	.90	70 (18.0)	80 (21.2)	0.82 (0.57-1.19)	.30
6-22 months	161 (39.0)	183 (40.4)	0.96 (0.72-1.28)	.79	167 (37.4)	177 (42.2)	0.81 (0.61-1.09)	.17
Any of asthma, reactive airway disease, BPD exacerbation, or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor								
6 months	95 (25.5)	109 (27.7)	0.91 (0.65-1.27)	.58	96 (24.7)	108 (28.7)	0.81 (0.58-1.13)	.22
6-22 months	204 (49.4)	241 (53.1)	0.91 (0.69-1.21)	.52	213 (47.7)	232 (55.2)	0.71 (0.53-0.95)	.02
Has your child had croup diagnosed by a doctor?								
6 months†	9 (2.4)	11 (2.8)	0.87 (0.36-2.08)	.75	7 (1.8)	13 (3.5)	0.52 (0.21-1.30)	.16
6-22 months*	46 (11.2)	39 (8.6)	1.35 (0.84-2.16)	.21	40 (9.0)	45 (10.8)	0.77 (0.49-1.23)	.28
Health services								
Has your child ever had to visit the doctor or emergency room for breathing or wheezing problems?								
6 months	167 (44.9)	188 (47.8)	0.82 (0.60-1.11)	.20	173 (44.6)	182 (48.3)	0.81 (0.60-1.10)	.18
6-22 months	292 (70.1)	319 (70.1)	0.98 (0.72-1.34)	.89	304 (68.0)	307 (72.9)	0.73 (0.53-1.00)	<.05
Has your child had to stay in a hospital overnight?								
6 months	105 (28.2)	118 (30.0)	0.89 (0.64-1.23)	.47	106 (27.3)	117 (31.0)	0.79 (0.57-1.10)	.17
6-22 months	169 (41.0)	199 (43.7)	0.90 (0.68-1.20)	.48	182 (40.7)	186 (44.3)	0.87 (0.66-1.16)	.35

(*continued*)

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Table IV. Continued

Outcome	Low oxygen saturation, n (%)	High oxygen saturation, n (%)	ARR (95% CI)	*P* value	CPAP	Intubation/surfactant	ARR (95% CI)	*P* value
Has your child had to stay in a hospital overnight for wheezing/breathing problems?								
6 months	69 (18.6)	73 (18.6)	0.98 (0.67-1.44)	.93	64 (16.5)	78 (20.7)	0.72 (0.49-1.05)	.09
6-22 months	129 (31.3)	140 (30.8)	1.04 (0.77-1.40)	.80	130 (29.1)	139 (33.1)	0.82 (0.61-1.11)	.21
Medications								
Treated with a diuretic medication?								
6 months*	27 (6.3)	24 (5.2)	1.29 (0.72-2.32)	.39	23 (5.0)	28 (6.5)	0.72 (0.40-1.29)	.27
6-22 months*	31 (7.1)	24 (5.0)	1.50 (0.85-2.64)	.16	24 (5.1)	31 (7.0)	0.68 (0.39-1.20)	.18
Treated with an inhaled steroid medication?								
6 months	51 (11.9)	53 (11.4)	1.12 (0.73-1.71)	.61	54 (11.7)	50 (11.6)	1.00 (0.66-1.53)	.99
6-22 months	112 (25.6)	129 (26.9)	0.97 (0.71-1.32)	.82	128 (27.1)	113 (25.5)	1.10 (0.80-1.50)	.56
Treated with a nebulized medication?								
6 months†	5 (1.2)	18 (3.9)	0.30 (0.11-0.81)	.02	13 (2.8)	10 (2.3)	1.22 (0.54-2.75)	.63
6-22 months*	29 (6.6)	42 (8.8)	0.73 (0.44-1.22)	.23	39 (8.3)	32 (7.2)	1.11 (0.67-1.84)	.69
Treated with a systemic steroid medication?								
6 months†	11 (2.6)	8 (1.7)	1.50 (0.61-3.70)	.38	12 (2.6)	7 (1.6)	1.61 (0.64-4.04)	.31
6-22 months	44 (10.1)	42 (8.8)	1.13 (0.71-1.80)	.62	48 (10.2)	38 (8.6)	1.22 (0.77-1.95)	.40
Treated with oxygen at home?								
6 months†	90 (24.3)	80 (20.3)	1.22 (0.83-1.79)	.31	80 (20.6)	90 (23.9)	0.82 (0.56-1.21)	.32
6-22 months	104 (25.2)	96 (21.1)	1.31 (0.92-1.88)	.14	94 (21.0)	106 (25.3)	0.80 (0.56-1.15)	.23
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)	.43	50 (12.9)	77 (20.4)	0.58 (0.39-0.87)	<.01
6-22 months	139 (33.7)	170 (37.4)	0.87 (0.65-1.17)	.36	145 (32.4)	164 (39.0)	0.74 (0.55-1.00)	<.05

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.
†If the 2 adjustment model failed to converge, unadjusted relative risks are reported.

18- to 22-month questionnaires; family history of inhaled allergies, food allergies, and asthma, chronic obstructive pulmonary disease, or emphysema, or other chronic respiratory illness; environmental exposure to tobacco smoke, daycare, children aged <12 years, and pets; and use of preventive therapies as outlined above. In addition, each patient's outcomes from SUPPORT were available for the Breathing Outcomes Study analysis.

Statistical Analyses

For the Breathing Outcomes Study, a sample size of 817 subjects was calculated as being necessary to detect an absolute risk difference of 0.1 in the incidence of the primary outcome of wheezing more than twice per week between groups, with 90% power and $\alpha = 0.05$, assuming an 80% minimum follow-up rate and 29% baseline incidence of wheezing more than twice per week.[24] Sample size calculations for SUPPORT have been reported previously.[12,13] Based on SUPPORT's target enrollment of 1310 patients and assuming a 22% mortality (National Institute of Child Health and Human Development historical data for calendar year 2000), we anticipated that 1021 patients would be potentially eligible for the Breathing Outcomes Study. Our 2 primary analyses used the number of patients with either wheezing more than twice per week during their worst 2-week period or cough lasting more than 3 days without a cold as the numerator and the number of infants for whom that outcome was known as the denominator. Secondary responses were tabulated similarly. To assess the robustness of our findings, we calculated respiratory outcomes as a composite outcome with death and also calculated respiratory outcomes for patients with and without BPD. Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using χ^2 tests for categorical variables. Using Poisson regression models to adjust for gestational age stratum, study center, and familial clustering, we calculated adjusted relative risk values and 95% CIs. When Poisson models did not converge, relative risk adjusted for gestational age and center is reported. When the 2 adjustment models failed to converge owing to low prevalence (<5%), unadjusted relative risks are reported. Results were considered statistically significant if the 2-sided *P* value was <.05; a trend toward significance was indicated by a 2-sided *P* value between .05 and .10 inclusive.

Given the 2 × 2 factorial design of our randomized trial, we considered the potential for interactions between primary outcomes of 1 arm on the other arm (CPAP vs intubation/surfactant and lower vs higher saturation target). Analysis

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by robust Poisson regression implemented in generalized estimating equation models conducted for the primary outcomes of the main trial did not identify significant interactions between the 2 treatment arms ($P > .05$ for all interaction terms). For this reason, only marginal (main) effects of each randomization are reported. No adjustments have been made for multiple comparisons. All calculations were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and provided consent to participate in the Breathing Outcomes Study. The 918 patients with at least 1 completed questionnaire composed the study cohort. Follow-up rates at each time point are listed in the Figure (available at www.jpeds.com).

Among the follow-up cohort, the group randomized to lower oxygen saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with BPD defined using the traditional criteria of supplemental oxygen use at 36 weeks postmenstrual age compared with the group with higher oxygen saturation targets. The CPAP group and intubation/surfactant group had similar demographic data and neonatal outcomes (Table I). Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and between the CPAP and intubation/surfactant groups (Table II; available at www.jpeds.com). Subjects with responses to all 4 questionnaires were similar in demographic characteristics, neonatal outcomes, and home environmental exposures, with the exception that those with fewer than 4 responses were more apt to have been discharged on respiratory medication (Table III; available at www.jpeds.com).

Overall in the Breathing Outcomes cohort during the first 18-22 months CA, wheezing more than twice per week during the worst 2-week period was reported in 47.9% of patients, cough lasting more than 3 days without a cold in 31.0%, and either wheezing more than twice per week or cough more than 3 days without a cold in 68.2%. Among cohort subjects, use of inhaled (26.3%) and/or systemic steroids (9.4%) was common. Cohort subjects also had high rates of physician visits (63.8%), emergency room visits (46.6%), and hospitalizations for wheezing or breathing problems (31.0%).

Primary Outcomes

There was no difference in incidence of the 2 primary outcomes—wheezing more than twice per week during the worst 2 week period and cough lasting more than 3 days without a cold—between the lower and higher oxygen saturation target groups or between the CPAP and intubation/surfactant groups (Table IV). Analyzed as a combined outcome, the incidence of death or cough lasting more than 3 days without a cold trended ($P = .05$) lower among patients in the CPAP group compared with the intubation/surfactant group. The incidence of the combined outcome of episodes of wheezing more than twice per week during the worst 2-week period or cough lasting more than 3 days without a cold was 64.6% for the overall cohort, and did not differ significantly between the lower and higher oxygen saturation target groups or between CPAP and intubation/surfactant groups when analyzed either alone or as a combined outcome with death (Tables IV and V).

Secondary Outcomes

Oxygen Saturation Targeting Intervention. At 6 months CA, infants randomized to the lower oxygen saturation target group had a lower incidence of wheezing and use of nebulized medications after hospital discharge compared with the higher oxygen saturation target group (Table IV). Over the first 18-22 months CA, infants in the lower oxygen saturation target group were less likely to have episodes of wheezing without a cold (Table IV). When analyzed as composite outcomes, the lower and higher oxygen saturation target groups had a similar incidences of death and respiratory morbidities, except for croup diagnosed by a doctor and treatment with a diuretic or oxygen at home (Table V).

Early CPAP Intervention. At 6 months CA, compared with the intubation/surfactant group, infants randomized to the CPAP group had lower rates of asthma, reactive airway disease, and BPD exacerbations or flare-ups diagnosed by a doctor since hospital discharge, along with a trend toward fewer hospitalizations for wheezing or breathing problems. Perhaps related to these differences, parents/primary caregivers of infants of 6 months CA in the CPAP group were less likely to report changing plans because of the child's breathing problems (Table V).

During the first 18-22 months CA, infants in the CPAP group were significantly less likely than those in the intubation/surfactant group to experience wheezing episodes without a cold (28.9% vs 36.5%; $P = .01$), respiratory illness diagnosed by a doctor (1 or more episodes of asthma, reactive airway disease, or BPD exacerbation or flare-up or bronchiolitis, bronchitis, or pneumonia; 47.7% vs 55.2%; $P = .02$), or wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs 72.9%; $P < .05$). Compared with parents/caregivers of infants in the intubation/surfactant group, parents or guardians of infants in the CPAP group were also less likely to report changing plans because of their child's breathing problems (32.4% vs 39.0%; $P < .05$). When outcomes were analyzed as composite outcomes with death, similar findings were observed, with additional differences noted in incidence of treatment with oxygen or diuretics at home and a trend toward a lower incidence of overnight hospitalization for breathing problems.

As expected, our study questionnaires were able to detect significant differences in respiratory outcomes for infants with BPD and those without BPD (Table VI). Although the incidence of wheezing more than twice per week differed between infants with BPD and those without BPD,

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Table V. Combined outcomes of death or respiratory morbidity for lower vs higher oxygen saturation target groups and early CPAP vs intubation/surfactant groups for the first 18-22 mo CA (combined responses to the 6-, 12-, and 18- to 22-mo interviews)

Outcomes with death	Low saturation (n = 586)	High saturation (n = 569)	ARR (95% CI)	P value	CPAP (n = 583)	Intubation/surfactant (n = 572)	ARR (95% CI)	P value
Primary outcomes								
Has your child's chest sounded wheezy or whistling more than twice in 1 wk?	337 (59.5)	344 (59.0)	1.06 (0.83-1.37)	.62	337 (58.0)	344 (60.6)	0.86 (0.67-1.11)	.26
Has your child had a cough for more than 3 days without a cold?	262 (47.9)	254 (45.0)	1.18 (0.91-1.51)	.21	240 (42.9)	276 (49.9)	0.78 (0.60-1.00)	.05
Secondary outcomes								
Symptoms								
Wheezing/whistling more than twice in 1 wk or cough for more than 3 d	410 (75.0)	425 (75.2)	0.99 (0.74-1.32)	.96	414 (74.1)	421 (76.1)	0.92 (0.69-1.23)	.56
Has your child's chest sounded wheezy or whistling?	379 (69.3)	395 (69.9)	0.98 (0.75-1.29)	.90	380 (68.0)	394 (71.2)	0.84 (0.64-1.10)	.21
Has your baby's chest sounded wheezy or whistling apart from colds?	252 (46.1)	275 (48.7)	0.91 (0.71-1.17)	.48	241 (43.1)	286 (51.7)	0.70 (0.54-0.90)	<.01*
Illnesses								
Has your child had asthma, reactive airway disease, or BPD exacerbation or flare-up diagnosed by a doctor?	274 (50.1)	270 (47.9)	1.17 (0.91-1.50)	.23	256 (45.8)	288 (52.2)	0.76 (0.59-0.98)	.03*
Has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	295 (53.9)	295 (52.3)	1.12 (0.87-1.44)	.39	279 (49.9)	311 (56.3)	0.78 (0.60-1.00)	.05
Any of asthma, reactive airway disease, BPD exacerbation or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	339 (62.0)	351 (62.2)	1.05 (0.81-1.36)	.71	326 (58.3)	364 (65.9)	0.71 (0.54-0.92)	<.01*
Has your child had croup diagnosed by a doctor?	180 (32.9)	153 (27.1)	1.35 (1.03-1.77)	.03*	154 (27.5)	179 (32.4)	0.78 (0.60-1.03)	.08
Health services								
Has your child ever had to visit the doctor or emergency room for breathing or wheezing problems?	427 (78.1)	430 (76.1)	1.11 (0.82-1.50)	.49	417 (74.6)	440 (79.6)	0.73 (0.54-0.99)	<.05*
Has your child had to stay in a hospital overnight?	303 (55.5)	310 (54.9)	1.06 (0.82-1.37)	.64	294 (52.6)	319 (57.8)	0.84 (0.65-1.08)	.17
Has your child had to stay in a hospital overnight for wheezing/breathing problems?	263 (48.2)	252 (44.6)	1.20 (0.93-1.54)	.17	242 (43.3)	273 (49.5)	0.78 (0.61-1.01)	.06
Medications								
Treated with a diuretic medication?	165 (29.0)	137 (23.4)	1.42 (1.07-1.88)	.02*	137 (23.5)	165 (28.8)	0.74 (0.56-0.98)	.04*
Treated with an inhaled steroid medication?	246 (43.2)	240 (41.0)	1.15 (0.89-1.47)	.29	241 (41.3)	245 (42.8)	0.96 (0.75-1.24)	.76
Treated with a nebulized medication?	16 3 (28.6)	155 (26.5)	1.15 (0.87-1.52)	.33	152 (26.1)	166 (29.0)	0.85 (0.64-1.13)	.27
Treated with a systemic steroid medication?	178 (31.3)	156 (26.6)	1.28 (0.98-1.68)	.07	162 (27.8)	172 (30.1)	0.88 (0.68-1.16)	.38
Treated with oxygen at home?	238 (43.5)	206 (36.5)	1.46 (1.11-1.91)	<.01*	206 (36.9)	238 (43.1)	0.76 (0.58-1.00)	.05*
Family								
Have you had to change your plans because of your child's breathing problems?	273 (49.9)	281 (49.7)	1.04 (0.81-1.34)	.74	257 (46.0)	297 (53.7)	0.72 (0.56-0.92)	.01*

*$P < .05$.

there was no difference in the incidence of cough lasting more than 3 days as an indicator of occult wheezing. Taken together, the combined incidence of either overt (wheezing more than twice per week) or potential occult (cough lasting more than 3 days) wheezing was significantly different between infants with BPD and those without BPD (Table VI).

Discussion

We report results of the Breathing Outcomes Study, a ~~sub-study of~~ SUPPORT, which sought to quantify respiratory morbidity by 18-22 months CA for extremely premature children born at 24-27 weeks gestation. We found no significant differences at 18-22 months CA in the incidence of either of the 2 primary outcomes (wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold) between the lower and higher oxygen saturation target groups or between the CPAP and intubation/surfactant groups.

In secondary analyses, although extremely preterm infants in the lower oxygen saturation target group were less likely than those in the higher oxygen saturation target group to have wheezing or to use a home nebulizer at 6 months CA and to have wheezing apart from a cold between discharge and 18-22 months CA, these differences were not seen when respiratory outcomes were analyzed as composite outcomes with death. In fact, when analyzed in this manner, the incidence of death or adverse respiratory outcome for some measures of morbidity was higher in the low oxygen

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Table VI. Respiratory outcomes for infants with traditional BPD (oxygen requirement at 36 wk postmenstrual age) for the first 18-22 mo CA (combined responses to the 6-, 12-, and 18- to 22-mo interviews)

Outcome	Traditional BPD (n = 377)	No traditional BPD (n = 539)	ARR (95% CI)	*P* value
Primary outcomes				
Has your child's chest sounded wheezy or whistling more than twice in 1 wk?	194 (52.0)	242 (45.1)	1.52 (1.15, 2.01)	<.01
Has your child had a cough for more than 3 days without a cold?	119 (33.7)	149 (29.0)	1.17 (0.86, 1.60)	.314
Secondary outcomes				
Symptoms				
Wheezing/whistling more than twice in 1 wk or cough more than 3 d	262 (74.2)	330 (64.1)	1.76 (1.27, 2.43)	<.01
Has your child's chest sounded wheezy or whistling?	231 (65.4)	300 (58.3)	1.61 (1.17, 2.21)	<.01
Has your baby's chest sounded wheezy or whistling apart from colds?	129 (36.8)	153 (29.7)	1.57 (1.16, 2.13)	<.01
Illnesses				
Has your child had asthma, reactive airway disease, or BPD flare-up diagnosed by a doctor?	133 (38.0)	165 (32.0)	1.58 (1.17, 2.13)	<.01
Has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	152 (43.2)	192 (37.4)	1.34 (1.00, 1.80)	.05
Any of asthma, reactive airway disease, BPD flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	195 (55.4)	250 (48.5)	1.47 (1.08, 2.00)	.01
Has your child had croup diagnosed by a doctor?	29 (8.2)	56 (10.9)	0.78 (0.46, 1.33)	.36
Health services				
Has your child ever had to visit the doctor or emergency room for breathing or wheezing problems?	267 (75.6)	344 (66.8)	1.56 (1.08, 2.25)	.02
Has your child had to stay in a hospital overnight?	186 (52.7)	182 (35.4)	2.22 (1.64, 3.02)	<.0001
Has your child had to stay in a hospital overnight for wheezing/breathing problems?	136 (38.5)	133 (25.9)	1.89 (1.40, 2.57)	<.0001
Medications				
Treated with a diuretic medication?*	47 (12.5)	8 (1.5)	11.86 (5.28, 26.62)	<.0001
Treated with an inhaled steroid medication?	135 (35.8)	106 (19.7)	2.40 (1.75, 3.29)	<.0001
Treated with a nebulized medication?*	35 (9.3)	36 (6.7)	1.53 (0.88, 2.67)	.14
Treated with a systemic steroid medication?	40 (10.6)	46 (8.5)	1.45 (0.93, 2.26)	.10
Treated with oxygen at home?	164 (46.5)	36 (7.0)	9.18 (5.81, 14.52)	<.0001
Family				
Have you had to change your plans because of your child's breathing problems?	143 (40.5)	166 (32.2)	1.34 (1.00, 1.79)	<.05

*Where models did not converge, adjustments are limited to center and gestational age.

saturation target group. Several pulmonary outcome studies have reported an association between neonatal oxygen exposure and expiratory flow dysfunction and airway hyperreactivity in infants with BPD and infants without BPD alike.[2,5,27-29] Although SUPPORT patients treated with lower oxygen saturation targets had a shorter duration of oxygen exposure than those with higher targets, they had greater mortality and a comparable incidence of BPD. Moreover, based on results of the Breathing Outcomes Study, survivors had a similar rate of use of outpatient services for respiratory care and only minor differences in the incidence of respiratory signs. Based on these findings, strategies aimed at reducing oxygen exposure and oxidant lung injury besides targeting lower oxygen saturation levels are needed to minimize oxygen-related pulmonary morbidity.[24,30]

Although the primary outcomes were similar in the CPAP and intubation/surfactant groups, patients in the CPAP group had lower rates of several important respiratory morbidities at 18-22 months CA, including respiratory illnesses diagnosed by a doctor, treatment with oxygen or diuretics at home, and a trend toward a lower rate of overnight hospitalization for breathing problems. Likely related to these findings was a significant reduction in the proportion of parents reporting the need to change daily plans because of their child's breathing difficulties. These differences persisted regardless of whether the outcome was analyzed only among survivors or as a composite outcome with death.

Respiratory benefits of CPAP and a limited ventilation strategy were found despite the fact that the proportion of children with BPD, defined using either the traditional or physiological criteria,[15] was similar in the CPAP and intubation/surfactant groups in both SUPPORT and the Breathing Outcomes Study follow-up cohort. Our data are consistent with follow-up data from the COIN trial, which,

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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 CA in a single-center subcohort of 39 study infants randomized to CPAP.[31,32] These observations suggest that treatment of infants of 25-27 6/7 weeks gestational age at risk for ~~RDS~~, with a limited ventilation strategy is associated with respiratory benefits that are not apparent or are underestimated based on the incidence of BPD alone. As confirmed in our analysis of respiratory morbidity, BPD has proven a useful surrogate for identifying infants at greatest risk for later morbidity. However, based on the high incidence of respiratory morbidity among infants without BPD, it is likely (although not proven in this study) that the prevalence of respiratory morbidity in preterm-born infants may be underrecognized. Given the potential for respiratory therapy to improve pulmonary outcomes in infants with BPD and infants without BPD, 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 signs and the use of health care services are common among infants at 24-27 6/7 weeks gestation during the first 18-22 months CA. More than two-thirds of subjects in the Breathing Outcomes Study cohort reported wheezing more than twice per week during their worst 2-week period or a cough lasting more than 3 days without a cold. Treatment of these respiratory signs was associated not only with frequent use of both inhaled and systemic steroids, medications with potential long-term effects on growth and development,[33,34] but also with frequent physician and emergency room visits and hospitalizations, health services that contribute greatly to health care costs.[8]

Strengths of this study include the large number of extremely preterm infants enrolled, high follow-up rates for enrolled patients, and use of comprehensive respiratory questionnaires administered in a scripted interview by trained personnel. Although it is not as objective as pulmonary function testing, respiratory history was used to assess outcome measures owing to clinical and financial concerns associated with invasive pulmonary testing and the potential complications of sedation in former preterm infants. In addition, parental report of wheezing has been shown to correlate with pulmonary function test findings 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.[16,35]

Among potential weaknesses, respiratory history data were obtained by parental report, which has the potential for classification and recall bias. To minimize classification bias, all primary and follow-up study data for this randomized trial were collected in a blinded manner. Thus, although classification bias might have affected the precision of point estimates, it is not likely 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.[16] As has been reported previously, the results of SUPPORT and thereby potentially the associated follow-up studies might 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 more common use of antenatal steroids compared with the entire eligible cohort.[36]

In summary, we found no significant differences in the incidence of wheezing more than twice per week during the worst 2-week period or cough lasting more than 3 days without a cold at 18-22 months CA between extremely preterm survivors who were randomized at delivery to either a lower or a higher oxygen saturation target and to either early CPAP and limited ventilation or intubation/surfactant. In secondary analyses, we found minor reductions in the incidence of wheezing and nebulizer use at 6 months CA and wheezing without a cold at 18-22 months CA, but an overall increase in the risk of death or respiratory morbidity (except for croup and treatment with oxygen or diuretics at home) for infants randomized to lower vs higher oxygen saturation targets. Also in secondary analyses, we report less respiratory morbidity among survivors and a lower incidence ~~of~~ respiratory morbidity or death among infants randomized to CPAP rather than to intubation/surfactant administration. Results of SUPPORT and neurodevelopmental follow-up of SUPPORT subjects identified no deleterious effects of CPAP over intubation/surfactant.[12-14] Those findings, coupled with the respiratory outcomes reported here, suggest that treatment of extremely preterm infants with CPAP and limited ventilation rather than with intubation and surfactant within 1 hour is safe and may result in less respiratory morbidity during the first 18-22 months CA. Finally, our findings indicate a high risk of postdischarge respiratory morbidities among preterm infants at 24-27 6/7 weeks gestation (with or without BPD) that not only require close medical monitoring, but also present potential burdens to families as well as to society by increasing health care costs. ■

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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 (2006-2011).

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Table II. Family and environmental exposure history of follow-up cohorts

	Low oxygen saturation (n = 439)	High oxygen saturation (n = 479)	CPAP (n = 474)	Intubation/surfactant (n = 444)
First-degree relative with asthma, n (%)	142 (31.8)	159 (32.4)	152 (31.3)	149 (33.0)
Family history, n (%)				
COPD, emphysema, etc	48 (10.7)	43 (8.8)	53 (10.9)	38 (8.4)
Food allergies	60 (14.4)	52 (11.3)	61 (13.5)	51 (11.9)
Inhaled allergies	140 (30.4)	129 (30.9)	136 (30.1)	133 (31.2)
Chronic respiratory disease	7 (1.7)	4 (0.9)	1 (0.2)	10 (2.5)
Any breast milk, n (%)	167 (37.4)	148 (30.1)	166 (34.2)	149 (33.0)
Smoking in house, n (%)	189 (44.1)	186 (39.3)	189 (40.6)	186 (42.7)
Spent time at daycare, n (%)	163 (41.5)	142 (33.2)	163 (38.4)	142 (35.8)
Living with children age <12 y, n (%)	241 (61.3)	264 (61.7)	255 (60.1)	250 (63.0)
Pets in home, n (%)	181 (40.5)	177 (36.1)	187 (38.5)	171 (37.8)
Flu vaccination, n (%)	307 (78.1)	342 (80.1)	335 (79.0)	314 (79.3)
RSV prophylaxis, n (%)	281 (71.5)	313 (73.1)	308 (72.6)	286 (72.0)

COPD, chronic obstructive pulmonary disease; *RSV*, respiratory syncytial virus.

Table III. Comparison of those who answered all 4 questionnaires and those who answered fewer than 4

Label	Answered <4 questionnaires (n = 50)	Answered all 4 questionnaires (n = 868)	*P* value
Birth weight, g, mean ± SD	852.94 ± 158.29	852.23 ± 189.68	.98
Gestational age, wk, mean ± SD	25.62 ± 1.03	25.90 ± 1.02	.06
Gestational age 24 wk 0 d to 25 wk 6 d, n (%)	23 (46.00)	307 (35.45)	.13
Gestational age 25 wk 0 d to 27 wk 6 d, n (%)	27 (54.00)	559 (64.55)	
Male sex, n (%)	24 (48.00)	452 (52.07)	.58
Race/ethnicity, n (%)			
Non-Hispanic black	13 (26.00)	309 (35.60)	.47*
Non-Hispanic white	25 (50.00)	365 (42.05)	
Hispanic	11 (22.00)	164 (18.89)	
Other/unknown	1 (2.00)	30 (3.46)	
Length of hospitalization, d, mean ± SD	109.24 ± 49.64	98.76 ± 37.62	.15
BPD (supplemental oxygen), n (%)	22 (44.00)	355 (40.90)	.66
BPD (physiological definition), n (%)	25 (50.00)	329 (37.90)	.09
Home on oxygen, n (%)	16 (32.00)	199 (23.03)	.15
Home on respiratory medication, n (%)	17 (43.59)	189 (26.21)	.02
Discharged home October-March, n (%)	22 (44.00)	435 (50.35)	.38
Family history of COPD, emphysema, etc, n (%)	2 (4.00)	89 (10.25)	.22*
First-degree relative with asthma, n (%)	13 (26.00)	288 (33.18)	.29
Family history of allergies, n (%)	6 (15.38)	141 (16.79)	.82
Family history of CRD, n (%)	0 (0.00)	11 (1.37)	.99*
Breastfed, n (%)	16 (32.00)	299 (34.45)	.72
Smoking in house, n (%)	23 (46.94)	352 (41.27)	.43
Spent time at daycare, n (%)	21 (47.73)	284 (36.55)	.14
Living with children age <12 y, n (%)	23 (52.27)	482 (62.03)	.20
Pets in home, n (%)	23 (46.00)	335 (38.59)	.30
Flu vaccination, n (%)	34 (77.27)	615 (79.25)	.75
RSV prophylaxis, n (%)	32 (72.73)	562 (72.33)	.95
CPAP, n (%)	28 (56.00)	446 (51.38)	.53
Oxygen saturation, n (%)	30 (60.00)	449 (51.73)	.25

*Fisher exact test.

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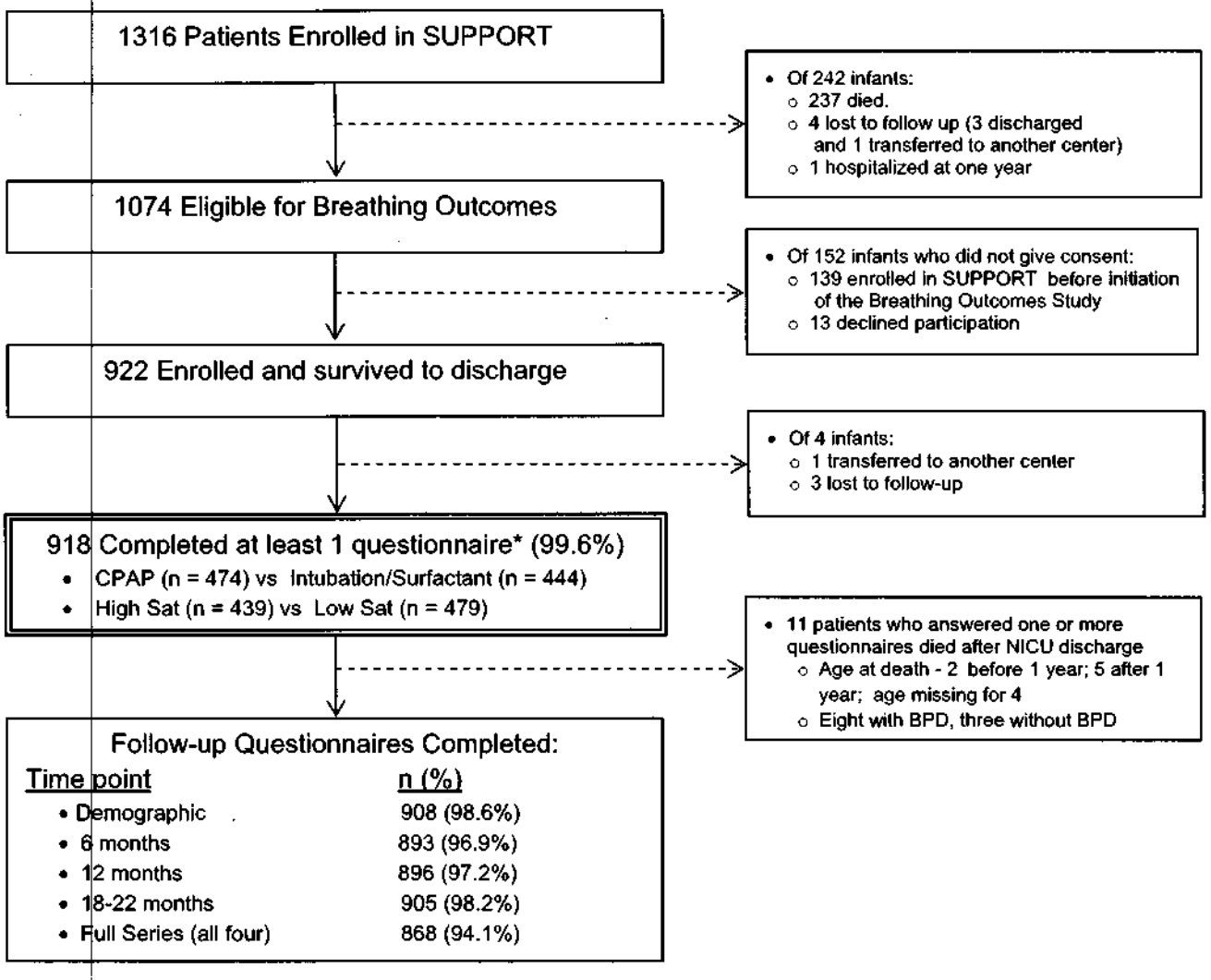

Figure. CONSORT diagram including follow-up rates. *Follow-up cohort.

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network, which stored, managed, and analyzed the data for this study. The authors declare no conflicts of interest. Q3 Registered with ClinicalTrials.gov: NCT00233324.

Acknowledgements

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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.

From: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: fyi - Now revised; I suspect Pediatrics will take
Date: Wednesday, March 26, 2014 5:02:10 PM
Attachments: SUPPORT_Peds_resubmitted_com (2) (2) (2).doc

Comparative Effectiveness Trials:
Generic Misassumptions Underlying the SUPPORT Controversy

Jon E. Tyson, MD, MPH[1]
Michele Walsh, MD[2]
Carl D'Angio, MD[3]

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Short Title: Comparative Effectiveness Trials: Generic Misassumptions

Word Count: 1100

Key Words: Bioethics, informed consent, clinical trial, comparative effectiveness research

Nonstandard words: Comparative Effectiveness (CE), Office for Human Research Protection (OHRP), Retinopathy of Prematurity (ROP), Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NICHD)

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Potential Conflict of Interest: The authors have indicated they have no potential conflicts of interest to disclose.

Jon E. Tyson: Dr. Tyson worked with Drs. Walsh and D'Angio conceptualizing the discussion, drafted the first manuscript and prepared the final revision.

Michele Walsh: Dr. Walsh worked with Drs. Tyson and D'Angio in conceptualizing the discussion, reviewed each draft of the manuscript and approved the final version.

Carl D'Angio: Dr. D'Angio worked with Drs. Tyson and Walsh in conceptualizing the discussion, reviewed each draft of the manuscript and approved the final version.

High priority should be given to promoting comparative effectiveness (**CE**) trials, trials that compare alternative therapies used in clinical practice and thus facilitate better informed decisions by clinicians, patients, third-party payers, and policy makers.[1,2] However, these trials fall under the regulatory requirements developed for trials of new experimental interventions. Yet, CE trials have no "experimental" arm and no "control" arm; the potential risks in one arm are potential benefits of the other; and the risks that should be specified on the consent form are unclear.

The regulation of CE trials was addressed in a public meeting in August 2013 held by the Office for Human Research Protection (**OHRP**) in response to heated controversy regarding the SUPPORT trial published in 2010 by the NICHD Neonatal Research Network.[3] This 20-center CE trial included 1316 infants 24-27 weeks gestation randomized to oxygen saturation goals of 85-89% or 91-95%, the upper and lower ends of the goal range (85-95%) suggested by the American Academy of Pediatrics. Caregivers were blinded to the saturation goal by offset oximeters. The lower goal reduced severe retinopathy of prematurity (**ROP**) as hypothesized but unexpectedly increased deaths, resulting in no significant difference between saturation groups in the composite primary outcome of death or severe ROP. Neurodevelopmental impairment rates were unaffected.[4]

In March, 2013 OHRP posted its determination on its website that SUPPORT violated regulatory requirements, that the consent form should have specified "substantial risks," and that the low saturation goal "could increase risk of... death." Public Citizen, an advocacy group, asserted that the involved parents were deliberately misled and that randomization to the two saturation goals was highly unethical. It also demanded the National Institutes of Health (**NIH**) issue a public apology and stop other Network trials—actions that have not occurred. A class action suit was then filed charging the Principal; Investigator at the University of Alabama, the members of its institutional review board (**IRB**), and other defendants with negligence, lack of informed consent, breach of fiduciary duty, and wrongful death. Although the plaintiffs have not been successful to date, litigation continues. [5]

Many non-medical ethicists have sided with OHRP.[6] Those who have defended SUPPORT include clinical ethicists, clinical investigators, clinicians, the editor of the New England Journal of Medicine, and the Director of the NIH.[7,8,9] In response, OHRP placed the compliance enforcement action on hold until after further consideration and its issuance of further guidance. In our view as participants in the August meeting and as SUPPORT investigators, the criticisms of SUPPORT rest on multiple misassumptions about CE trials. If unchallenged, these misassumptions could seriously undermine proper trials in any area of medicine important to advancing evidence-based care and outcomes. The misassumptions that we consider to be most important are addressed below:

Misassumption 1. Participation in randomized trials increases the risk of adverse outcomes.

To the contrary, systematic reviews indicate that the overall risk of adverse outcomes in randomized trials are not increased and may be reduced among participants than similar nonparticipants[10] because of increased attention to optimizing patient evaluation and supportive care. Likewise, the risk adjusted mortality in SUPPORT was lower among participants than among eligible non-enrolled infants although the difference did not reach statistical significance (relative risk=0.88 [95% confidence interval = 0.73-1.06]; p=0.16).[11]

Misassumption 2. Treatment risks can be accurately assessed by persons without a clear understanding of the clinical and research issues.

The assertion that the increased mortality with an 85-89% saturation goal was clearly foreseeable is based on studies performed more than 50 years ago when saturation monitoring and mechanical ventilation were unavailable and no more than 40-50% oxygen was administered even to deeply cyanotic infants with a saturation far below 85%. These studies are irrelevant to current care and to SUPPORT in which saturation was monitored continuously and mechanical ventilation and 100% oxygen were provided if necessary to meet the saturation goal. Mortality can be increased even in term infants by a brief exposure to too much oxygen.[12] The best evidence in contemporary cohort studies and randomized trials that included preterm infants and were

conducted before SUPPORT suggested that saturation goals of 85-89% and perhaps as low as 70% would not increase and might decrease mortality while reducing ROP below that with a 91-95% goal.[1,13]

Misassumption 3. Major treatment hazards viewed as highly plausible after trial completion should have been reasonably foreseeable before trial inception.

By definition, the foreseeability of hazards must be assessed using information known beforehand. The information required for truly informed treatment decisions is unknown before starting any legitimate randomized trial. Surprises are sometimes unavoidable and unforeseeable. Even with the accruing data in hand, an independent Data Safety Monitoring Committee judged the relative value of the two saturation goals sufficiently uncertain to recommend continuation of the trial on three occasions based on standard stopping rules.

Misassumption 4. A composite primary outcome that includes death indicates that the investigators expected an effect on mortality.

This misassumption underlies the assertion that the investigators deliberately misled the parents. Yet, the primary outcome in trials of high-risk patients is often a composite outcome that includes deaths when no effect on mortality is expected. Such patients may die before they can develop the outcome the intervention is hypothesized to prevent (e.g., severe ROP in SUPPORT). Death is then a competing outcome. Failure to account for differences in mortality would violate the intention-to-treat principle[14] and can seriously bias the primary analysis. Had the primary outcome in SUPPORT been limited to severe ROP without including deaths, the primary outcome would have favored the low saturation goal.

Misassumption 5. The consent form should list virtually any plausible hazard.

As emphasized by OHRP, only the *incremental* risks of the research need be considered under the Common Rule.[15] Moreover, listing any treatment hazard that might seem plausible despite evidence to the contrary would likely be misleading and distract from important known hazards.

The criteria for reasonably foreseeable hazards are undefined. We would suggest criteria like the following:

1) biologically plausible hazards that have not been well evaluated in clinical studies (as assessed using criteria like the GRADE or U.S. Preventive Task Force criteria), and

2) hazards that are at least marginally associated with the treatment ($p \leq 0.10$-0.15) in a systematic review of relevant clinical trials or in the absence of such a review, one or more trials or well performed cohort studies.

As the evidence was judged by the SUPPORT investigators and the IRBs in their 20 centers, mortality was not a reasonably foreseeable risk of the 85-89% goal. SUPPORT critics contend that the threshold for foreseeable risk should be low enough to have required listing death as a risk for this goal. Such a low threshold would also have required listing death for the higher goal as well. While this might satisfy SUPPORT critics, we doubt that the parents would have been better informed or their wants or needs better met.

Moving forward. Even when treatment risks are well known, the most desirable disclosure and consent process requires study of such issues as patient/surrogate wants and needs in emergent and routine circumstances; the effects of differing approaches to risk disclosure (including nocebo effects); and factors that augment the validity of informed consent.

The central problem for consent in SUPPORT was the very reason for the trial: uncertain risks and benefits of different saturation goals since saturation monitoring was introduced in the 1980s. Ironically, the long delay in conducting this and other important trials in all areas of medicine is due partly to systematically different requirements in patient care and CE trials for administering the same unproven, possibly harmful treatment. As Fost has emphasized, it is not plausible to

presume that a patient would want a therapy never properly tested for safety or efficacy with no prior review but would object to the same treatment being given with all the safeguards of a controlled trials.[16]

In moving forward, the regulatory requirements for CE trials would be better based on the foreseeable risks than on simplistic and outmoded distinctions between practice and research.[17] As Faden, Beauchamp, and Kass recently noted, "in a mature learning health care system ... some randomized comparative effectiveness studies may justifiably proceed with a streamlined consent process and others may not require... consent at all." [18] While regulatory refinements are being developed to promote a learning health care system, IRBs can exercise the discretion allowed under current regulations to facilitate CE trials involving minimal or reduced risk.[19]

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[19] See 45 CFR 46.116 & 46.117 and Informed Consent Requirements in Emergency Research. www.hhs.gov/ohrp/policy/hsdc97-01.html, section for research not regulated by the FDA.

From: Archer, Stephanie (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131439R1 submitted to JPediatr
Date: Friday, February 28, 2014 2:37:31 PM

Thanks. I asked him to send it to me on Monday, but he hasn't yet.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, February 28, 2014 2:35 PM
To: 'Stevens, Timothy'; Newman, Jamie <newman@rti.org> (newman@rti.org); Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131439R1 submitted to JPediatr

Can I get a copy of the accepted version and the anticipated publication date?

Thanks
Rose

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-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Monday, February 24, 2014 11:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Newman, Jamie <newman@rti.org> (newman@rti.org); Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Your Manuscript # 20131439R1 submitted to JPediatr

Our revised manuscript has been accepted!

Thanks to all for your contributions!

Tim

-----Original Message-----
From: ees.jpeds.0.277c91.7adc825a@eesmail.elsevier.com
[mailto:ees.jpeds.0.277c91.7adc825a@eesmail.elsevier.com] On Behalf Of Journal Office
Sent: Monday, February 24, 2014 10:38 AM
To: Stevens, Timothy
Subject: Your Manuscript # 20131439R1 submitted to JPediatr

Ref.: Ms. No. 20131439R1
Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial The Journal of Pediatrics

Dear Dr. Stevens,

Thank you for revising and resubmitting your manuscript. The Editors appreciate your efforts. We are pleased to accept your revised manuscript for publication in The Journal of Pediatrics. Tables II and III and the Figure will be published in the online version of The Journal; a reference to the electronic material will appear in the print version. We have made other editorial changes, which you will see in the proofs.

We will forward your manuscript to Elsevier, Inc. Before the final publication date, the publisher will send you galley proofs and other relevant material. Please read the proofs carefully and contact the publisher if anything is unclear or incorrect; the authors have final responsibility for the accuracy of the publication.

Congratulations.

Clyde J. Wright, MD
Guest Editor

William F. Balistreri, M.D.
Editor

/mlh

From: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org
Subject: Should the NICHD Network respond to request from Drazen and IOM ref views about procedures for open data?
Date: Sunday, February 16, 2014 4:11:51 PM

See Dr. Drazen's editorial Open Data. NJEM 2014;370: 662.
I would think PIs would have something to say worthwhile on this subject.

From:	Wally Carlo, M.D.
To:	Namasivayam Ambalavanan; Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc:	Walsh, Michele; Abhik Das; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
Subject:	RE: PaCO2 manuscript : Rejection from Pediatrics: Reformatted for J Pediatrics
Date:	Wednesday, March 26, 2014 4:31:51 PM

Ambal:

Great job.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Division of Neonatology
Director, Newborn Nurseries
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-----Original Message-----
From: Namasivayam Ambalavanan
Sent: Wednesday, March 26, 2014 2:32 PM
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Namasivayam Ambalavanan
Subject: RE: PaCO2 manuscript : Rejection from Pediatrics: Reformatted for J Pediatrics

Dear All,
I have made some changes to the manuscript, based on suggestions by Wally and Lisa. There is an additional supplemental table which shows the analysis of PCO2 by SUPPORT treatment groups. If there are no additional changes, I will submit next Monday (March 31).
Thanks,
Ambal

-----Original Message-----
From: Namasivayam Ambalavanan
Sent: Tuesday, March 18, 2014 1:43 PM
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Namasivayam Ambalavanan
Subject: RE: PaCO2 manuscript : Rejection from Pediatrics: Reformatted for J Pediatrics

Dear Co-authors,
I have reformatted and slightly modified our manuscript (made it a bit easier to read) for J Pediatrics. If there are no major comments, I will submit next Monday (24th March).
Thanks,
Ambal

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

From: Namasivayam Ambalavanan
Sent: Tuesday, February 18, 2014 9:09 PM
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
Subject: RE: PaCO2 manuscript : Rejection from Pediatrics

Dear All,
Pediatrics has rejected our manuscript. See reviewer comments below - not difficult to address, but I suppose the Editors have different priorities. I think we can probably submit to J Peds, unless people there are better choices?
Ambal

18-Feb-2014

RE: MS ID 2014-0061

PaCO2 and outcomes in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Dr. Ambalavanan:

Thank you for submitting your manuscript to Pediatrics. We are sorry that we are not accepting it for publication. Because of the large number of submissions, the editors must reject many worthy manuscripts. Rejection reflects the priorities of the journal; it does not necessarily indicate that your manuscript is unsuitable for publication elsewhere.

Comments from our reviewers are included below. Reviewer input is one of several factors involved in making decisions on papers. Because of space limitations, even papers receiving positive comments from the reviewers are often rejected.

We look forward to receiving other articles from you in the future.

Sincerely,

Lewis R. First, MD
Editor-in-Chief, Pediatrics
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics, Vermont Children's Hospital at Fletcher Allen Health Care
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Reviewer: 1

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

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From: Namasivayam Ambalavanan
Sent: Sunday, January 05, 2014 12:58 PM
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Higgins, Rosemary (NIH/NICHD)
Subject: RE: PaCO2 manuscript : Final uploaded draft and Submission pdf - plan submission on Jan 8, 2014

Dear All,
Attached is the final draft of the manuscript that has been uploaded to the Pediatrics journal website, and the pdf of the submission for your records. I will look over it and then click "submit" in a couple of days (Wednesday Jan 8, 2014 am), if no one has any major comments.
Thanks,
Ambal

From: Namasivayam Ambalavanan
Sent: Sunday, December 29, 2013 2:23 PM
Subject: RE: PaCO2 manuscript : Final draft (Dec 29, 2013) before submission on Jan 8, 2014

Dear All,
Attached is the most recent draft of our manuscript on PaCO2 in relation to outcome in SUPPORT. I have made some changes following NICHD clearance, Publication Subcommittee reviews, and comments by co-authors on the previous draft. One change is to emphasize that PaCO2 is a marker of illness severity and that there is for the most part no interaction between SUPPORT treatment group allocation and PaCO2. I will submit on Jan 8th (Wednesday; about 10 days from now) to Pediatrics if there are no further comments/suggestions.
Thank you,
Ambal

From: Poe, Grace (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report
Date: Monday, March 24, 2014 10:41:16 AM

Can they send to us, therefore, I can upload the table into the grant folder. Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:40 AM
To: Poe, Grace (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

They didn't attach their enrollment table either – the DCC sent the email and they can get them from the private website

Thanks
Rose

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From: Poe, Grace (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Please await for their response. Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:36 AM
To: Poe, Grace (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: FW: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Grace
UCSD is not in compliance with the PUB MED CENTRAL rules about submitting a paper – should I complete the check list or should we await their response?

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:34 AM
To: 'Orojian, Arpa'; 'Nakanishi, Kyle'; Brooks, Daryl (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Poe, Grace (NIH/NICHD) [E]; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Hi
NEJM Dec. 27, 2012 manuscript with Dr. Yvonne Vaucher as first author has not been submitted to PUB MED CENTRAL. This needs to be done with documentation sent to us as it is not in compliance with the NIH guidance for manuscripts.

Let me if this can be done today.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Orojian, Arpa [mailto:aorojian@ucsd.edu]
Sent: Friday, March 21, 2014 5:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Nakanishi, Kyle'; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD)

[E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Dear Dr. Higgins,

Please see the signed HHS 596 IRB approval form attached.

Thank you,

Arpa Orojian
Phone: (858) 534-1890
E-mail: arpa@ucsd.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 21, 2014 1:48 PM
To: 'Nakanishi, Kyle'; Orojian, Arpa; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Please send us the current approval through 4/2014

Rosemary D. Higgins, MD
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From: Nakanishi, Kyle [mailto:knakanishi@ucsd.edu]
Sent: Friday, March 21, 2014 4:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Orojian, Arpa'; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Dear Dr. Higgins,
Our IRB expires 4/3/14. We have submitted the renewal to IRB and should hear soon about the approval or if there are additional questions.

Thank you,
Kyle

Kyle Nakanishi | Director of Sponsored Projects | Department of Pediatrics
UC San Diego Health Sciences | 9500 Gilman Drive #0831 | La Jolla, CA 92093-0831
T: 858-246-0008 | F: 858-246-1981 | www.pediatrics.ucsd.edu | knakanishi@ucsd.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 21, 2014 1:20 PM
To: 'Orojian, Arpa'; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Nakanishi, Kyle; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Hi
I have looked this over and we need your current IRB approval for the NEURO 6-7 year follow up. Please send that to us as soon as you can. I will let you know if we need additional items.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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: Orojian, Arpa [mailto:aorojian@ucsd.edu]
Sent: Friday, March 21, 2014 3:24 PM
To: Brooks, Daryl (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Poe, Grace (NIH/NICHD) [E]; Kyle Nakanishi (knakanishi@ucsd.edu); Isaac, Sylvia (sisaac@ucsd.edu)
Subject: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Dear Mr. Brooks,

Please find the Progress Report for Dr. Finer's U10 HD040461 application attached. Please let us know if any additional documentation is required.

Thank you,

Arpa Orojian
Grant Analyst
University of California, San Diego
Health Sciences Sponsored Project Pre-Award Office
Health Sciences Research Service Core

9500 Gilman Drive, MC 0041
La Jolla, CA 92093-0041
Phone: (858) 534-1890
Fax: (858) 822-0834
E-mail: arpa@ucsd.edu

From: Poe, Grace (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report
Date: Monday, March 24, 2014 1:41:40 PM

Yes. we need the accepted FFR as well.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 1:40 PM
To: Poe, Grace (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: FW: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Grace
Please upload to the official grant file. We still need them to take care of the NEJM paper in PUB MED CENTRAL.

Thanks
Rose

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

From: Orojian, Arpa [mailto:aorojian@ucsd.edu]
Sent: Monday, March 24, 2014 1:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Brooks, Daryl (NIH/NICHD) [E]; Finer, Neil
Cc: Poe, Grace (NIH/NICHD) [E]; Kyle Nakanishi (knakanishi@ucsd.edu); Isaac, Sylvia (sisaac@ucsd.edu); Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Hi Dr. Higgins,

Please find the requested enrollment report attached.

Thank you,

Arpa Orojian
Phone: (858) 534-1890
E-mail: arpa@ucsd.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 24, 2014 7:39 AM
To: Orojian, Arpa; Brooks, Daryl (NIH/NICHD) [E]; Finer, Neil
Cc: Poe, Grace (NIH/NICHD) [E]; Kyle Nakanishi (knakanishi@ucsd.edu); Isaac, Sylvia (sisaac@ucsd.edu); Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Hi

We will also need the enrollment table for the NEURO follow up study. Please submit this to us.

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: Orojian, Arpa [mailto:aorojian@ucsd.edu]
Sent: Friday, March 21, 2014 3:24 PM
To: Brooks, Daryl (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Poe, Grace (NIH/NICHD) [E]; Kyle Nakanishi (knakanishi@ucsd.edu); Isaac, Sylvia (sisaac@ucsd.edu)
Subject: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Dear Mr. Brooks,

Please find the Progress Report for Dr. Finer's U10 HD040461 application attached. Please let us know if any additional documentation is required.

Thank you,

Arpa Orojian
Grant Analyst
University of California, San Diego
Health Sciences Sponsored Project Pre-Award Office
Health Sciences Research Service Core
9500 Gilman Drive, MC 0041
La Jolla, CA 92093-0041
Phone: (858) 534-1890
Fax: (858) 822-0834
E-mail: arpa@ucsd.edu

From: Poe, Grace (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Brooks, Daryl (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report
Date: Monday, March 24, 2014 10:14:43 AM

Yes.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:14 AM
To: Poe, Grace (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Brooks, Daryl (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

I think we are good with the UCSD IRB – as you said, reviewed and approved on 3/6/2014 so it is current. I will complete his checklist.

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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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: Poe, Grace (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 10:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Brooks, Daryl (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Hi Rose,

If the approval date is 3/6/2014, the expires date should be 3/5/2015. By the way, do you have a copy of Dr. Bell's progress Report? It's still not in the system. Thanks.

~Grace

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 24, 2014 6:40 AM
To: Poe, Grace (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]

Subject: FW: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Please upload to Finer's official grant file. Note, the date on the attached form for IRB approval is 3/6/2014. If their IRB expires on 4/3/14 as they state in the email, can we (b)(5) (b)(5) I think (b)(5)

Thanks
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Orojian, Arpa [mailto:aorojian@ucsd.edu]
Sent: Friday, March 21, 2014 5:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Nakanishi, Kyle'; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Dear Dr. Higgins,

Please see the signed HHS 596 IRB approval form attached.

Thank you,

Arpa Orojian
Phone: (858) 534-1890
E-mail: arpa@ucsd.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 21, 2014 1:48 PM
To: 'Nakanishi, Kyle'; Orojian, Arpa; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Please send us the current approval through 4/2014

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

NIH
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Nakanishi, Kyle [mailto:knakanishi@ucsd.edu]
Sent: Friday, March 21, 2014 4:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Orojian, Arpa'; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Dear Dr. Higgins,
Our IRB expires 4/3/14. We have submitted the renewal to IRB and should hear soon about the approval or if there are additional questions.

Thank you,
Kyle

--
Kyle Nakanishi | Director of Sponsored Projects | Department of Pediatrics
UC San Diego Health Sciences | 9500 Gilman Drive #0831 | La Jolla, CA 92093-0831
T: 858-246-0008 | F: 858-246-1981 | www.pediatrics.ucsd.edu | knakanishi@ucsd.edu

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 21, 2014 1:20 PM
To: 'Orojian, Arpa'; Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Nakanishi, Kyle; Isaac, Sylvia; Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Hi
I have looked this over and we need your current IRB approval for the NEURO 6-7 year follow up. Please send that to us as soon as you can. I will let you know if we need additional items.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Orojian, Arpa [mailto:aorojian@ucsd.edu]
Sent: Friday, March 21, 2014 3:24 PM
To: Brooks, Daryl (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Poe, Grace (NIH/NICHD) [E]; Kyle Nakanishi (knakanishi@ucsd.edu); Isaac, Sylvia (sisaac@ucsd.edu)
Subject: Grant Number: 5 U10 HD040461-09 PI Name: Finer, Neil- Progress Report

Dear Mr. Brooks,

Please find the Progress Report for Dr. Finer's U10 HD040461 application attached. Please let us know if any additional documentation is required.

Thank you,

Arpa Orojian
Grant Analyst
University of California, San Diego
Health Sciences Sponsored Project Pre-Award Office
Health Sciences Research Service Core
9500 Gilman Drive, MC 0041
La Jolla, CA 92093-0041
Phone: (858) 534-1890
Fax: (858) 822-0834
E-mail: arpa@ucsd.edu

From: Vaucher, Yvonne
To: Archer, Stephanie (NIH/NICHD) [E]; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Bill Truog (wtruog@cmh.edu)
Subject: RE: Publications | Vaucher
Date: Saturday, March 22, 2014 5:29:40 AM

Update: paper is still in progress. Draft should be available by July 1.

Yvonne

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Friday, March 21, 2014 1:23 PM
To: Vaucher, Yvonne; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Bill Truog (wtruog@cmh.edu)
Subject: RE: Publications | Vaucher

Hi Yvonne and Neil,

I'm updating the NRN publications tracker. Can you please update the information below?

It has been 10 months since the last update about this paper. It is NRN policy that if we do not receive an update at least every 12 months, we will mark the paper as withdrawn, and no further NRN resources will be available to complete it.

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
archerst@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, January 08, 2014 3:22 PM
To: Yvonne Vaucher (yvaucher@ucsd.edu)
Cc: Neil Finer (nfiner@ucsd.edu)
Subject: Publications | Vaucher

Hi Yvonne,

I'm updating the NRN publications tracker. Can you please update the information below?

Current Status	Authors	Paper Working Title	Abst. Year	Comments/Status	Last Update
1. Pending	Vaucher YE; Hintz SR; Rich W	Antenatal Enrollment in Clinical Trials: Is Neurodevelopmental Outcome Representative?	2013	11/15/12 Submitted for PAS 2013 2/11/13 PAS Accepted 5/1/13 Presented at PAS	5/1/13

Thanks!

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: Raju, Tonse (NIH/NICHD) [E]
Subject: Fwd: Sharyl Attkisson resigns from CBS News - POLITICO.com
Date: Tuesday, March 11, 2014 4:00:30 PM

FYI

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

From: "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>
Date: March 11, 2014 at 3:02:07 PM EDT
To: "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov>, "Rogers, Christine (NIH/NICHD) [E]" <Christine.Rogers@nih.gov>
Cc: "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov>, "Glavin, Sarah (NIH/NICHD) [E]" <glavins@mail.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Subject: RE: Sharyl Attkisson resigns from CBS News - POLITICO.com

I am fully supportive of her career decision.

Thanks! Alan

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Tuesday, March 11, 2014 2:58 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Rogers, Christine (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Sharyl Attkisson resigns from CBS News - POLITICO.com

Not sure what this means for the SUPPORT story she was working on – but I'm inclined to think this is a good thing. Kerri

---

From: Myles, Renate (NIH/OD) [E]
Sent: Tuesday, March 11, 2014 2:51 PM
To: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: Sharyl Attkisson resigns from CBS News - POLITICO.com

Have you heard? Although I hear Fox News is wooing her.
http://www.politico.com/blogs/media/2014/03/sharyl-attkisson-to-leave-cbs-news-184836.html?ml=m_po

From: Poe, Grace (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: UCSD Type 5 NRN application
Date: Friday, March 21, 2014 2:12:09 PM

I am working at home.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, March 21, 2014 2:11 PM
To: Poe, Grace (NIH/NICHD) [E]
Subject: RE: UCSD Type 5 NRN application

Are you in?

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: Poe, Grace (NIH/NICHD) [E]
Sent: Friday, March 21, 2014 2:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: UCSD Type 5 NRN application

OK. Thanks.

~Grace

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, March 21, 2014 2:08 PM
To: Poe, Grace (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: UCSD Type 5 NRN application

Grace
I just got off the phone with the UCSD folks – Dr. Finer is signing the rest of the items today and they will submit. I addition to sending to the usual address, I asked them to scan it and email it to you and I so we can at least get started given that it is so delayed.

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

From: Martin, Richard
To: Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: nice news
Date: Thursday, March 20, 2014 8:27:12 AM

I think the R03 got a (b) percentile if I am reading right!
Richard.

Richard J. Martin, M.D.
Drusinsky-Fanaroff Chair in Neonatology
Rainbow Babies & Children's Hospital
Professor of Pediatrics
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106-6010
Phone: (216) 844-3387
Fax: (216) 844-3380
email to: rxm6@case.edu

From: Brooks, Daryl (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Date: Wednesday, March 19, 2014 3:55:17 PM
Attachments: bell.pdf

Hi Rosemary, this is copy to review. I will send this to Lucy to upload. I will keep you posted on new info. Thanks

Daryl

Form Approved Through 08/31/2015

OMB No. 0925-0002

Department of Health and Human Services
Public Health Services

Grant Progress Report

Review Group	Type	Activity	Grant Number
	5	U10	HD053109-09

Total Project Period
From: 04/05/2006 Through: 03/31/2016

Requested Budget Period
From: 04/01/2014 Through: 03/31/2015

1. TITLE OF PROJECT
NICHD Cooperative Multicenter Neonatal Research Network

2a. PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR (Name and address, street, city, state, zip code)
Edward F. Bell, MD
University of Iowa
200 Hawkins Drive, 8811 JPP
Iowa City, IA 52242

2b. E-MAIL ADDRESS
edward-bell@uiowa.edu

2c. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Department of Pediatrics

2d. MAJOR SUBDIVISION
Roy J. and Lucille A. Carver College of Medicine

2e. Tel: 319.356.4006 Fax: 319.356.4685

3a. APPLICANT ORGANIZATION (Name and address, street, city, state, zip code)
The University of Iowa
Iowa City, IA 52242

3b. Tel: 319.335.2123 Fax: 319.335.2130

3c. DUNS: 062761671

4. ENTITY IDENTIFICATION NUMBER
1 42 6004 813 A1

6. HUMAN SUBJECTS ☐ No ☒ Yes

6a. Research Exempt	If Exempt ("Yes" in 6a): Exemption No.	If Not Exempt ("No" in 6a): IRB approval date
☒ No ☐ Yes		12/20/13

6b. Federal Wide Assurance No. FWA00003007

6c. NIH-Defined Phase III Clinical Trial ☒ No ☐ Yes

5. NAME, TITLE AND ADDRESS OF ADMINISTRATIVE OFFICIAL
Jennifer Lassner, Executive Director
Division of Sponsored Programs
2 Gilmore Hall, Iowa City, IA 52242

Tel: 319.335.2123 Fax: 319.335.2130

E-MAIL: nih@uiowa.edu

7. VERTEBRATE ANIMALS ☒ No ☐ Yes

7a. If "Yes," IACUC approval Date

7b. Animal Welfare Assurance No. A3021-01

10. PROJECT/PERFORMANCE SITE(S)

Organizational Name: applicant

DUNS:

8. COSTS REQUESTED FOR NEXT BUDGET PERIOD

8a. DIRECT $196,187 8b. TOTAL $296,242

Street 1:

Street 2:

City: County:

State: Province:

Country: Zip/Postal Code:

Congressional Districts:

9. INVENTIONS AND PATENTS ☒ No ☐ Yes

If "Yes," ☐ Previously Reported ☐ Not Previously Reported

11. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Item 13)*
Daniel Reed , Vice President for Research

TEL: 319.335.2123 FAX: 319.335.2130 E-MAIL: nih@uiowa.edu

12. Corrections to Page 1 Face Page

13. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 11. *(In ink)* Linda Meyer Acting for Daniel Reed

DATE 8/28/2014

Program Director/Principal Investigator (Last, First, Middle): Bell, Edward F.

DETAILED BUDGET FOR NEXT BUDGET PERIOD – DIRECT COSTS ONLY	FROM 04/01/2014	THROUGH 03/31/2015	GRANT NUMBER HD053109

List PERSONNEL *(Applicant organization only)*
Use Cal, Acad, or Summer to Enter Months Devoted to Project
Enter Dollar Amounts Requested *(omit cents)* for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	SALARY REQUESTED	FRINGE BENEFITS	TOTALS
Edward F. Bell	PD/PI	(b)(6)			18,150	3,884	22,034
Tarah T. Colaizy	Alternate PI				7,260	1,554	8,814
Jane E. Brumbaugh	Follow up PI				7,240	1,549	8,789
Jeffrey C. Murray	Investigator				1,815	388	2,203
Karen J. Johnson	Research Coord				78,620	27,124	105,744
Jacky R. Walker	Data Entry				23,062	7,956	31,018
SUBTOTALS					136,146	42,456	178,602

CONSULTANT COSTS	
EQUIPMENT *(Itemize)*	
SUPPLIES *(Itemize by category)* Office and computer supplies Laboratory supplies	1,600
TRAVEL 10 trips to DC area at $1475 per trip	14,750
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS *(Itemize by category)*	
OTHER EXPENSES *(Itemize by category)* Publications	1,235
SUBTOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD	$ 196,187
CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS	
CONSORTIUM/CONTRACTUAL COSTS — FACILITIES AND ADMINISTRATIVE COSTS	
TOTAL DIRECT COSTS FOR NEXT BUDGET PERIOD *(Item 8a, Face Page)*	$ 196,187

Program Director/Principal Investigator (Last, First, Middle): Bell, Edward F.

BUDGET JUSTIFICATION	GRANT NUMBER HD053109

Provide a detailed budget justification for those line items and amounts that represent a significant change from that previously recommended. Use continuation pages if necessary.

There has been no significant change in the budget from the previous year.

CURRENT BUDGET PERIOD	FROM 04/01/2013	THROUGH 03/31/2014

Explain any estimated unobligated balance (including prior year carryover) that is greater than 25% of the current year's total budget.

Base award carry over is less than 25% of year's total budget.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Bell, Edward F.	Professor of Pediatrics University of Iowa Iowa City, Iowa
eRA COMMONS USER NAME (credential, e.g., agency login) (b)(5)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Washington and Jefferson College	B.A.	06/69	Mathematics
Columbia University	M.D.	05/73	Medicine
Residency, Columbia-Presbyterian Med. Center		07/73-06/76	Pediatrics
Fellowship, McMaster University Med. Centre		07/76-06/77	Neonatology
Fellowship, Women & Infants Hosp. of Rhode Isl.		07/77-06/79	Neonatology

A. Personal Statement

The primary aim of the University of Iowa center in the NICHD Neonatal Research Network is to participate in all aspects of the work of the Network. We recognize that many crucial questions in neonatal medicine can only be addressed by large multicenter clinical trials. We believe it is our responsibility to offer our participation in such trials in order to provide clear answers more quickly than is possible with single-center trials. We have considerable expertise and resources to contribute to this effort.

As center Principal Investigator, I have the expertise, experience, and leadership skills necessary to continue leading our center's participation in the Network, as I have done since we were admitted to the Network in 2006. I have been involved in clinical research throughout my career. I was trained in clinical research design and developed my first experiences as a clinical investigator during my fellowships in neonatology at McMaster University Medical Centre and the Women and Infants Hospital of Rhode Island. I have designed and conducted single-center physiological research studies and randomized clinical trials in infants, and I have designed and participated in the multicenter clinical trials of the Neonatal Research Network.

As PI, Project Leader, or co-Investigator on several previous NIH-funded grants, I have developed a broad range of skills in research design, physiological measurements, and data management and analysis. As Director of Neonatology at the University of Iowa for 17 years and now, as Vice Chair for Faculty Development in the Department of Pediatrics, I have accumulated considerable skills in administration and team building. As PI of the University of Iowa center in the Neonatal Research Network, I have demonstrated my ability to function well in this role. In summary, I have a record of successful and productive research projects focused on various aspects of caring for critically-ill and prematurely-born infants. This experience and track record and my demonstrated success in leading the Iowa center of the Neonatal Research Network have prepared me well to continue as center PI.

B. Positions and Honors

Positions and Employment

1979-1983	Assistant Professor of Pediatrics, University of Iowa, Iowa City, IA
1983-1988	Associate Professor of Pediatrics, University of Iowa, Iowa City, IA
1992-1997	Associate Director, General Clinical Research Center, University of Iowa, Iowa City, IA
1988-present	Professor of Pediatrics, University of Iowa, Iowa City, IA
1988-2005	Director, Division of Neonatology, University of Iowa, Iowa City, IA
2005-present	Vice Chair for Faculty Development, Dept. of Pediatrics, University of Iowa, Iowa City, IA

Other Experience and Professional Memberships

Memberships:

1983-present	Member, Midwest Society for Pediatric Research (President, 1991-1992)
1984-present	Member, Society for Pediatric Research (Council Member, 1990-1993)
1987-present	Member, Perinatal Research Society
1987-1993	Member, American Academy of Pediatrics Committee on Nutrition
1989-present	Member, American Pediatric Society
1995-2000	Member, Subboard of Neonatal-Perinatal Medicine, American Board of Pediatrics
2001-2007	Member, American Academy of Pediatrics Committee on Fetus and Newborn

Editorial Positions:

1986-1999	Editorial Board, Early Human Development
1999-2005	Editorial Board, NeoReviews
2009-2011	Editorial Board, Anemia

NIH Monitoring and Review Groups:

1993-1999	Data and Safety Monitoring Committee, Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) Trial
2006-present	Steering Committee, NICHD Neonatal Research Network (U10 HD53109)
2009	Ad hoc reviewer, RFA ZHD1 DSR-K (29): Preterm birth in nulliparous women research network
2009-2012	Chair, Data Safety and Monitoring Board, Lactoferrin Enhances Growth and Reduces Nosocomial Infection in Preterm Infants (R44 HD057744, PI K Petrak)

Honors

1981	Young Investigator Award, American Academy of Pediatrics Section on Perinatal Pediatrics
2001	Humanism in Medicine Award, Healthcare Foundation of New Jersey
2002	Humanism in Medicine Award, Association of American Medical Colleges
2007	Founders Award, Midwest Society for Pediatric Research

C. Selected Peer-Reviewed Publications (selected from more than 100 peer-reviewed publications)

Most relevant to the current application

1. Bell, E.F., Strauss, R.G., Widness, J.A., Mahoney, L.T., Mock, D.M., Seward, V.J., Cress, G.A., Johnson, K.J., Kromer, I.J. & Zimmerman, M.B. (2005). Randomized trial of liberal *versus* restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics, 115(6), 1685-1691.
2. Bell, E.F. (2008). When to transfuse preterm babies. Archives of Disease in Childhood Fetal and Neonatal Edition, 93(6), F469-F473. PMCID: PMC2664522.
3. Bell, E.F., Hansen, N.I., Morriss, F.H. Jr., Stoll, B.J., Ambalavanan, N., Gould, J.B., Laptook, A.R., Walsh, M.C., Carlo, W.A., Shankaran, S., Das, A. & Higgins, R.D., for the NICHD Neonatal Research Network. (2010). Impact of timing of birth and resident duty-hour restrictions on outcome of small preterm infants. Pediatrics, 126(2), 222-231. PMCID: PMC2924191.
4. Boghossian, N.S., Hansen, N.I., Bell, E.F., Stoll, B.J., Murray, J.C., Laptook, A.R., Shankaran, S., Walsh, M.C., Das, A. & Higgins, R.D., for the NICHD Neonatal Research Network. (2010). Survival and morbidity outcomes of very low birth weight infants with Down syndrome. Pediatrics, 126(6), 1132-1140. PMCID: PMC3059605.
5. Abu-Maziad, A., Schaa, K., Bell, E.F., Dagle, J.M., Cooper, M., Marazita, M.L. & Murray, J.C. (2010). Role of polymorphic variants as genetic modulators of infection in neonatal sepsis. Pediatric Research, 68(4), 323-329. PMCID: PMC2940937.

6. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo, W.A., Finer, N.N., Walsh, M.C., Rich, W., Gantz, M.G., Laptook, A.R., Yoder, B.A., Faix, R.G., Das, A., Poole, W.K., Schibler, K., Newman, N.S., Ambalavanan, N., Frantz, I.D. 3rd, Piazza, A.J., Sánchez, P.J., Morris, B.H., Laroia, N., Phelps, D.L., Poindexter, B.B., Cotten, C.M., Van Meurs, K.P., Duara, S., Narendran, V., Sood, B.G., O'Shea, T.M., Bell, E.F., Ehrenkranz, R.A., Watterberg, K.L., Higgins, R.D. (2010). Target ranges of oxygen saturation in extremely preterm infants. New England Journal of Medicine, 362(21), 1959-1969. PMCID: PMC2891970.

7. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer, N.N., Carlo, W.A., Walsh, M.C., Rich, W., Gantz, M.G., Laptook, A.R., Yoder, B.A., Faix, R.G., Das, A., Poole, W.K., Donovan, E.F., Newman, N.S., Ambalavanan, N., Frantz, I.D. 3rd, Buchter, S., Sánchez, P.J., Kennedy, K.A., Laroia, N., Poindexter, B.B., Cotten, C.M., Van Meurs, K.P., Duara, S., Narendran, V., Sood, B.G., O'Shea, T.M., Bell, E.F., Bhandari, V., Watterberg, K.L., Higgins, R.D. (2010). Early CPAP versus surfactant in extremely preterm infants. New England Journal of Medicine, 362(21), 1970-1979. PMCID: PMC3071534.

8. Stoll, B.J., Hansen, N.I., Bell, E.F., Shankaran, S., Laptook, A.R., Walsh, M.C., Hale, E.C., Newman, N.S., Schibler, K., Carlo, W.A., Kennedy, K., Poindexter, B.B., Finer, N.N., Ehrenkranz, R.A., Duara, S., Sanchez, P.J., O'Shea, T.M., Goldberg, R.N., Van Meurs, K.P., Faix, R.G., Phelps, D.L., Frantz, I.D. III, Watterberg, K.L., Saha, S., Das, A. & Higgins, R.D., for the NICHD Neonatal Research Network. (2010). Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics, 126(3), 443-456. PMCID: PMC2982806.

9. Nopoulos, P.C., Conrad, A.L., Bell, E.F., Strauss, R.G., Widness, J.A., Magnotta, V.A., Zimmerman, M.B., Georgieff, M.K., Lindgren, S.D. & Richman, L.C. (2011). Long-term outcome of brain structure in premature infants: effects of liberal versus restricted red blood cell transfusions. Archives of Pediatrics and Adolescent Medicine, 165(5), 443-450.

10. Bell, E.F. & Zumbach, D.K. (2011). The tiniest babies: a registry of survivors with birth weight below 400 grams. Pediatrics, 127(1), 58-61.

11. Fredrickson, L.K., Bell, E.F., Cress, G.A., Johnson, K.J., Zimmerman, M.B., Mahoney, L.T., Widness, J.A. & Strauss, R.G. (2011). Acute physiological effects of packed RBC transfusion in preterm infants with different degrees of anaemia. Archives of Diseases of Childhood Fetal and Neonatal Edition, 96(4), F249-F253. PMCID: PMC3114194.

12. McCoy, T.E., Conrad, A.L., Richman, L.C., Lindgren, S.D., Nopoulos, P. & Bell, E.F. (2011). Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion. Child Neuropsychology, 17(4), 347-367. PMCID: PMC3115491.

13. Carlo, W.A., McDonald, S.A., Fanaroff, A.A., Vohr, B.R., Stoll, B.J., Ehrenkranz, R.A., Andrews, W.W., Wallace, D., Das, A., Bell, E.F., Walsh, M.C., Laptook, A.R., Shankaran, S., Poindexter, B.B., Hale, E.C., Newman, N.S., Davis, A.S., Schibler, K., Kennedy, K.A., Sanchez, P.J., Van Meurs, K.P., Goldberg, R.N., Watterberg, K.L., Faix, R.G., Frantz, I.D. III & Higgins, R.D., for the NICHD Neonatal Research Network. (2011). Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA, 306(21), 2348-2358. PMCID: PMC3565238.

14. Bell, E.F., Hansen, N.I., Brion, L.P., Ehrenkranz, R.A., Kennedy, K.A., Walsh, M.C., Shankaran, S., Acarregui, M.J., Johnson, K.J., Hale, E.C., Messina, L.A., Crawford, M.M., Laptook, A.R., Goldberg, R.N., Van Meurs, K.P., Carlo, W.A., Poindexter, B.B., Faix, R.G., Carlton, D.P., Watterberg, K.L., Ellsbury, D.L., Das, A., Higgins, R.D., for the NICHD Neonatal Research Network (2013). Serum tocopherol levels in very preterm infants after a single dose of vitamin E at birth. Pediatrics, 132(6):e1626-e1633. PMCID: PMC3838534.

15. (b)(4),(b)(6)

D. Research Support

Ongoing Research Support

U10 HD053109 Bell EF (PI) 2006-2016
NIH
NICHD Cooperative Multicenter Neonatal Research Network
This award funds the University of Iowa's participation in the NICHD Neonatal Research Network, a multicenter clinical program designed to investigate problems in neonatal medicine, particularly those related to low birth weight, prematurity, and common neonatal medical problems.
Role: Principal Investigator

P01 HL046925 Widness JA (PI) 2006-2016
NIH
Neonatal anemia: pathophysiology and treatment
This program project grant is designed to learn more about the pathophysiology of anemia in newborn infants, to find better ways to determine when erythrocyte transfusions are needed, and to improve the safety of erythrocyte transfusions.
Role: Co-Investigator

U01 HL112776 Kirpalani H and Bell EF (MPIs) 2012-2017
NIH
Transfusion-associate brain improvement (TABI) trial
Administered by Children's Hospital of Philadelphia
This award supports a clinical trial comparing the effects of high and low hemoglobin transfusion thresholds on neurodevelopmental outcome of preterm infants.
Role: Principal Investigator

R01 EY021137 Binenbaum G (PI) 2012-2017
NIH
Postnatal growth and retinopathy of prematurity (G-ROP) studies
Subaward from Children's Hospital of Philadelphia
This study will examine the relationship between growth rate and risk for retinopathy of prematurity in preterm infants.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Colaizy, Tarah T.	Associate Professor of Pediatrics University of Iowa Iowa City, Iowa
eRA COMMONS USER NAME (credential, e.g., agency login) (b)(6)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Wisconsin, Madison, WI	BS	1990-1994	Molecular Biology
University of Wisconsin, Madison, WI	MD	1994-1998	Medicine
Oregon Health & Science University, Portland, OR	MPH	2002-2005	Epidemiology and Biostatistics

A. Personal Statement

As a center investigator for the University of Iowa center in the NICHD Neonatal Research Network, I have assisted in enrollment of subjects and conduct of NRN sponsored multicenter clinical trials. My role also includes development and presentation of novel trial protocols to the NRN. My NRSA-funded fellowship training in clinical research and neonatal follow-up, including an MPH degree in Epidemiology and Biostatistics, has served as a foundation to aid me in design of protocols for the NRN. I have had supplemental training during fellowship in developmental follow-up combined with six years of experience as a clinician in an active developmental clinic for preterm infants, which has prepared me well for the role of NRN Alternate PI for the Iowa center.

B. Positions and Honors

Positions and Employment

1998-2001	Resident in Pediatrics, Oregon Health & Sciences University, Portland, OR
2001-2004	Fellow in Neonatal-Perinatal Pediatrics, Oregon Health & Science University, Portland, OR
2004-2013	Assistant Professor of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, IA
2013-present	Associate Professor of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, IA

Other Experience and Professional Memberships

2005-present	Member, American Academy of Pediatrics, (Iowa Chapter Breastfeeding Coordinator 2009-present)
2005-present	Member, Academy of Breastfeeding Medicine
2008-present	Member, Midwest Society for Pediatric Research
2009-present	Member, Society for Pediatric Research
2006-present	Medical Director, Mother's Milk Bank of Iowa
2011-present	Medical Director, University of Iowa High-Risk Infant Follow-Up Program
2011-present	Editor, Neonatology Section, *Pediatric Research*

Honors

2005	Ortho-McNeil Infectious Disease Scholar Award, Western Society for Pediatric Research
2004	Pediatric Fellow Research Award, Oregon Health & Science University
2003	Fellow Teaching Award, Oregon Health & Science University
2002	Mead Johnson Nutritionals Perinatal Travel Grant recipient
2001	Resident Teaching Award, Oregon Health & Science University
1997	AOA membership

C. Selected peer-reviewed publications (in chronological order)

1. Colaizy TT, Kuforiji TA, Sklar RS, Pillers DM. PCR Methods in Clinical Investigations of Human Ureaplasmas: A Mini Review. *Molecular Genetics and Metabolism* 80: 389-97; 2003.
2. Colaizy TT, Morris CD, Lapidus J, Sklar RS, Pillers DM. Detection of Ureaplasma DNA in endotracheal samples is associated with bronchopulmonary dysplasia after adjustment for multiple risk factors. *Pediatric Research*, 61:578-83; 2007.
3. Colaizy TT, Morriss FM. Positive Effect of NICU Admission on Breastfeeding of Preterm US Infants in 2000-2003. *Journal of Perinatol.* 28:505-10, 2008
4. Colaizy TT, Younis U, Bell EF, Klein JM. Nasal High Frequency Ventilation for Premature Infants. *Acta Paediatrica.* 97:1518-22, 2008.
5. Mohamed S, Schaa K, Cooper ME, Ahrens E, Alvarado A, Colaizy T, Marazita ML, Murray JC, Dagle JM. Genetic Contributions to the Development of Retinopathy of Prematurity. *Pediatr Res.* 65:193-7, 2009.
6. Swingle H, Colaizy TT, Zimmerman B, Morriss F. Abortion and the Risk of Subsequent Preterm Birth: A Systematic Review with Meta-analyses. *Journal of Reproductive Medicine.* 54:95-108, 2009.
7. Mascio CE, Wayment M, Colaizy TT, Mahoney LT, Burkhart HM. The Modified Fontan Procedure and Prolonged Pleural Effusions. *Am Surg.* 75:175-7, 2009.
8. Colaizy, TT, Saftlas, A, Morriss, FH. Maternal Intention to Breastfeed and Breastfeeding Outcomes in Term and Preterm Infants: PRAMS 2000-2003. *J. Pub Health Nut.* 22:1-9, 2011
9. Baack, M, Yao, JR, Norris, A, Colaizy, TT. Long Chain Polyunsaturated Fatty Acids in U.S. Donor Human Milk: Are Levels Adequate? *Journal of Perinatology* 32(8):598-603,2012.
10. Colaizy, TT, Carlson, SC, Saftlas, AF, Morriss, FH. Growth in VLBW infants fed predominantly fortified maternal and donor human milk diets: a retrospective cohort study. *BMC Pediatrics*,;12:124, 2012.
11. Mohammed, S, Dagle, JM, Murray, JC, Colaizy, TT. Hyperglycemia as a risk factor for the development of retinopathy of prematurity., *BMC Pediatrics 13:78, 2012*
12. Whitmore LC, Hilkin BM, Goss KL, Wahle EM, Colaizy TT, Boggiatto PM, Varga SM, Miller FJ, Moreland JG. NOX2 Protects against Prolonged Inflammation, Lung Injury, and Mortality following Systemic Insults. *J. Innate Immun. April 27, 2013, epub ahead of print.*
13. (b)(4),(b)(6)

D. Research Support

U10 HD053109 Bell, Edward (PI) 4/1/2011 – 03/31/2016 (b)(6) cal
NICHD Cooperative Multicenter Neonatal Research Network
Role: Center Alternate PI, (b)(ffort
Project PI for NRN-approved multicenter clinical trial, Neurodevelopmental Effects of Donor Human Milk vs. Preterm Formula in ELBW infants: The MILK trial, enrollment underway 7/12.

Major goals: To determine the effect of donor human milk on 18-22 mo neurodevelopmental outcomes in VLBW infants.

Research Grant Colaizy (PI) 3/1/2011 – 2/28/2014 (b)(6) cal
(b)(4),(b)(6)
Donor Human Milk and Neurodevelopmental Outcomes in Very Low Birthweight Infants. Double blind randomized controlled trial of the impact of donor human milk in VLBW infants on neurodevelopmental outcomes.

Major goal : 1). To determine the effect of donor human milk on 18-22mo neurodevelopmental outcomes in VLBW infants.

1K23HD057232-01A1 Colaizy (PI) 9/15/2008 – 8/31/2013
NICHD, NIH (Mentored Patient-Oriented Research Career Development Award (K23))
Clinical Epidemiologic and Biologic Studies of Donor Human Milk and Breastfeeding. Double-blind randomized controlled trial of donor human milk vs. preterm infant formula in VLBW infants.

Major goals: 1). To determine the effect of donor human milk on 18-22mo neurodevelopmental outcomes in VLBW infants. 2). To determine the effect of donor human milk on in-hospital growth of VLBW infants. 3). To support Dr. Colaizy's development as an independent clinical investigator.

Research Grant Colaizy (PI) 1/01/2008-12/31/2009
(b)(4),(b)(6) University of Iowa Children's Hospital
Breastfeeding behavior of late preterm mother/infant dyads: comparison of NICU-admitted and non-admitted infants.

Major goals: 1) To characterize the breastfeeding duration and behavior of late preterm infant/mother dyads, 2) To explore breastfeeding barriers in this population, and 3) To compare breastfeeding behavior between NICU-admitted and non-admitted late preterm infants.

New Investigator Grant Colaizy (PI) 1/01/2005-5/01/2006
University of Iowa College of Public Health-Carver College of Medicine
PCR Differentiation of *Ureaplasma* species and serovar in a cohort of VLBW infants in whom *Ureaplasma* colonization is associated with chronic lung disease of prematurity

Major goals: 1) To speciate and determine serovars of *Ureaplasma* isolates from a cohort of very low birthweight infants in whom *Ureaplasma* is associated with CLD, using PCR and DNA sequencing methods. 2) To investigate the role of sub-species in pathogenicity of *Ureaplasma* species in this population.

F32 HDO44332 Colaizy (PI) 5/2003-11/2004
NRSA, NIH
Prospective cohort study of lung disease of prematurity.
Prospective cohort study of very low birthweight infants to determine factors contributing to development of chronic lung disease of prematurity.

Major goals: 1) To investigate the association between neonatal pulmonary colonization with *Ureaplasma urealyticum*, Adenovirus, and *Chalmydia sp.* and chronic lung disease of prematurity (CLD); 2) To determine other risk factors for chronic lung disease of prematurity; 3) To build a multivariate logistic model to statistically determine the individual contributions of infectious microorganisms to CLD, after adjustment for other important risk factors. 4) To train Dr. Colaizy in clinical research techniques, including study leading to an MPH.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Jane E. Brumbaugh, M.D.	Associate
eRA COMMONS USER NAME (credential, e.g., agency login) (b)(6)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Minnesota, Minneapolis, MN	B.S.	05/02	Biochemistry
University of Minnesota, Minneapolis, MN	B.A.	05/02	Spanish
University of Minnesota, Minneapolis, MN	M.D.	05/06	Medicine
University of Minnesota, Minneapolis, MN	Residency	06/09	Pediatrics
University of Minnesota, Minneapolis, MN	Fellowship	06/12	Neonatal-Perinatal Medicine

A. Personal Statement

Jane Brumbaugh is an Associate in the Division of Neonatology, Department of Pediatrics at the University of Iowa, who is committed to a career in research. Dr. Brumbaugh's research focus is cognition, behavior, and neuroimaging in the low risk preterm population. As a Neonatal-Perinatal Medicine Fellow, she developed skills in neuropsychological assessment and application of event-related potentials for functional assessment under Dr. Kathleen M. Thomas, Institute of Child Development, University of Minnesota. Dr. Brumbaugh is now mentored by Dr. Peggy C. Nopoulos, the Kate Daum Research Professor of Psychiatry, Pediatrics and Neurology, at the University of Iowa. Dr. Nopoulos's research expertise is in the structure-function assessment of the developing brain using quantitative magnetic resonance imaging. Dr. Brumbaugh is laying the foundation as a physician scientist to utilize multiple modalities to assess brain development following preterm birth. The overlap of her research interests with the Neonatal Research Network makes her an ideal candidate for the role of Follow-Up Principal Investigator at the University of Iowa.

B. Positions and Honors

Positions and Employment

2006 – 2009 Resident, Department of Pediatrics, University of Minnesota, Minneapolis, MN
2009 – 2012 Fellow, Department of Pediatrics, University of Minnesota, Minneapolis, MN
2012 – Associate, Department of Pediatrics, University of Iowa, Iowa City, IA

Other Experience and Professional Memberships

2002 – 2012 Member, Minnesota Medical Association
2006 – Member, American Academy of Pediatrics
2009 – Member, American Academy of Pediatrics, Perinatal Section
2013 – Trustee, Iowa Chapter of the American Academy of Pediatrics
2013 – Member, Midwest Society for Pediatric Research

Honors

2003 – 2004 Dr. Nellie N. Barsness Scholarship
2004 – 2005 Dr. Nellie N. Barsness Scholarship, two-time recipient
2005 *Alpha Omega Alpha*
2011 Center for Neurobehavioral Development Travel Award
2012 Center for Neurobehavioral Development Travel Award, two-time recipient

C. Selected Peer-reviewed Publications

1. **Brumbaugh JE**, Morgan S, Beck JC, Zantek N, Bendel CM, Roberts KD. Blueberry muffin rash, hyperbilirubinemia, and hypoglycemia: A case of hemolytic disease of the fetus and newborn due to anti-Kp^a. *J Perinatol*. 2011;31(5):373-76.

2. Sen P, Yang Y, Navarro C, Silva I, Szafranski P, Kolodziejska KE, Dharmadhikari AV, Mostafa H, Kozakewich H, Kearney D, Cahill JB, Whitt M, Bilic M, Margraf L, Charles A, Goldblatt J, Gibson K, Lantz PE, Garvin AJ, Petty J, Kiblawi Z, Zuppan C, McConkie-Rosell A, McDonald MT, Peterson-Carmichael SL, Gaede JT, Shivanna B, Schady D, Friedlich PS, Hays SR, Palafoll IV, Siebers-Renelt U, Bohring A, Finn LS, Siebert JR, Galambos C, Nguyen L, Riley M, Chassaing N, Vigouroux A, Rocha G, Fernandes S, **Brumbaugh J**, Roberts K, Ho-Ming L, Lo IF, Lam S, Gerychova R, Jezova M, Valaskova I, Fellmann F, Afshar K, Giannoni E, Muhlethaler V, Liang J, Beckmann JS, Lioy J, Deshmukh H, Srinivasan L, Swarr DT, Sloman M, Shaw-Smith C, van Loon RL, Hagman C, Sznajer Y, Barrea C, Galant C, Detaille T, Wambach JA, Cole FS, Hamvas A, Prince LS, Diderich KE, Brooks AS, Verdijk RM, Ravindranathan H, Sugo E, Mowat D, Baker ML, Langston C, Welty S, Stankiewicz P. Novel FOXF1 mutations in sporadic and familial cases of alveolar capillary dysplasia with misaligned pulmonary veins imply a role for its DNA binding domain. *Hum Mutat*. 2013;34(6):801-11. PMCID: PMC3663886.

(b)(4),(b)(6)

(b)(4),(b)(6)

D. Research Support

Ongoing Research Support

(b)(4),(b)(6) 07/12 – 06/15
Start up funds
Award: $210,000
Role: PI

Completed Research Support

T32 DA022616-05 (PI Low) 05/10 – 05/11
Translational Research in Neurobiology of Disease
National Institutes of Health
Impairment of executive function secondary to prematurity: Insights into the neurocognitive morbidities associated with moderate to late preterm birth at 32 to 36 weeks gestation
Award: $3,750
Role: Trainee

Center for Neurobehavioral Development Seed Grant 05/10 – 05/11
University of Minnesota
Impact of prematurity on executive function in preschool-aged children born moderately-to-late preterm
Award: $2,000
Role: PI

Iowa Neonatology Investment Program 01/13 – 01/14
Division of Neonatology, University of Iowa
Characterization of the long-term outcomes of the late preterm brain at 9 – 11 years of age
Award: $25,000
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Jeffrey C. Murray, MD	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) (b)(6)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Massachusetts Institute of Technology	BS	1972	Biology
Tufts University, Boston, Massachusetts	MD	1978	

A. Personal Statement

Dr. Murray has a longstanding career commitment to understanding the genetic and environmental causes of complex pediatric diseases. He is trained as a pediatrician/geneticist and in the area of human molecular genetics. He has used human gene mapping approaches and epidemiology to discover the underlying causes of birth defects and preterm birth. In the area of preterm birth he has been the Director of the University of Iowa's Neonatal Research DNA Banks since 1999 and oversees preterm birth projects in Denmark, India and Argentina. The focus of these efforts has been on using genome-wide association, linkage, sequencing, and metabolomics approaches to identifying genetic causes and then coupling these to environmental covariates. In addition to investigating the specific causes of preterm birth, he has published on health outcomes related to term infants, and on the genetic components of the complications of prematurity (e.g. ROP, IVH, sepsis). His laboratory has skills and background in epidemiology, quantitative analysis, gene mapping and molecular analysis. Dr. Murray will continue to provide input on genetic aspects of preterm birth and continue his position on the genomics subcommittee.

B. Positions

1972-1973 Lab Technician to H.G. Khorana/M. Caruthers, Dept. of Biology, Massachusetts Inst. of Technol.
1978-1981 Pediatrics Residency, New England Medical Center Hospital, Boston
1982-1984 Postdoctoral Fellowship with Dr. Arno Motulsky, Univ. of Washington, School of Med., Seattle
1984-1988 Assistant Professor, Dept. of Pediatrics, Univ. of Iowa College of Medicine, Iowa City
1988-1993 Associate Professor, Dept. of Pediatrics, Univ. of Iowa College of Medicine, Iowa City
1993-present Professor, Dept. of Pediatrics, Univ. of Iowa College of Medicine, Iowa City
1994-present Professor, Dept. of Biological Sciences, Univ. of Iowa College of Liberal Arts, Iowa City
1998-present Professor, Dept. of Preventive Medicine, Univ. of Iowa, Iowa City
2000-present Professor of Epidemiology, College of Public Health, Univ. of Iowa, Iowa City

Other Experience and Professional Memberships

Member, NIH Mammalian Genetics Study Section, 1990-94, 2000-04 (Chair 2002-2004)
Member, NIH NHGRI National Advisory Council for Human Genome Research, 2004-2007
Member, NIH Advisory Committee to the Director (ACD), 2009-2012

Honors

E. Mead Johnson Awardee, Society of Pediatric Research, 1998
Elected member, Institute of Medicine of the National Academies, 2005
Curt Stern Award, American Society of Human Genetics, 2007
Mentor of the Year Award, Graduate College, University of Iowa, 2009

C. Selected Peer-reviewed Publications (over 400 publications)

291. Boyd HA, Poulsen G, Wohlfahrt J, **Murray JC**, Feenstra B and Melbye Mads. Maternal Contributions to Preterm Delivery. ***Am J Epidemiol*** 170(11):1358-64, 2009. PMCID: PMC2800264.
338. Ryckman KK, Feenstra B, Shaffer JR, Bream EN, Geller F, Feingold E, Weeks DE, Gadow E, Cosentino V, Saleme C, Simhan HN, Merrill D, Fong CT, Busch T, Berends SK, Comas B, Camelo JL, Boyd H, Laurie CC, Crosslin D, Zhang Q, Doheny KF, Pugh E, Melbye M, Marazita ML, Dagle JM, **Murray JC**.

Replication of a Genome-Wide Association Study of Birth Weight in Preterm Neonates. ***J Pediatr*** 160(1):19-24.e4, 2012. Epub 2011 Aug 31. PMCID: PMC3237813.

339. Ryckman KK, Dagle JM, Kelsey K, Momany A, **Murray JC**. Genetic associations of surfactant protein D and angiotensin-converting enzyme with lung disease in preterm neonates. ***J Perinatol*** 2012 May;32(5):349-55. doi: 10.1038/jp.2011.104. Epub 2011 Sep 29. PMCID: PMC3370386.
353. Kim J, Zhao K, Jiang P, Lu ZX, Wang J. **Murray JC**, Xing Y. Transcriptome Landscape of the Human Placenta. ***BMC Genomics*** 2012 Mar 27; 13(1): 115 [Epub ahead of print]. PMCID: PMC3368734.
358. Kitzman JO, Snyder MW, Ventura M, Lewis AP, Qiu R, Simmons LE, Gammill HS, Rubens CE, Santillan DA, **Murray JC**, Tabor HK, Bamshad MJ, Eichler EE, Shendure J. Noninvasive whole-genome sequencing of a human fetus. ***Sci Transl Med***, 2012 Jun 6; 4(137):137ra76. PMCID: PMC3379884.
368. Alleman B, Myking S, Ryckman K, Myhre R, Feingold E, Feenstra B, Geller F, Boyd H, Shaffer J, Zhang Q, Begum F, Crosslin D, Doheny K, Pugh E, Pay A, Ostensen I, Morken N-H, Magnus P, Marazita M, Jacobsson B, Melbye M, **Murray JC**. No observed association for mitochondrial SNPs with preterm delivery and related outcomes. ***Pediatr Res*** 2012 Aug 17. Doi: 10.1038/pr2012.112. PMCID: PMC3694399.
377. Ryckman KK, Berberich SL, Shchelochkov OA, Cook DE, **Murray JC**. Clinical and environmental influences on metabolic biomarkers collected for newborn screening. ***Clin Biochem***. 2012 Sep 23. Epub ahead of print. PMCID: PMC3534803.
380. Bream ENA, Zimmerman CR, Cooper ME, Dagle JM, Merrill DC, Christensen K, Simhan HN, Fong CT, Hallmann M, Muglia LJ, Marazita ML, **Murray JC**. Candidate gene linkage approach to identify DNA variants that predispose to preterm birth. ***Pediatr Res***, in press, 2012. Nov 20. Doi: 10.1038/pr.2012.166. [Epub ahead of print]. PMCID: PMC3740714.
381. (b)(4),(b)(6)
386. Alul F, Shchelochkov OA, Berberich SL, **Murray JC**, Ryckman KK. Genetic associations with neonatal thyroid stimulating hormone levels. ***Pediatr Res***. 2013 Jan 23. Doi: 10.1038/pr.2013.18. [Epub ahead of print]. PMCID: PMC3775497.
387. Kim J, Pitlick MM, Christine PJ, Schaefer AR, Saleme C, Comas B, Costentino V, Gadow E, **Murray JC**. Genome-wide analysis of DNA methylation in human amnion. ***Scientific World Journal*** 2013:. Doi: 10.1155/2013/678156. Epub 2012 Dec 31. PMCID: PMC3549342.
388. Boghossian NS, Page GP, Bell EF, Stoll BJ, **Murray JC**, Cotten CM, Shankaran S, Walsh MC, Laptook AR, Newman NS, Hale EC, McDonald SA, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. ***J Pediatr***. 2013 Jan 13. Pii: S0022-3476(12)01423-0. Doi: 10.1016/j.peds. 2012.11.089. [Epub ahead of print]. PMCID: PMC3633723 [Available on 2014/6/1].
392. Ryckman KK, Dagle JM, Shchelochkov OA, Ehinger N, Poole SD, Berberich SL, Reese J, **Murray JC**. Association of amino acids with common complications of prematurity. ***Pediatr Res*** 2013 Mar 12. Doi: 10.1038/pr.2013.43. [Epub ahead of print]. PMCID: PMC3660469.
393. Myking S, Boyd HA, Myhre R, Feenstra B, Jugessur A, Devold Pay AS, Østensen IH, Morken NH, Busch T, Ryckman KK, Geller F, Magnus P, Gjessing HK, Melbye M, Jacobsson B, **Murray JC**. X-chromosomal maternal and fetal SNPs and the risk of spontaneous preterm delivery in a Danish/Norwegian genome-wide association study. ***PLoS One***, 2013 Apr 16;8(4):e61781. doi: 10.1371/journal.pone.0061781. PMCID: PMC3628886.
395. Alleman BW, Smith AR, Byers HM, Bedell B, Ryckman KK, **Murray JC**, Borowski KS. A proposed method to predict preterm birth using clinical data, standard maternal serum screening, and cholesterol. ***Am J Obstet Gynecol***, 2013 Mar 15. Doi: 10.1016/j.ajob.2013.03.005. [Epub ahead of print.] PMCID: PMC3765002.

D. Research Support

ACTIVE

(b)(4),(b)(6) **Murray)** **6/1/08-5/31/14**

Genetic Studies of Maternal/Fetal Effects in Prematurity

This project investigates genetic causes of premature birth in Argentina. Dr. Murray is the PI and oversees data collection and laboratory analysis.

(b)(4),(b)(6) **Murray)** **3/1/13-2/28/16**

A Population, Genomic and Environmental Variable Approach to Prematurity

This proposal studies families and a large birth cohort (100,000 women and infants) in Denmark to investigate causes of prematurity. Dr. Murray oversees the US component.

NIH R01 HD57192 (Murray) **9/3/09-5/31/14**

NIH

A Family and Population Approach to Gene Discovery for Preterm Birth

This is a three year project to investigate and replicate information arising from a genome-wide association study carried out in the Danish population. It will focus on fine-mapping and replication using additional samples from Denmark as well as from Iowa and Argentina. It will also carry out gene discovery using DNA sequence analysis.

NIH U01 DE-20057 (Murray, Marazita, Multiple PI's) **9/21/09-4/30/14**

NIH

FaceBase Management and Coordination Hub

This project will coordinate ten individual research and technical support grants to develop a database and web presence to coordinate research investigations into craniofacial anomalies, in particular, cleft lip and palate. We are responsible for administering the hub, coordinating meetings, and carrying out biorepository activities.

R37 DE-08559 (Murray) **9/1/09-8/31/14**

NIH

Molecular Genetic Epidemiology of Cleft Lip and Palate

This proposal supports gene-environment studies in the Philippines and sample collection. Dr. Murray is the PI.

NIH R01 DE-21071 (John Manak, PI) **7/1/10 – 6/30/15**

Genomic Identification of Copy Number Variants
To Identify Clefting Loci

Dr. Murray (Co-Investigator) oversees the analysis of copy number variants and provides samples for a study looking for evidence of deletions and duplications in DNA from cases with cleft lip and palate. Dr. Murray oversees candidate gene selection for high resolution microarrays and directly supervises Dr. Petrin in the copy number variant analysis.

NIH R01 DE016148 (Mary Marazita, PI, Murray, Co-PI) **9/25/09-6/30/14**

Extending the Phenotype of Nonsyndromic
Orofacial Clefts

Dr. Murray oversees genotyping and gene/SNP selection with Dr. Marazita as PI.

NIH R01 DE-020895 (Wehby, PI) **8/1/10-7/31/15**

Genetic Instrumental Variable Studies of
Maternal Risk Behaviors for Oral Clefts

Dr. Murray oversees genetic studies and genotyping. His effort on this project overlaps with his CTSA effort.

U10HD-053109 (Bell) **4/1/11-3/31/16**

NIH

NICHD Cooperative Multicenter Neonatal Research Network

Dr. Murray is a Co-I on this proposal to be a participant in the Neonatal Research Clinical Trials Network. Dr. Murray provides advice on genetic aspects of clinical trials.

(b)(4),(b)(6) **(Murray)** **4/1/11-3/30/15**

(b)(4),(b)(6)

Transcriptome Signature of Preterm Birth
Predicting Children's Response to Distraction from Pain

Dr. Murray oversees genetic investigations and molecular genotyping. His effort on this project overlaps with his CTSA effort (see above).

OVERLAP: No Overlap

Program Director/Principal Investigator: (Last, first) Bell, Edward F.

PHS 2590/RPPR OTHER SUPPORT FORMAT PAGE

BELL, E.F.

ACTIVE

U10 HD053109 (Bell) NIH – NICHD Cooperative Multicenter Neonatal Research Network	04/05/2006 – 03/31/2016 $200,000	(b)(6) cal mo

This award funds the University of Iowa's participation in the NICHD Neonatal Research Network, a multicenter clinical program designed to investigate problems in neonatal medicine, particularly those related to low birth weight, prematurity, and common neonatal medical problems.

Current Grant

P01 HL046925 (Widness) NIH NHLB Neonatal Anemia Pathophysiology and Treatment	07/01/2012 – 06/30/2017 $9,634,989	(b)(6) cal mo

This program project grant is designed to learn more about the pathophysiology of anemia in newborn infants, to find better ways to determine when erythrocyte transfusions are needed, and to improve the safety of erythrocyte transfusions.

OVERLAP No Overlap

U01 HL112776 (Kirpalani & Bell) NIH / CHOP Impact of a Liberal Red Blood Cell Transfusion Strategy on Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants: The Transfusion and Brain Injury (TABI) Trial	08/01/2012 – 05/31/2013 $36,743	(b)(6) cal mo

This award supports a clinical trial comparing the effects of high and low hemoglobin transfusion thresholds on neurodevelopmental outcome of preterm infants.

OVERLAP No Overlap

R01 EY021137(Binenbaum) NIH / CHOP Postnatal Growth and Retinopathy of Prematurity (G-ROP) Studies	09/30/2012 – 08/31/2013 $25,457	(b)(6) cal mo

This grant supports efforts to develop a prognostic model using postnatal weight gain to identify the patients who are likely to develop severe retinopathy of prematurity among a large, diverse cohort of premature infants.

OVERLAP No Overlap

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED
For Non-competing Progress Reports (PHS 2590) – Submit only Active Support for Key Personnel

PHS 398/2590 OTHER SUPPORT

COLAIZY, TARAH TRINITY

ACTIVE

Research Grant (Colaizy PI) 3/1/2011 – 2/28/2014 (b)(6) calendar
Thrasher Research Fund
Donor Human Milk and Neurodevelopmental Outcomes in Very Low Birthweight Infants. Double blind randomized controlled trial of the impact of donor human milk in VLBW infants on neurodevelopmental outcomes.

Major goal: To determine the effect of donor human milk on 18–22 mo neurodevelopmental outcomes in VLBW infants.

U10 HD053109 Bell, Edward (PI) 4/1/2011 – 03/31/2016 (b)(6) calendar
NICHD Cooperative Multicenter Neonatal Research Network
Role: Center Alternate PI,
Project PI for NRN-approved multicenter clinical trial, Neurodevelopmental Effects of Donor Human Milk vs. Preterm Formula in ELBW infants: The MILK trial, enrollment underway 7/12.

Major goal: To design and conduct high quality multicenter trials in newborn infants to enhance lifelong health and well-being in this vulnerable population.

PHS 2590/RPPR OTHER SUPPORT FORMAT PAGE

BRUMGAUGH, JANE
ACTIVE

U10 HD053109 (Bell) NIH – NICHD Cooperative Multicenter Neonatal Research Network	04/05/2006 – 03/31/2016 $200,000	(b)(6) cal mo

This award funds the University of Iowa's participation in the NICHD Neonatal Research Network, a multicenter clinical program designed to investigate problems in neonatal medicine, particularly those related to low birth weight, prematurity, and common neonatal medical problems.

OVERLAP No Overlap

PHS 2590/RPPR OTHER SUPPORT FORMAT PAGE

MURRAY, J.

ACTIVE

5 R37 DE-008559-23 (Murray) 9/1/2009 – 8/31/2014 (b)(6) calendar
NIH/NIDCR $497,807
Molecular Genetic Epidemiology of Cleft Lip and Palate

This proposal supports gene-environment studies in the Philippines and sample collection.

5 R01 HD-057192-03 (Murray) 9/3/2009 – 5/31/2014 (b)(6) calendar
NIH $448,315
A Family and Population Approach to Gene Discovery for Preterm Birth

This project studies the role of genetics in preterm birth.

(b)(4),(b)(6) (Murray) 6/1/2008 – 5/31/2014 (b)(6) calendar
(b)(4),(b)(6) $110,093
Genetic Studies of Maternal/Fetal Effects in Prematurity

This project investigates genetic causes of premature birth in South America. Dr. Murray is the PI and oversees data collection and laboratory analysis.

(b)(4),(b)(6) (Murray) 3/1/2013 – 2/28/2016 (b)(6) calendar
(b)(4),(b)(6) $58,104
A Population, Genomic and Environmental Variable Approach to Prematurity

This study examines the contributions of genetics and environment to causes of preterm birth using a collection of samples and data from Denmark. The samples include extended family members that allow association and other genetic approaches coupled to exposure data.

5 U01 DE-020057-05 (Murray/Marazita) 9/21/2009 – 4/30/2014 (b)(6) calendar
NIH/NIDCR $1,382,568
FaceBase Management and Coordination Hub

Dr. Murray is a shared PI of this project to develop a web presence to enhance cleft lip and palate research.

(b)(4),(b)(6) (Murray) 4/1/2013 – 3/31/2014 (b)(6) calendar
(b)(4),(b)(6) $127,035
Interim Deputy Director of Discovery/Family Health

This project assists in creating a vision to develop and apply a basic and preclinical research program that aims to generate new global health and development solutions.

(b)(4),(b)(6) (Murray) 2/1/2010 – 1/31/2014 (b)(6) calendar
$40,000
Prize for Excellence in Academic Pediatrics

This project is to build programs to study preterm birth in low and middle income countries where obtaining pilot data and establishing relationships can be a challenge.

5 R01 DE-021071-03 (Manak) 7/1/2010 – 6/30/2015 (b)(6) calendar

NIH $62,033
Genomic Identification of Copy Number Variants to Identify Clefting Loci

Dr. Murray provides samples, clinical phenotypes and collaborates on gene identification in this proposal to use array-based copy number variant detection to identify genes for cleft lip and palate.

5 R01 DE-016148-08 (Marazita) 9/25/2009 – 6/30/2014 (b)(6) calendar
NIH/NIDCR $76,103
Extending the Phenotype of Nonsyndromic Orofacial Clefts

Dr. Murray oversees genetic studies and genotyping.

5 U10 HD-053109-07 (Bell) 4/1/2011 – 3/31/2016 (b)(6) calendar
NIH $200,000
NICHD Cooperative Multicenter Neonatal Research Network

Dr. Murray is a Co-I on this proposal to be a participant in the Neonatal Research Clinical Trials Network. Dr. Murray provides advice on genetic aspects of clinical trials.

(b)(4),(b)(6) (Murray) 4/1/2011 – 3/31/2015 (b)(6) calendar
(b)(4),(b)(6) $190,421
Transcriptome Signature of Preterm Birth

Dr. Murray uses RNA sequence analysis to investigate the gene expression profile of placentas coming from term and preterm infants. Dr. Murray provides the overall supervision, oversees the placental collection, analysis and input on genetic integration.

OVERLAP
N/A

Program Director/Principal Investigator (Last, First, Middle): Bell, Edward F.

PROGRESS REPORT SUMMARY	GRANT NUMBER HD053109	
	PERIOD COVERED BY THIS REPORT	
PROGRAM DIRECTOR / PRINCIPAL INVESTIGATOR Bell, Edward F.	FROM 04/01/2013	THROUGH 03/31/2014

APPLICANT ORGANIZATION
University of Iowa

TITLE OF PROJECT (Repeat title shown in Item 1 on first page)
NICHD Cooperative Multicenter Neonatal Research Network

A. Human Subjects (Complete Item 6 on the Face Page)		
Involvement of Human Subjects	☒ No Change Since Previous Submission	☐ Change
B. Vertebrate Animals (Complete Item 7 on the Face Page)		
Use of Vertebrate Animals	☒ No Change Since Previous Submission	☐ Change
C. Select Agent Research	☒ No Change Since Previous Submission	☐ Change
D. Multiple PD/PI Leadership Plan	☒ No Change Since Previous Submission	☐ Change
E. Human Embryonic Stem Cell Line(s) Used	☒ No Change Since Previous Submission	☐ Change

SEE PHS 2590 INSTRUCTIONS.

WOMEN AND MINORITY INCLUSION: See PHS 398 Instructions. Use Inclusion Enrollment Report Format Page and, if necessary, Targeted/Planned Enrollment Format Page.

A. Specific Aims

Our specific aims are
1. To continue identifying clinically important neonatal health problems that lend themselves well to multicenter collaboration in the Neonatal Research Network;
2. To continue our role in the design of studies that are directed toward these problems and conducted by the Network;
3. To participate in the analysis, interpretation, and presentation of the results of these studies;
4. To help advance the broad integration of genetics and genomics into the evaluation of new therapies in the clinical studies of the Network; and
5. To capitalize on the opportunities provided by Network membership to help foster the research career development of our junior faculty members and trainees.

B. Studies and Results

The table below summarizes the IRB approvals and subjects recruited during the past 8 years (04-01-06 through 12/31/13) at our two sites, the University of Iowa Children's Hospital and Mercy Medical Center (Mercy). NA = not applicable (not participating).

		University of Iowa			Mercy Medical Center			
Abbreviated protocol name	Clinical Trials ID	Protocol number	Approval date	Approved through	Protocol number	Approval date	Approved through	Subjects enrolled
Survey of morbidity and mortality in VLBW infants (GDB)	NCT000 63063	2006 02748	12/19/13	12/20/14	2009-54	08/16/13	08/30/14	840
Follow-up of high-risk infants	NCT000 09633	2006 02748	12/19/13	12/20/14	2009-61	10/01/13	10/17/14	158
Physiologic definition of BPD	NCT012 23287	2006 02748	Inactive	Study completed	NA	-	-	17
Moderate preterm study	Pending	2006 02748	12/19/13	12/20/14	2012-11	03/01/13	02/28/14	495
Early diagnosis of Candida	NCT001 09525	2006 02755	Inactive	Study completed	NA	-	-	15
Early-onset sepsis	NCT008 74367	2006 07742	04/04/13	04/05/14	2009-55	Inactive	Study completed	22
SUPPORT	NCT002 33324	2006 05740	02/28/13	02/28/14	NA	-	-	29
SUPPORT antenatal consent	NCT002 33324	2006 05740	02/28/13	02/28/14	NA	-	-	50
SUPPORT MRI	NCT002 33324	2006 05740	02/28/13	02/28/14	NA	-	-	29
SUPPORT breathing outcomes	NCT002 33324	2006 05470	02/28/13	02/28/14	NA	-	-	24
SUPPORT growth	NCT002 33324	2006 05470	02/28/13	02/28/14	NA	-	-	29
SUPPORT extended follow-up	NCT002 33324	2006 05470	02/28/13	02/28/14	NA	-	-	29
Optimizing cooling strategies for HIE	NCT011 92776	2010 08758	12/06/13	07/29/14	2011-43	09/20/13	09/30/14	21
Amplitude-integrated EEG to predict outcome in HIE	NCT011 92776	2010 08758	12/06/13	07/29/14	NA	-	-	5
Amplitude-integrated EEG during rewarming	NCT011 92776	2010 08758	12/06/13	07/29/14	NA	-	-	5
Hypothermia initiated after 6 hours in HIE	NCT006 14744	2008 02796	01/02/14	01/02/15	2010-05	02/01/13	01/31/14	8
NEC surgery trial	NCT010 29353	2009 10721	09/09/13	09/09/14	2010-01	02/01/13	01/31/14	3
NEC surgery trial preference cohort	NCT010 29353	2009 10721	09/09/13	09/09/14	2010-01	02/01/13	01/31/14	14

		University of Iowa			Mercy Medical Center			
Abbreviated protocol name	Clinical Trials ID	Protocol number	Approval date	Approved through	Protocol number	Approval date	Approved through	Subjects enrolled
Hypotension in the term infant	NCT00882284	200903705	12/19/13	12/20/14	NA	-	-	51
Early blood pressure management in preterms	NCT00874393	200912736	Inactive	Study completed	2010-42	04/04/13	04/30/14	34
Hydrocortisone for preventing BPD	NCT01353313	201105727	05/30/13	05/30/14	2011-44	09/20/13	09/30/14	23
Single-dose vitamin E	NCT01193270	201006736	Inactive	Study completed	2010-54	08/16/13	08/31/14	1
Phase II study of multiple doses of inositol	NCT01030575	200911721	11/05/12	11/05/13	2010-11	Inactive	Study completed	8
Inositol to reduce ROP	NCT01954082	Pending	-	-	Pending	-	-	0
Phase II pilot trial of inhaled prostaglandin E_1	NCT01467076	201111721	Inactive	Study ended	NA	-	-	1
Neurodevelopmental effects of donor milk vs preterm formula	NCT01534481	201210773	11/04/13	11/04/14	NA	-	-	5
Transfusion of prematures	NCT01702805	201211720	12/05/13	12/05/14	Pending	-	-	31

Investigators from Iowa have submitted 14 proposals for prospective studies. These are listed in the table below. In addition, we have helped with the preparation of many other proposals.

Principal Investigator	Abbreviated Title	Status
Dagle	Genetic risk factors for PDA	Approved; analyses in progress
Bell	Vitamin E prevention of IVH	Pilot study completed; RCT proposed but withdrawn after approval with modest enthusiasm
Colaizy	Donor human milk and neurodevelopmental outcome	Study underway
Ziegler	Human milk fortification	Concept not approved
Dagle	Hyperglycemia and ROP	Concept not approved
Bell and Kirpalani (U. Penn)	Transfusion of prematures	Study underway; co-funded by U01 grant from NHLBI (Kirpalani and Bell, MPIs)
Lindower	Positional plagiocephaly in preterm infants	Concept not approved
Bell	Umbilical cord milking at birth	Protocol approved; waiting in queue
Colaizy	Photoprotection of TPN solutions	Concept not approved

Ellsbury	Reduction of central-line-associated bloodstream infections	Concept not approved
Brophy and Askenazi (Alabama)	Acute kidney injury (secondary to Optimizing Cooling)	Protocol approved; not begun because main study was halted
Colaizy	Exclusive use of human milk to prevent NEC	Concept approved; protocol submitted
Morriss	Impact of surgery and anesthesia on neurodevelopmental outcome	Concept approved; protocol not approved
Ziegler	High vs low-protein fortifier for human milk feedings to ELBWs	Concept not approved

Members of the Iowa team have proposed 9 new analyses of data from existing databases. These are summarized in the table below.

Principal Investigator	Abbreviated Title	Status
Bell	Impact of timing of birth on VLBW outcomes	Published in *Pediatrics*
Boghossian	VLBW infants with Down syndrome	Published in *Pediatrics*
Boghossian	VLBW infants with trisomy 18 and trisomy 13	Published in *Pediatrics*
Alleman	Center effects on VLBW mortality	Published in *Pediatrics*
Boghossian	Hospital-acquired sepsis in VLBW singletons and twins of same and opposite sex	Published in *Journal of Pediatrics*
Morriss	Impact of surgery under general anesthesia on neurodevelopmental outcome	Provisionally accepted for publication in *JAMA Pediatrics*
Boghossian	Birthweight discordance in multiples and VLBW outcome	Proposal approved; analysis underway
Boghossian	Impact of maternal insulin-dependent diabetes on VLBW outcome	Proposal approved; analysis underway
Rysavy	Center effects on ELBW outcome	Proposal approved; analysis underway

Members of the Iowa team serve on various Network committees and subcommittees, as shown below.

- Steering – Bell
- Follow-Up – Brumbaugh
- Coordinators – Johnson, Campbell
- Generic Database (GDB) – Bell
- Moderate Preterm Registry – Bell
- Genomics – Murray (vice chair), Bell, Johnson
- Biospecimen Repository – Murray (vice chair), Bell, Johnson
- Trisomy 18 and 13 Study – Boghossian (chair), Bell,
- Milk Study – Colaizy (chair), Bell, Johnson, Carlson

- Vitamin E – Bell (chair), Acarregui, Johnson, Messina
- Benefits of Larger Placental Transfusion (BoLT) – Bell (chair), Colaizy, Widness, Johnson
- Transfusion of Prematures (TOP) – Bell (vice chair), Widness, Johnson
- Regional tissue oximetry before and after transfusion – Bell
- Probiotics – Bell
- Optimizing Cooling – Bell
- Amplitude-Integrated EEG During Rewarming Study – Bell
- Amplitude-Integrated EEG for Prediction of Outcome in Hypoxic-Ischemic Encephalopathy – Bell
- Acute Kidney Injury in Cooled Infants – Brophy, Jetton
- Biomarkers in Brain Injury – Bell
- Late Hypothermia – Bell
- High-Dose Caffeine – Bell
- Darbepoietin Study – Bell
- $IPGE_1$ – Klein
- Omegaven – Bell
- Low-dose soybean oil for patients with liver disease – Colaizy
- Volume-targeted ventilation – Klein

C. Significance

The research studies of the Neonatal Research Network, particularly the prospective therapeutic trials, are a powerful approach to testing the effectiveness and safety of new therapies for premature and critically-ill infants. Several of the studies listed above have a high likelihood of improving the care and outcomes of premature infants.

D. Plan

The University of Iowa team in the Neonatal Research Network plans to enroll as many patients as possible in all approved Network studies. We will continue to submit proposals for prospective studies and for analyses of existing Network data. We will continue to develop the protocols described above and bring as many of them to fruition as possible. We plan to continue to contribute to the important work of the Network committees on which we serve. In particular, we are working with other members of the Genomics Subcommittee to assure that genetic risk factors are considered in Network projects whenever appropriate.

E. Publications (Network publications with **Iowa investigators** as authors)

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID 3rd, Piazza AJ, Sánchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, **Bell EF**, Ehrenkranz RA, Watterberg KL, Higgins RD. Target ranges of oxygen saturation in extremely preterm infants *N Engl J Med.* 2010; 362:1959-69. Epub 2010 May 16. PMCID: PMC2891970.

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Donovan EF, Newman NS, Ambalavanan N, Frantz ID 3rd, Buchter S, Sánchez PJ, Kennedy KA, Laroia N, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, **Bell EF**, Bhandari V, Watterberg KL, Higgins RD. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med.* 2010; 362:1970-9. Epub 2010 May 16. PMCID: PMC3071534.

Davis AS, Hintz SR, Van Meurs KP, Li L, Das A, Stoll BJ, Walsh MC, Pappas A, **Bell EF**, Laptook AR, Higgins RD, for the NICHD Neonatal Research Network. Seizures in extremely low birth weight infants are associated with adverse outcomes. *J Pediatr.* 2010; 157:720-5.e1-2. Epub 2010 Jun 14. PMCID: PMC2939969.

Bell EF, Hansen NI, **Morriss FH Jr**, Stoll BJ, Ambalavanan N, Gould JB, Laptook AR, Walsh MC, Carlo WA, Shankaran S, Das A, Higgins RD, for the NICHD Neonatal Research Network. Impact of timing of birth and resident duty-hour restrictions on outcome of small preterm infants. *Pediatrics*. 2010; 126:222-31. Epub 2010 Jul 19. PMCID: PMC2924191.

Stoll BJ, Hansen NI, **Bell EF**, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy K, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sanchez PJ, O'Shea TM, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Frantz ID III, Watterberg KL, Saha S, Das A, Higgins RD, for the NICHD Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010; 126:443-56. Epub 2010 Aug 23. PMCID: PMC2982806.

Benjamin DK Jr, Stoll BJ, Gantz MG, Walsh MC, Sanchez PJ, Das A, Shankaran S, Higgins RD, Auten KJ, Miller NA, Walsh TJ, Laptook AR, Carlo WA, Kennedy KA, Finer NN, Duara S, Schibler K, Chapman RL, Van Meurs KP, Frantz ID III, Phelps DL, Poindexter BB, **Bell EF**, O'Shea TM, Watterberg KL, Goldberg RN, for the NICHD Neonatal Research Network. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics*. 2010; 126:e865-73. Epub 2010 Sep 27. PMCID: PMC3045840.

Boghossian NS, Hansen NI, **Bell EF**, Stoll BJ, **Murray JC**, Laptook AR, Shankaran S, Walsh MC, Das A, Higgins RD, for the NICHD Neonatal Research Network. Survival and morbidity outcomes of very low birth weight infants with Down syndrome. *Pediatrics*. 2010; 126:1132-40. Epub 2010 Nov 22. PMCID: PMC3059605.

Hintz SR, Kendrick DE, Wilson-Costello D, Das A, **Bell EF**, Vohr BR, Higgins RD, for the NICHD Neonatal Research Network. Neurodevelopmental outcomes in early childhood are not improving for extremely preterm infants born at less than 25 weeks gestational age. *Pediatrics*. 2011; 127:62-70. Epub 2010 Dec 27. PMCID: PMC3375467.

Wadhawan R, Oh W, Vohr BR, Wrage L, Das A, **Bell EF**, Laptook AR, Shankaran S, Stoll BJ, Walsh MC, Higgins RD, for the NICHD Neonatal Research Network. Neurodevelopmental outcomes of triplets or higher order extremely low birth weight infants. *Pediatrics*. 2011; 127:e654-60. Epub 2011 Feb 28. PMCID: PMC3304548.

Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, Bizzarro MJ, Goldberg RN, Frantz ID III, Hale EC, Shankaran S, Kennedy K, Carlo WA, Watterberg KL, **Bell EF**, Walsh MC, Schibler K, Laptook AR, Shane AL, Schrag SJ, Das A, Higgins RD, for the NICHD Neonatal Research Network. Early onset neonatal sepsis: the burden of group B streptococcal and *E. coli* disease continues. *Pediatrics*. 2011; 127:817-26. Epub 2011 Apr 25. PMCID: PMC3081183.

Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, Andrews WW, Wallace D, Das A, **Bell EF**, Walsh MC, Laptook AR, Shankaran S, Poindexter BB, Hale EC, Newman NS, Davis AS, Schibler K, Kennedy KA, Sanchez PJ, Van Meurs KP, Goldberg RN, Watterberg KL, Faix RG, Frantz ID III, Higgins RD, for the NICHD Neonatal Research Network. Antenatal corticosteroids and infants born around the limits of viability. *JAMA*. 2011; 306:2348-58. PMCID: PMC3565238.

Cole CR, Hansen NI, Higgins RD, **Bell EF**, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Das A, Stoll BJ, for the NICHD Neonatal Research Network. Bloodstream infections in very low birth weight infants with intestinal failure. *J Pediatr*. 2012; 160:54-9.e2. Epub 2011 Aug 15. PMCID: PMC3419271.

Natarajan G, Pappas A, Shankaran S, Kendrick DE, Das A, Higgins RD, Laptook AR, **Bell EF**, Stoll BJ, Newman N, Hale EC, Bara R, Walsh MC, for the NICHD Neonatal Research Network. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. *Early Hum Dev*. 2012; 88:509-15. Epub 2012 Jan 10. PMCID: PMC3686277.

De Jesus LC, Pappas A, Shankaran S, Kendrick D, Das A, Higgins RD, **Bell EF**, Stoll BJ, Laptook AR, Walsh MC, for the NICHD Neonatal Research Network. Risk factors for post-neonatal intensive care unit discharge mortality among extremely low birth weight infants. *J Pediatr*. 2012; 161:70-4.e2. Epub 2012 Feb 9. PMCID: PMC3366175.

Shane AL, Hansen NI, Stoll BJ, **Bell EF**, Sanchez PJ, Shankaran S, Laptook AR, Das A, Walsh MC, Hale EC, Newman NS, Schrag SJ, Higgins RD, for the NICHD Neonatal Research Network. Methicillin-resistant and susceptible *Staphylococcus aureus* bacteremia and meningitis in preterm infants. *Pediatrics.* 2012; 129:e914-22. Epub 2012 Mar 12. PMCID: PMC3313632.

Vohr BR, Stephens BE, Higgins RD, Bann CM, Hintz SR, Das A, Newman JE, Peralta-Carcelen M, Yolton K, Dusick AM, Evans PW, Goldstein RF, Ehrenkranz RA, Pappas A, Adams-Chapman I, Wilson-Costello DE, Bauer CR, Bodnar A, Heyne RJ, Vaucher YE, Dillard RG, **Acarregui MJ**, McGowan EC, Myers GJ, Fuller J, for the NICHD Neonatal Research Network. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. *J Pediatr.* 2012; 161:222-8.e3. Epub 2012 Mar 14. PMCID: PMC3796892.

Greenberg RG, Benjamin DK Jr, Gantz MG, Cotten CM, Stoll BJ, Walsh MC, Sanchez PJ, Shankaran S, Das A, Higgins RD, Miller NA, Auten KJ, Walsh TJ, Laptook AR, Carlo WA, Kennedy KA, Finer NN, Duara S, Schibler K, Ehrenkranz RA, Van Meurs KP, Frantz ID III, Phelps DL, Poindexter BB, **Bell EF**, O'Shea TM, Watterberg KL, Goldberg RN, Smith PB, for the NICHD Neonatal Research Network. Empiric antifungal therapy and outcomes in extremely-low-birth-weight infants with invasive candidiasis. *J Pediatr.* 2012; 161:264-9.e2. Epub 2012 Mar 15. PMCID: PMC3380169.

Smith PB, Ambalavanan N, Li L, Cotten CM, Laughon M, Walsh MC, Das A, **Bell EF**, Carlo WA, Stoll BJ, Shankaran S, Laptook AR, Higgins RD, Goldberg RN, for the NICHD Neonatal Research Network. Approach to infants born at 22 to 24 weeks' gestation: relationship to outcomes of more-mature infants. *Pediatrics.* 2012; 129:e1508-16. Epub 2012 May 28. PMCID: PMC3362905.

(b)(4),(b)(6)

Pappas A, Shankaran S, Hansen NI, **Bell EF**, Stoll BJ, Laptook AR, Walsh MC, Das A, Bara R, Hale EC, Newman NS, **Boghossian NS**, **Murray JC**, Cotten CM, Adams-Chapman I, Hamrick S, Higgins RD, for the NICHD Neonatal Research Network. Outcome of extremely preterm infants (<1000 g) with congenital heart defects from the NICHD Neonatal Research Network. *Pediatr Cardiol.* 2012; 33:1415-26. Epub 2012 May 30. PMCID: PMC3687358.

Adams-Chapman I, Bann CM, Das A, Goldberg RN, Stoll BJ, Walsh MC, Sánchez PJ, Higgins RD, Shankaran S, Watterberg KL, Duara S, Miller NA, Heyne RJ, Peralta-Carcelen M, Goldstein RF, Steichen JJ, Bauer CR, Hintz SR, Evans PW, **Acarregui MJ**, Myers GJ, Vohr BR, Wilson-Costello DE, Pappas A, Vaucher YE, Ehrenkranz RA, McGowan EC, Dillard RG, Fuller J, Benjamin DK Jr, for the NICHD Neonatal Research Network. Neurodevelopmental outcome of extremely low birth weight infants with *Candida* infection. *J Pediatr.* 2013; 163:961-7.e3. PMCID: PMC3786056.

Wadhawan R, Oh W, Vohr BR, Saha S, Das A, **Bell EF**, Laptook A, Shankaran S, Stoll BJ, Walsh MC, Higgins R, for the NICHD Neonatal Research Network. Spontaneous intestinal perforation in extremely low birth weight infants: association with indometacin therapy and effects on neurodevelopmental outcomes at 18-22 months corrected age. *Arch Dis Child Fetal Neonatal Ed.* 2013; 98:F127-32. Epub 2012 Jun 9. PMCID: PMC3753803.

Wynn JL, Hansen NI, Das A, Cotten CM, Goldberg RN, Sanchez PJ, **Bell EF**, Van Meurs KP, Carlo WA, Laptook AR, Higgins RD, Benjamin DK Jr, Stoll BJ, for the NICHD Neonatal Research Network. Early sepsis does not increase the risk of late sepsis in very low birth weight neonates. *J Pediatr.* 2013; 162:942-8.e1-3. Epub 2013 Jan 5. PMCID: PMC3622770.

Boghossian NS, Page GP, **Bell EF**, Stoll BJ, **Murray JC**, Cotten MC, Shankaran S, Walsh MC, Laptook AR, Newman NS, Hale EC, McDonald SA, Das A, Higgins RD, for the NICHD Neonatal Research Network. Late-onset sepsis in very low birth weight infants from singleton and multiple gestation births. *J Pediatr.* 2013; 162:1120-4.e1. Epub 2013 Jan 13. PMCID: PMC3633723.

(b)(4),(b)(6)

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Adams-Chapman I, Hansen NI, Shankaran S, **Bell EF**, **Boghossian NS**, **Murray JC**, Laptook AR, Walsh MC, Carlo WA, Sanchez PJ, Van Meurs KP, Das A, Hale EC, Newman NS, Ball MB, Higgins RD, Stoll BJ, for the NICHD Neonatal Research Network. Ten-year review of major birth defects in VLBW infants. *Pediatrics*. 2013; 132:49-61. Epub 2013 Jun 3. PMCID: PMC3691532.

Alleman BW, **Bell EF**, Li L, **Dagle JM**, Smith PB, Ambalavanan N, Laughon MM, Stoll BJ, Goldberg RN, Carlo WA, **Murray JC**, Cotten CM, Shankaran S, Walsh MC, Laptook AR, **Ellsbury DL**, Hale EC, Newman NS, Wallace DD, Das A, Higgins RD, for the NICHD Neonatal Research Network. Individual and center-level factors affecting mortality among extremely low birth weight infants. *Pediatrics*. 2013; 132:e175-84. Epub 2013 Jun 10. PMCID: PMC3691533.

(b)(4),(b)(6)

Bell EF, Hansen NI, Brion LP, Ehrenkranz RA, Kennedy KA, Walsh MC, Shankaran S, **Acarregui MJ**, **Johnson KJ**, Hale EC, **Messina LA**, Crawford MM, Laptook AR, Goldberg RN, Van Meurs KP, Carlo WA, Poindexter BB, Faix RG, Carlton DP, Watterberg KL, **Ellsbury DL**, Das A, Higgins RD, for the NICHD Neonatal Research Network. Serum tocopherol levels in very preterm infants after a single dose of vitamin E at birth. *Pediatrics*. 2013; 132:e1626-33. Epub 2013 Nov 11. PMCID: PMC3838534.

(b)(4),(b)(6)

Wadhawan R, Oh W, Hintz SR, Blakely ML, Das A, **Bell EF**, Saha S, Laptook AR, Shankaran S, Stoll BJ, Walsh MC, Higgins RD, for the NICHD Neonatal Research Network. Neurodevelopmental outcomes of extremely low birth weight infants with spontaneous intestinal perforation or surgical necrotizing enterocolitis. *J Perinatol*. 2014; 34:64-70. Epub 2013 Oct 17. PMCID: PMC3877158.

(b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

F. Project-Generated Resources

Considerable practice-changing knowledge has been generated from this cooperative agreement but not yet any significant new resources beyond the publications resulting from Network research.

Program Director/Principal Investigator (Last, first, middle): Bell, Edward F.

GRANT NUMBER
HD053109

CHECKLIST

1. PROGRAM INCOME ***(See instructions.)***
All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)
None		

2. ASSURANCES/CERTIFICATIONS ***(See instructions.)***
In signing the application Face Page, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the application instructions when applicable. Descriptions of individual assurances/certifications are provided in Part III of the PHS 398, and listed in Part I, 4.1 under Item 14. If unable to certify compliance, where applicable, provide an explanation and place it after the Progress Report (Form Page 5).

3. FACILITIES AND ADMINSTRATIVE (F&A) COSTS
Indicate the applicant organization's most recent F&A cost rate established with the appropriate DHHS Regional Office, or, in the case of for-profit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office.

F&A costs will *not* be paid on construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Service Awards, Small Business Innovation Research/Small Business Technology Transfer Grants, foreign grants, and specialized grant applications.

☒ DHHS Agreement dated: 3/20/13 ☐ No Facilities and Administrative Costs Requested.

☐ No DHHS Agreement, but rate established with _____ Date _____

CALCULATION*

Entire proposed budget period: Amount of base $ 196,187 x Rate applied 51.00 % = F&A costs $ 100,055

Add to total direct costs from Form Page 2 and enter new total on Face Page, Item 8b.

*Check appropriate box(es):

☐ Salary and wages base ☒ Modified total direct cost base ☐ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

Explanation *(Attach separate sheet, if necessary.):*

Program Director/Principal Investigator (Last, First, Middle): Bell, Edward F.

ALL PERSONNEL REPORT

Place this form at the end of the signed original copy of the application. Do not duplicate.

GRANT NUMBER
HD053109

Always list the PD/PI(s). In addition, list all other personnel who participated in the project during the current budget period for at least one person month or more, regardless of the source of compensation (a person month equals approximately 160 hours or 8.3% of annualized effort). Use the following abbreviated categories for describing Role on Project:

- **PD/PI***
- **Co-Investigator**
- **Faculty**
- **Postdoctoral (scholar, fellow, or other postdoctoral position)***
- **Technician**
- **Staff Scientist (doctoral level)**
- **Statistician**
- **Graduate Student (research assistant)**
- **Non-student Research Assistant**
- **Undergraduate Student**
- **High School Student**
- **Consultant**
- **Other (please specify)**

If personnel are supported by a Reentry or Diversity Supplement please indicate such after the Role on Project, using the following abbreviations: RS - Reentry Supplement; DS - Diversity Supplement.

***Commons ID required for any personnel holding this Role on Project and for all individuals supported by a Reenty or Diversity Supplement. The Commons ID will be required in the future for all individuals with a graduate student, or undergraduate role. The Commons ID is strongly encouraged, but not required, for all other Project Personnel.**

Use Cal (calendar), Acad, or Summer to enter months devoted to project.

Commons ID*	Name	Degree(s)	SSN (last 4 digits)	Role on Project	DoB (MM /YY)	Cal	Acad	Summer
(b)(6)	Edward F. Bell	MD	(b)(6)	PI	(b)(6)	(b)(6)		
	Tarah T. Colaizy	MD, MPH		Alternate PI				
	Jane E. Brumbaugh	MD		Follow up PI				
	Jeffrey C. Murray	MD		Investigator				
	Karen J. Johnson	BSN		Research Coord				
	Jacky R. Walker	BSN		Data Entry				

Program Director/Principal Investigator (Last, First, Middle): Bell, Edward F.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: NICHD Cooperative Multicenter Neonatal Research Network

Total Planned Enrollment: 300

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	10	10	20
Not Hispanic or Latino	140	140	280
Ethnic Category: Total of All Subjects *	150	150	300
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	3	3	6
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	18	18	36
White	127	127	254
Racial Categories: Total of All Subjects *	150	150	300

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

Program Director/Principal Investigator (Last, First, Middle): Bell, Edward F.

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: NICHD Cooperative Multicenter Neonatal Research Network

Total Enrollment: 1616 (04/01/06 through 12/31/13) **Protocol Number:** Multiple (total)

Grant Number: U10 HD053109

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Females	Males	Sex/Gender Unknown or Not Reported	Total
Hispanic or Latino	52	45	0	97 **
Not Hispanic or Latino	738	759	6	1,503
Unknown (individuals not reporting ethnicity)	9	6	1	16
Ethnic Category: Total of All Subjects*	799	810	7	1,616 *
Racial Categories				
American Indian/Alaska Native	4	3	0	7
Asian	21	10	0	31
Native Hawaiian or Other Pacific Islander	0	3	0	3
Black or African American	94	95	2	191
White	652	673	4	1,329
More Than One Race	16	10	0	26
Unknown or Not Reported	12	16	1	29
Racial Categories: Total of All Subjects*	799	810	7	1,616 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Sex/Gender Unknown or Not Reported	Total
American Indian or Alaska Native	3	0	0	3
Asian	0	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	5	5	0	10
White	38	27	0	65
More Than One Race	3	0	0	3
Unknown or Not Reported	3	11	0	14
Racial Categories: Total of Hispanics or Latinos**	52	45	0	97 **

* These totals must agree.
** These totals must agree.

From: Brooks, Daryl (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Grant Number: 5U10HD040461 - 09 PI Name: FINER, NEIL Norman
Date: Wednesday, March 19, 2014 3:03:27 PM

The Dr. Bell grant was submitted, Still waiting for Lucy Rowser to give an update. I call the grantee and their going to send me a copy and also, resend to Commons. I will keep you posted on the next update as soon as I get it. Sorry for the delay.

Daryl

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, March 19, 2014 2:31 PM
To: Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Grant Number: 5U10HD040461 - 09 PI Name: FINER, NEIL Norman

This one from Dr. Finer has never been submitted – what about Dr. Bell's grant?
Thanks for the follow up

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Brooks, Daryl (NIH/NICHD) [E]
Sent: Wednesday, March 19, 2014 2:29 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Grant Number: 5U10HD040461 - 09 PI Name: FINER, NEIL Norman

Hi Rosemary, I talked to Elisabeth and she's working on resubmitting by the end of the week. Thanks

Daryl

From: Brooks, Daryl (NIH/NICHD) [E]
Sent: Monday, March 17, 2014 10:17 AM
To: Poe, Grace (NIH/NICHD) [E]; 'NFINER@UCSD.EDU'; 'vchsgrants@ucsd.edu'
Subject: Grant Number: 5U10HD040461 - 09 PI Name: FINER, NEIL Norman

Dear Grantee, For some reason the Progress report won't show up in the system. I would like to request a resubmit of your RPPR. Sorry for this! Thanks

Daryl Brooks
Grants Clerk (OA)
Eunice Kennedy Shriver
National Institute of Child Health
and Human Development
Closeout Specialist GMB/NICHD/NIH
Office : 301-435-7013
FAX : 301-451-5510
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Bethesda, MD 20892-7510
**if sending FEDEX, replace last line with: Rockville, MD 20852*
In support of NICHD electronic Grants Management, please use e-mail, NICHD e-Fax (301.451.5510) and the NIH eRA Commons. https://commons.era.nih.gov/commons
Please note: All e-mail correspondence must be e-mailed by the business official with a copy to the PI

From: Brooks, Daryl (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09
Date: Tuesday, March 18, 2014 9:39:56 AM

Hi Rose, I sent an E-mail to the grantee to resubmit the RPPR yesterday. I will give you an update later today. Thanks

Daryl

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, March 18, 2014 8:27 AM
To: Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09

Hi
Ed Bell's Type 5 application is still not in the system. Can we please get it uploaded?
Thanks
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Brooks, Daryl (NIH/NICHD) [E]
Sent: Monday, March 17, 2014 8:45 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09

I will check on original submission, and have them redo the process. Thanks

Daryl

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 17, 2014 8:38 AM
To: Brooks, Daryl (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09

Do we know what happened to the original submission from Dr. Bell, University of Iowa? Also, the request should come from the submission center, not us!

Rosemary D. Higgins, MD
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From: Brooks, Daryl (NIH/NICHD) [E]
Sent: Monday, March 17, 2014 8:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poe, Grace (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09

Hi Dr. Higgins, I called and talked to Lucy and left a message and no feedback. Grace also e-mailed. I think a request might be the way to go, if we want things to get moving. Thanks

Daryl

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 17, 2014 8:29 AM
To: Poe, Grace (NIH/NICHD) [E]; Rowser, Lucy (NIH/OD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Brooks, Daryl (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09
Importance: High

Hi
Can I get an update on the status of this submission? Dr. Bell's Type 5 application was received on 2/4/2014 and still does not appear in the system. The start date is 4/1/2014. Do we need to request another copy from the institution to get this moving??
thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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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: Poe, Grace (NIH/NICHD) [E]
Sent: Thursday, March 13, 2014 10:31 AM
To: Rowser, Lucy (NIH/OD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Brooks, Daryl (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09

Hi Lucy,

The type of the above referenced grants were submitted to NIH, the system shows NIH received. But it's not scan into the IMPAC system yet. the start date of these two grant are April 1, and we need time to review. Would you please take care of this ASAP? Thanks.

~Grace

From: Poe, Grace (NIH/NICHD) [E]
Sent: Thursday, March 13, 2014 10:25 AM
To: Brooks, Daryl (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD 053109-09 and 5U10HD040461-09

Hi Daryl,

The type 5 is still not in the system. Please give me the name and email address of your contact. Thanks.

~Grace

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, March 07, 2014 2:20 PM
To: Poe, Grace (NIH/NICHD) [E]; Brooks, Daryl (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD040461-09

Daryl
Do we have any follow up on this type 5 submission? It was received by NIH and still not in the system. Let us know

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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, March 04, 2014 2:17 PM
To: Poe, Grace (NIH/NICHD) [E]
Cc: Brooks, Daryl (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD040461-09

HI

I still do not see Ed bell's Type 5 in the ERA system

Daryl – can you give us an update?

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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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: Poe, Grace (NIH/NICHD) [E]
Sent: Monday, March 03, 2014 7:57 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Brooks, Daryl (NIH/NICHD) [E]
Subject: RE: Re: NIH Grant 5U10HD040461-09

OK. Thanks.

Daryl,

Would you please check why the workload system shows the following grant has been received, but it's not in the IMPAC system. Thanks very much.

U10 HD 053109 BELL , EDWARD F UNIVERSITY OF IOWA – Need Progress Report

~Grace

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, March 03, 2014 7:51 AM
To: Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: FW: Re: NIH Grant 5U10HD040461-09

Grace
Finer's is not yet received – I will also give them a call.

Ed Bell's Type 5 application has not yet been scanned. Any updates on this one?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
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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: Monday, March 03, 2014 7:47 AM
To: 'NFINER@UCSD.EDU'
Cc: 'vchsgrants@ucsd.edu'; NICHD HD eRA Notifications (NIH/NICHD); Poe, Grace (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: NIH Grant 5U10HD040461-09

Hi Neil –
We have not received your Type 5 Application for the above listed grant. Pleases submit this as soon as possible.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH

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higginsr@mail.nih.gov

From: Juliann DiFiore
To: Pickett, James
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele; Gantz, Marie; Zaterka-Baxter, Kristin
Subject: Re: IH and mortality data
Date: Monday, March 17, 2014 3:28:14 PM

Hi James,

I've worked around the previous discussed data issues as much as I can but I need them now resolved so I can move forward with the data analysis. At this point I am going to have to assume that most of the data listed in the previous emails below was lost, but I would like try to recover the following if possible:

1. Do you have data for the following infants who died and had >1wk of data?

(b)(6)

2. You sent me data for an infant with the (b)(6). This infant is not listed on the spreadsheet you sent me (ihdatarequest201407) with the survival status, GA etc. Can you please give me that information?

Thank you,

Julie

On 1/31/2014 12:02 PM, Pickett, James wrote:

> Hi Julie,
> I have been able to do some research into your previous list and I will send you findings shortly. With regards to this current request, I will put it on my list to review (no ETA for it yet) and I'll get back to you as soon as I can on it.
>
> Thanks,
>
> J
>
> James Pickett - Res. Programmer / Analyst - Clinical Research Informatics * (919) 541-1253 * Haynes 399L *
> japickett@rti.org
> RTI International * 3040 Cornwallis Road * P.O. Box 12194 *
> Research Triangle Park, NC 27709-2194
>
> -----Original Message-----
> From: Juliann DiFiore [mailto:jmd3@case.edu]
> Sent: Tuesday, January 28, 2014 3:04 PM
> To: Pickett, James
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele; Auman, Jeanette O.; Gantz, Marie; Zaterka-Baxter, Kristin
> Subject: Re: IH and mortality data

Hi James,

I was wondering if you had looked at the list of missing infants yet?

Also, I was rather surprised to see that about 20% of the infants on the DVD have missing data during the first week of monitoring. I have attached a spreadsheet with the individual data for the infants in question. Some of the missing data could be explained by token errors when converting the files. I have removed those from the list. Others had either the first download missing or questionable starting dates as categorized by the following:

1) the first download missing - Please verify that you do not have the missing files
2) the first file contained old data followed by empty days then a delayed start date for correct infant - Please verify 1st day of monitoring
3) No explanation. - Please, again, verify 1st day of monitoring.

Thanks!

Julie

On 1/9/2014 5:10 PM, Juliann DiFiore wrote:

> Sounds good.
>
> Regards,
>
> Julie
>
> On 1/9/2014 5:08 PM, Pickett, James wrote:
>
> > Hi Julie,
> > Thanks, I hope your year is off to a glowing start.
> > I will be happy to review your data and see what additional details I
> > can provide. I won't be able to review immediately as I am currently
> > on deadline to complete activities for the INS3 trial that will be
> > launching shortly. I am putting this on my schedule to review on
> > Monday (1/13) and respond asap with results.
> >
> > J
> >
> > James Pickett - Res. Programmer / Analyst - Clinical Research
> > Informatics * (919) 541-1253 *
> > Haynes 399L *
> > japickett@rti.org
> > RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research
> > Triangle Park, NC 27709-2194
> >
> > -----Original Message-----
> > From: Juliann DiFiore [mailto:jmd3@case.edu]
> > Sent: Thursday, January 09, 2014 1:51 PM
> > To: Pickett, James
> > Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele;
> > Auman, Jeanette O.; Gantz, Marie; Zaterka-Baxter, Kristin
> > Subject: Re: IH and mortality data
> >
> > Hi James,
> >
> > Happy New Year!
> >
> > I am following up on the missing infant data

that we discussed before
the holidays. I have attached a spreadsheet
which shows the specific
infants that were not on the DVD. This list was
extrapolated from the
zipped raw waveform files on the DVD and the
Excel file
ihdatarequest_forJulie.xlsx. In summary, there
are a total of (b)(6)
infants missing with the following criteria:
1. 24 died.
a. 18 of the infants died within 1-5 days
of life. Not
expecting any data from those.
b. 6 of the infants who died had >1wk of
data (8-20 days). I
was hoping we could find those infants as they
would be useable for
this analysis.
2. 39 infants survived with all infants having
50+ days of data
(52-291 days). Can you please look this list
over and verify that you
do not have these infants?

Lastly, in the Excel files,
ihdatarequest20140107.xlsx and
ihdatarequest_forJulie.xlsx infant (b)(6) is
missing. (This infant
is included in the raw waveform files on the
DVD) Would you please
send me the information for that infant?

Thanks!

Julie

with the the On 12/23/2013 3:23 PM, Pickett,
James wrote:

> Hello Juliann,
> No, there were no additional discs
> to send. You have all the data
> that is available. With regards to
> infant count vs. recording
> availability, not all infants will
> have recordings. For example,
> there are 28 infants on that subject
> listing that met status (death)
> at day of life 1 that we are
> unlikely to have any oximeter data
> for
> -- I have verified that is the case
> for 3 via spot check. That one
> example covers approximately 50% of
> your missing data. I will be
> more than happy to work with you
> after the holidays to assist you
> with the remaining subjects in
> question.
>
> Regards,
>
> J
>
> James Pickett - Res. Programmer /
> Analyst - Clinical Research
> Informatics * (919) 541-1253
> * Haynes 399L *
> japickett@rti.org
> RTI International * 3040 Cornwallis
> Road * P.O. Box 12194 * Research
> Triangle Park, NC 27709-2194

-----Original Message-----
From: Juliann DiFiore
[mailto:jmd3@case.edu]
Sent: Monday, December 23, 2013 2:47 PM
To: Pickett, James
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele
Subject: IH and mortality data

Hello James,

I have been working through the data sent on the DVD for the IH and mortality secondary study. I noticed that there are infants missing in the zipped files. There are 1316 infants listed in the IHdatarequest.xlsx spreadsheet but only 1255 zipped files are enclosed on the DVD. The missing infants seem to be random by site. (ie missing per site: 4-site J, 8-site I, 1- site M, 5-site F...). Was there a 2nd DVD that was not enclosed in the envelope you sent in september?

Regards,

Julie

--
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

--

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

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Juliann Di Fiore
Research Engineer
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Rainbow Babies & Children's Hospital
Division of Neonatology, Room 3100
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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

From: Juliann DiFiore
To: Zaterka-Baxter, Kristin; Walsh, Michele
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Data Request for IH and mortality ancillary study
Date: Friday, March 14, 2014 2:13:19 PM
Attachments: SUPPORT trial proposal Patterns of intermittent hypoxia associated with mortality Final REVISED 3_12_14.docx

Kristen,

Attached is the revise protocol with the new text in red. Please let me know if you need anything else.

Thanks,

Julie

On 3/12/2014 11:10 AM, Zaterka-Baxter, Kristin wrote:

> Hi Julie,
>
> My apologies, Rose sent a response to my inquiring whether the additional requested data needed further approval on Feb 18th. I filed that without responding to you. She's requesting that you send a revised protocol because the current version does not list the additional morbidities and we can send to the subcommittee for hopefully a quick email vote. Once that is done, James (copied here) can pull the data and send rather quickly.
>
> Thanks
> Kris
>
> ---
>
> **From:** Juliann DiFiore [mailto:jmd3@case.edu]
> **Sent:** Wednesday, March 12, 2014 10:26 AM
> **To:** Zaterka-Baxter, Kristin; Walsh, Michele
> **Subject:** Re: Data Request for IH and mortality ancillary study
>
> Hi Kris,
>
> Just following up on our conversation a month ago about the request for additional data for the IH and mortality ancillary study. Any progress?
>
> Julie
>
> On 2/17/2014 6:35 PM, Zaterka-Baxter, Kristin wrote:
>
> > Hi Julie,
> >
> > So not ignoring you at all, just trying to determine it the additional data requested needs further approvals .... Will let you know soon.
> >
> > Thanks,

Kris

From: Juliann DiFiore [mailto:jmd3@case.edu]
Sent: Monday, February 17, 2014 12:25 PM
To: Zaterka-Baxter, Kristin
Cc: Walsh, Michele
Subject: Fwd: Data Request for IH and mortality ancillary study

Hi Kristen,

I am following up on the data request below. When do you think you will be able to update the DUA? I am hoping we can move it through our legal dept on this end much more quickly than the last time!

Regards,

Julie

-------- Original Message --------
Subject: Data Request for IH and mortality ancillary study
Date: Fri, 07 Feb 2014 11:57:01 -0500
From: Juliann DiFiore <jmd3@case.edu>
To: Pickett, James <japickett@rti.org>, Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>, Das, Abhik <adas@rti.org>, Gantz, Marie <mgantz@rti.org>, Zaterka-Baxter, Kristin <kzaterka@rti.org>, Walsh, Michele <Michele.Walsh@uhhospitals.org>, rxm6@case.edu <rxm6@case.edu>

RE: IH and mortality ancillary study

After discussions with Michele and Richard regarding the IH and mortality study we feel we need to include additional covariates that may influence IH. Therefore, I am asking for one more amendment to the DUA (and hopefully the last). Would you please add the following:

Early Sepsis (< 72 hrs) and Late Sepsis (>= 72 hrs)
IVH: Any and Severe
NEC- any and medical vs surgical.
Cause of Death.
Thank you,
Julie

--
Juliann Di Fiore
Research Engineer

Case Western Reserve University
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of the Freedom of Information and Privacy Act

Page 0643 of 2000

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Page 0644 of 2000

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of the Freedom of Information and Privacy Act

Page 0645 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 0646 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

From: Walsh, Michele
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Data Request for IH and mortality ancillary study
Date: Wednesday, March 12, 2014 11:15:33 AM

Wow.... This is disappointing- we have been waiting for over a month.
How do we expedite this.

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

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, March 12, 2014 11:10 AM
To: Juliann DiFiore; Walsh, Michele
Cc: Pickett, James
Subject: RE: Data Request for IH and mortality ancillary study

Hi Julie,

My apologies, Rose sent a response to my inquiring whether the additional requested data needed further approval on Feb 18th. I filed that without responding to you. She's requesting that you send a revised protocol because the current version does not list the additional morbidities and we can send to the subcommittee for hopefully a quick email vote. Once that is done, James (copied here) can pull the data and send rather quickly.

Thanks
Kris

From: Juliann DiFiore [mailto:jmd3@case.edu]
Sent: Wednesday, March 12, 2014 10:26 AM
To: Zaterka-Baxter, Kristin; Walsh, Michele
Subject: Re: Data Request for IH and mortality ancillary study

Hi Kris,

Just following up on our conversation a month ago about the request for additional data for the IH and mortality ancillary study. Any progress?

Julie

On 2/17/2014 6:35 PM, Zaterka-Baxter, Kristin wrote:

Hi Julie,

So not ignoring you at all, just trying to determine it the additional data requested needs further approvals .... Will let you know soon.

Thanks,
Kris

From: Juliann DiFiore [mailto:jmd3@case.edu]
Sent: Monday, February 17, 2014 12:25 PM
To: Zaterka-Baxter, Kristin
Cc: Walsh, Michele
Subject: Fwd: Data Request for IH and mortality ancillary study

Hi Kristen,

I am following up on the data request below. When do you think you will be able to update the DUA? I am hoping we can move it through our legal dept on this end much more quickly than the last time!

Regards,

Julie

-------- Original Message --------
Subject: Data Request for IH and mortality ancillary study
Date: Fri, 07 Feb 2014 11:57:01 -0500
From: Juliann DiFiore <jmd3@case.edu>
To: Pickett, James <japickett@rti.org>, Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>, Das, Abhik <adas@rti.org>, Gantz, Marie <mgantz@rti.org>, Zaterka-Baxter, Kristin <kzaterka@rti.org>, Walsh, Michele <Michele.Walsh@uhhospitals.org>, rxm6@case.edu <rxm6@case.edu>

RE: IH and mortality ancillary study

After discussions with Michele and Richard regarding the IH and mortality study we feel we need to include additional covariates that may influence IH. Therefore, I am asking for one more amendment to the DUA (and hopefully the last). Would you please add the following:

Early Sepsis (< 72 hrs) and Late Sepsis (>= 72 hrs)
IVH: Any and Severe
NEC- any and medical vs surgical.
Cause of Death.
Thank you,

Julie

--
Juliann Di Fiore
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From: Walsh, Michele
To: Juliann DiFiore; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Abhik " <adas@rti.org>, " Wrage@ndb-mr2.cc.emory.edu
Subject: RE: Data Request for IH and mortality ancillary study
Date: Wednesday, March 12, 2014 11:06:44 AM

Kristin: what is the determination- how can we get the data?

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

From: Juliann DiFiore [mailto:jmd3@case.edu]
Sent: Wednesday, March 12, 2014 10:26 AM
To: Zaterka-Baxter, Kristin; Walsh, Michele
Subject: Re: Data Request for IH and mortality ancillary study

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>
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> Kris
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> **Sent:** Monday, February 17, 2014 12:25 PM
> **To:** Zaterka-Baxter, Kristin
> **Cc:** Walsh, Michele
> **Subject:** Fwd: Data Request for IH and mortality ancillary study
>
> Hi Kristen,

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Julie

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Date: Fri, 07 Feb 2014 11:57:01 -0500
From: Juliann DiFiore <jmd3@case.edu>
To: Pickett, James <japickett@rti.org>, Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>, Das, Abhik <adas@rti.org>, Gantz, Marie <mgantz@rti.org>, Zaterka-Baxter, Kristin <kzaterka@rti.org>, Walsh, Michele <Michele.Walsh@uhhospitals.org>, rxm6@case.edu <rxm6@case.edu>

RE: IH and mortality ancillary study

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IVH: Any and Severe
NEC- any and medical vs surgical.
Cause of Death.
Thank you,
Julie

--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
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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

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Raju, Tonse (NIH/NICHD) [E]
Subject: Fwd: Sharyl Attkisson resigns from CBS News - POLITICO.com
Date: Tuesday, March 11, 2014 4:00:30 PM

FYI

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

From: "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>
Date: March 11, 2014 at 3:02:07 PM EDT
To: "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov>, "Rogers, Christine (NIH/NICHD) [E]" <Christine.Rogers@nih.gov>
Cc: "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov>, "Glavin, Sarah (NIH/NICHD) [E]" <glavins@mail.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Subject: RE: Sharyl Attkisson resigns from CBS News - POLITICO.com

I am fully supportive of her career decision.

Thanks! Alan

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Tuesday, March 11, 2014 2:58 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Rogers, Christine (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Sharyl Attkisson resigns from CBS News - POLITICO.com

Not sure what this means for the SUPPORT story she was working on – but I'm inclined to think this is a good thing. Kerri

---

From: Myles, Renate (NIH/OD) [E]
Sent: Tuesday, March 11, 2014 2:51 PM
To: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: Sharyl Attkisson resigns from CBS News - POLITICO.com

Have you heard? Although I hear Fox News is wooing her.
http://www.politico.com/blogs/media/2014/03/sharyl-attkisson-to-leave-cbs-news-184836.html?ml=m_po

Blansfield, Earl (NIH/NICHD) [E]

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 8:22 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Thanks for including me – looks like it is figured out

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:34 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Got it, thanks!

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:34 PM
To: Kaeser, Lisa (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

(b)(5)

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
31 Center Drive
Building 31, Room 2A03
Bethesda, MD 20892-2425

Phone: 301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:28 PM

To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

R and I spoke earlier – we would like to recommend (b)(5)

(b)(5)

But what do you think?

Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:25 PM
To: Kaeser, Lisa (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

"However, OHRP did 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)(2): A description of any reasonably foreseeable risks and discomforts." is certainly not (b)(5)

Alan

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 4:06 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Hi all – we've been asked for clearance for the Secretary's response to the most recent Carome letter. In my opinion, (b)(5)

(b)(5) We tried to revise last time, without much success.

What do you all think? Due Friday.

Thanks,

Lisa

Lisa Kaeser, J.D.

Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Ott, Sandra (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 3:30 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Note from Exec Sec:

OS Clearance (please clear by 3:00 p.m., Friday, March 7, 2014).

Hello,

Please clear the Draft letters from the Secretary regarding the " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" located in the Draft Response folder, entitled, "Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14." The Incoming or Source Document is also located in the Draft Response folder. Please provide all comments by 3:00 p.m., Friday, March 7, 2014.

Note: NICHD, OER, and OSP are being asked to please clear.

Thank you:)
Monica Dozier

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
Sent: Wednesday, March 05, 2014 2:54 PM
To: Brown, Crystal (NIH/NICHD) [C]; EDRMS_NO_REPLY (NIH/OD); EDRMS_NO_REPLY (NIH/OD); Ott, Sandra (NIH/NICHD) [E]; EDRMS_NO_REPLY (NIH/OD); Wood, Vandora (NIH/CIT) [C]
Subject: WF 328659 - Preview Clearance Status (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

You have received a task notification requiring your attention.

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Task

Please do not reply to this email, this is an automated message.

If you have concerns please contact the NIH Help Desk at (301) 496-4357.

Work Folder Information
Work Folder: WF 328659

Process: IC Clearance WF 328659
Due Date: March 07, 2014
Program Analyst: Dozier, Monica (NIH/OD) [E]
WF Subject: "The Surfactant Positive Airway Pressure and Pulse Oximertry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial -Inadequate Safety Monitoring." This is a "Follow-up letter from the Public Citizen's Health Research group regarding the NIH-funded SUPPORT study involving extremely premature infants."
IC:NICHD
From: Wolfe, Sidney;Carome, Michael;
To: Sebelius, Kathleen;
Remarks: OS Clearance (please clear by 3:00 p.m., Friday, March 7, 2014). Hello, Please clear the Draft letters from the Secretary regarding the " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" located in the Draft Response folder, entitled, "Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14." The Incoming or Source Document is also located in the Draft Response folder. Please provide all comments by 3:00 p.m., Friday, March 7, 2014. Note: NICHD, OER, and OSP are being asked to please clear. Thank you:)

From: Kaeser, Lisa (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study
Date: Wednesday, March 05, 2014 4:05:34 PM
Attachments: 328659 - Draft Response - Source Document.pdf
328659 - Draft Response - Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14.pdf

Hi all – we've been asked for clearance for the Secretary's response to the most recent Carome letter. In my opinion,(b)(5)

(b)(5)

What do you all think? Due Friday.

Thanks,

Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Ott, Sandra (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 3:30 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Note from Exec Sec:

OS Clearance (please clear by 3:00 p.m., Friday, March 7, 2014).

Hello,

Please clear the Draft letters from the Secretary regarding the " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" located in the Draft Response folder, entitled, "Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14." The Incoming or Source Document is also located in the Draft Response folder. Please provide all comments by 3:00 p.m., Friday, March 7, 2014.

Note: NICHD, OER, and OSP are being asked to please clear.

Thank you:)
Monica Dozier

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
Sent: Wednesday, March 05, 2014 2:54 PM

To: Brown, Crystal (NIH/NICHD) [C]; EDRMS_NO_REPLY (NIH/OD); EDRMS_NO_REPLY (NIH/OD); Ott, Sandra (NIH/NICHD) [E]; EDRMS_NO_REPLY (NIH/OD); Wood, Vandora (NIH/CIT) [C]
Subject: WF 328659 - Preview Clearance Status (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

You have received a task notification requiring your attention.

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Task

Please do not reply to this email, this is an automated message.

If you have concerns please contact the NIH Help Desk at (301) 496-4357.

Work Folder Information
Work Folder: WF 328659
Process: IC Clearance WF 328659
Due Date: March 07, 2014
Program Analyst: Dozier, Monica (NIH/OD) [E]
WF Subject: "The Surfactant Positive Airway Pressure and Pulse Oximertry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial -Inadequate Safety Monitoring." This is a "Follow-up letter from the Public Citizen's Health Research group regarding the NIH-funded SUPPORT study involving extremely premature infants."
IC: NICHD
From: Wolfe, Sidney;Carome, Michael;
To: Sebelius, Kathleen;
Remarks: OS Clearance (please clear by 3:00 p.m., Friday, March 7, 2014). Hello, Please clear the Draft letters from the Secretary regarding the " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" located in the Draft Response folder, entitled, "Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14." The Incoming or Source Document is also located in the Draft Response folder. Please provide all comments by 3:00 p.m., Friday, March 7, 2014. Note: NICHD, OER, and OSP are being asked to please clear. Thank you:)

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Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0664 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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2014 FEB 3 PM 4 43

January 27, 2014

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

RE: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial – Inadequate Safety Monitoring

Dear Secretary Sebelius:

We are writing in follow-up to Public Citizen's April 10, 2013, letter and May 8, 2013, report regarding the SUPPORT study funded by the National Institutes of Health (NIH) and conducted by approximately two dozen academic medical institutions of the Neonatal Research Network.[1,2] That letter and report highlighted important and material factual omissions regarding the purpose, nature, and risks of the research in the consent forms approved by the institutional review boards (IRBs) and signed by parents of infants enrolled in the SUPPORT study, and also brought to light deficiencies in the study design that resulted in a failure to ensure that risks to subjects were minimized.

To date, the Department of Health and Human Services' (HHS's) response to the serious ethical lapses in the conduct of the SUPPORT study has been unsatisfactory. Rather than taking substantive steps to remedy these ethical lapses, HHS bowed to pressure from NIH and an academic research establishment dependent on NIH for support and stifled appropriate compliance oversight enforcement action by the Office for Human Research Protections (OHRP).

We write to you now to highlight the following additional important issues related to the SUPPORT study that have come to our attention and also have not been adequately addressed by HHS:

(1) The SUPPORT study protocol appears to have lacked a safety monitoring plan for *separately* monitoring for differences in severe retinopathy of prematurity (ROP) between the two experimental oxygen study groups. If such a plan had been

[1] Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. April 10, 2013. http://www.citizen.org/documents/2111.pdf. Accessed January 20, 2014.
[2] Carome M, Wolfe S, Macklin R. Analysis of the complete protocol and consent form for the SUPPORT study: Lack of informed consent and a failure to ensure that risks were minimized. May 8, 2013. http://www.citizen.org/documents/2124.pdf. Accessed January 20, 2014.

implemented, the study likely would have been terminated early, sparing some extremely premature infants enrolled in the study from suffering severe ROP or death.

(2) In spite of evidence we presented previously,[3] the SUPPORT study investigators — in an attempt to defend the adequacy of their study consent forms — have continued to repeatedly assert that they all had no expectation that the low-oxygen group subjects would have a higher mortality rate than the high-oxygen group subjects and indeed were surprised when the final study results revealed such an outcome. We provide below additional clear evidence that before the study began, there was an awareness among at least some of the investigators — including among the lead investigators who developed the study protocol — that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study. Moreover, as neonatology experts, the SUPPORT study investigators had an ethical obligation to thoroughly research the literature, to understand areas of ongoing uncertainty regarding oxygen management, and to be aware of all plausible study risks. To not have known that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study would have constituted reckless ignorance.

(3) The SUPPORT study was one of five concurrently planned, coordinated, and conducted studies around the world using nearly identical study designs for testing low- versus high-oxygen interventions in extremely premature infants. To minimize risks to subjects across all five studies, the protocols should have specified a mechanism for joint safety monitoring. Ideally, there should have been a formal data and safety monitoring plan involving interim analyses of pooled data from all five studies combined. At a minimum, there should have been a plan for informally sharing any troubling safety signal arising in one study with the investigators and data monitoring committees for the other studies. No such formal or informal plan was described in the SUPPORT protocol. Of note, the members of the data monitoring committee for at least one of the five studies recognized early on the need to see interim data from the other four parallel studies to ensure the safety of subjects across all trials, but their attempts to obtain data from the other studies were either ignored or rebuffed.

We describe below each of these issues in detail and conclude by asking key questions for which the parents of SUPPORT study subjects and the public deserve clear answers from HHS.

A. Background

As you are aware, the SUPPORT study involved two simultaneous complex experiments. In one experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing (ventilation of the lungs) following delivery.[4]

For the other experiment (the oxygen experiment), babies assigned to each of the two ventilation groups were further randomly divided between a low-oxygen group and a high-oxygen group.[5]

---

[3] *Ibid.*

[4] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely premature infants. *N Engl J Med.* 2010;362(21):1970-1979.

For the low-oxygen group, the SUPPORT study investigators tried to maintain the babies' blood oxygen levels in a low target range (oxygen saturation level of 85 to 89 percent), and for the high-oxygen group in a high target range (oxygen saturation level of 91 to 95 percent), regardless of the infants' clinical status.

The primary efficacy outcome measure for the oxygen experiment was a combination of severe retinopathy of prematurity (ROP, which can lead to visual impairment and blindness and often requires surgery to preserve vision), death before discharge from the hospital, or both.

For both experimental oxygen groups, oxygen monitors relied upon by the medical teams caring for the infants in the study displayed either intentionally falsely high (low-oxygen group) or intentionally falsely low (high-oxygen group) values when the infants' actual oxygen saturation levels were between 85 and 95 percent.

Premature infants enrolled in the SUPPORT study were not given the same care with respect to oxygen management that otherwise similar infants would have received at the same participating hospitals. In particular, oxygen management of enrolled infants lacked the following features of usual care:

(1) fully functional, properly operating pulse oximeters that displayed accurate oxygen saturations for use by health care providers to guide care;

(2) access to the entire range of target oxygen saturations endorsed in guidelines (85 to 95 percent) for management of premature infants, including the possibility of employing the center of this range (88 to 92 percent); and

(3) adjustment of supplemental oxygen and oxygen saturation targets based on an assessment of risks and benefits for each infant's particular characteristics. Some of the clinical factors that are often considered in individualizing oxygen management include level of prematurity; capillary refill time (a simple physical exam test to assess the adequacy of tissue perfusion); cardiopulmonary, hepatic, and renal function; hematocrit; intravascular volume; acid-base status; oxygen requirements in the toxic range; and clinical signs suggestive of impending necrotizing enterocolitis.

For the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. The low-oxygen intervention presented the foreseeable risks of neurologic injury and death.

In contrast, for the high-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 91 to 95 percent using oxygen monitors that displayed falsely *low* readings predictably caused, on average, higher levels of oxygen exposure than

[5] 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.

would have occurred under usual care using accurately reading oxygen monitors. The high-oxygen intervention presented the foreseeable risk of severe ROP.

B. Inadequate safety monitoring plan: Apparent failure to monitor for severe ROP as a separate adverse event and to terminate the study early because of harm to subjects in the high-oxygen group

Minimization of risks to research subjects requires adequate safety monitoring. Both death and severe ROP comprised the primary risks of the SUPPORT study's oxygen experiment, and each should have been monitored *separately as adverse events* during the conduct of the trial in order to minimize risks to subjects. If separate monitoring of both had been implemented, the study likely would have been terminated early, sparing some extremely premature infants enrolled in the study from suffering severe ROP or death.

However, as reflected in the following excerpts from the data and safety monitoring plan in the SUPPORT study protocol, it appears that unlike death, severe ROP was not monitored *separately as an adverse event* during the course of the trial. Instead, severe ROP apparently was monitored only in combination with death as a component of the composite primary efficacy endpoint, and the study was not terminated early. The protocol stated:[6]

> **4.4 Adverse Events**
>
> Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:
>
> 1. Air leak on admission to the NICU, or during the initial 14 days of life
> 2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
> 3. The occurrence of severe IVH (Grades 3-4, Papile)
> 4. Death
>
> These outcomes will be evaluated on a monthly basis by RTI [Research Triangle Institute], and if the incidence of any of these outcomes is determined to be 5% -10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.
>
> **4.5 Data Safety Monitoring Committee**
>
> The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome

[6] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

Monitoring of the *composite* primary efficacy endpoint of severe ROP or death before discharge during the conduct of the SUPPORT study as designed was not sufficient for monitoring safety related to the occurrence of severe ROP because of the following factors:

(1) The SUPPORT study's oxygen experiment involved only two experimental groups (the low-oxygen group and the high-oxygen group) and no usual care (or current-practice) control group; and

(2) The two components of the composite primary efficacy endpoint — death and severe ROP — were countervailing, but asymmetric, potential harms:

(a) For the high-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 91 to 95 percent using oxygen monitors that displayed falsely low readings predictably caused, on average, higher levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. As a result, the research procedures for these subjects presented a reasonably foreseeable increased risk of suffering severe ROP (a risk that was not described in 20 of 22 IRB-approved SUPPORT study consent forms as required by HHS human subjects protection regulations at 45 CFR 46.116(a)(2)).[7]

(b) For the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. As a result, the research procedures for these subjects presented a reasonably foreseeable risk of death (a risk that was not disclosed in any of 22 IRB-approved SUPPORT study consent forms).

Adequate safety monitoring of the study as designed would have required periodic checking for differences between the low-oxygen and high-oxygen groups for *both* death and retinopathy *separately*. The importance of such separate comparisons was reflected in the way the results were presented in the published paper describing the primary results of the study (see Table 1 below).[8]

[7] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed January 20, 2014.

[8] 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.

Table 1: Key Major Outcomes from SUPPORT Study

Outcome	Low-Oxygen Group *no./total no.(%)*	High-Oxygen Group *no./total no.(%)*	Adjusted Relative Risk (95% Confidence Interval)	P-value
Primary efficacy outcome: severe ROP or death before discharge	171/605 (28.3%)	198/616 (32.1%)	0.90 (0.76-1.06)	0.20
Severe ROP	41/475 (8.6%)	91/509 (17.9%)	0.52 (0.37-0.73)	<0.001
Death before discharge	130/654 (19.9%)	107/662 (16.2%)	1.27 (1.01-1.60)	0.04

Because severe ROP often requires surgery and can lead to blindness, it represented a clear potential harm to the high-oxygen group infants of significant-enough degree to require separate safety monitoring, as was done for death. Yet the protocol's data and safety monitoring plan did not indicate that it was separately monitored. Indeed, the problem of ROP in premature infants was considered such a serious health problem in premature infants that NIH spent more than $20 million on the SUPPORT study to find out whether using the low-oxygen intervention would reduce the incidence of this important adverse outcome in comparison to the high-oxygen intervention without causing an increase in mortality or brain injury.

In what obviously came as no surprise to the SUPPORT study investigators and was not an unexpected finding, the study results, after SUPPORT was concluded, demonstrated that the high-oxygen group babies had a highly significant increase in retinopathy in comparison to the low-oxygen group babies (17.9 percent versus 8.6 percent, respectively; $p<0.001$).[9]

If the incidence of severe ROP had been monitored separately as an important adverse event in the high-oxygen group at increased risk for this adverse outcome and compared to the incidence in the low-oxygen group, the trial conceivably could have been stopped early, thus preventing the occurrence of retinopathy and avoiding retinal surgery in many high-oxygen group infants.

To estimate the approximate point at which one of the planned interim analyses of study data would have demonstrated a statistically significant difference in the rate of severe ROP between the high- and low-oxygen groups, we performed a series of hypothetical interim analyses using the chi-square test based on enrollments of 25, 50, and 75 percent of the actual final enrollment (i.e., 1,316 infants). Because interim data were not available to us for these analyses, we assumed that the following factors remained constant throughout the study: the incidence of severe ROP, the proportion of high- and low-oxygen group subjects, and the proportion of subjects in each group who survived to the time of discharge and had a determination made regarding whether severe ROP had developed.

[9] *Ibid.*

The contingency tables below (Tables 2-4) summarize our analysis. Following each table is the chi-square statistic without Yates correction and two-tailed P-value (uncorrected for multiple looks):

Table 2: 25 Percent of Final Enrollment*Group	No Severe ROP	Severe ROP	Total
High-Oxygen	104	23	127
Low-Oxygen	109	10	119
Total	213	33	246

*Assumes 329 subjects enrolled and 246 survived to discharge and had retinopathy status determined
χ^2=4.984; P=0.0256

Table 3: 50 Percent of Final Enrollment*

Group	No Severe ROP	Severe ROP	Total
High-Oxygen	209	45	254
Low-Oxygen	217	21	238
Total	426	66	492

*Assumes 658 subjects enrolled and 492 survived to discharge and had retinopathy status determined
χ^2=8.366; P=0.0038

Table 4: 75 Percent of Final Enrollment*

Group	No Severe ROP	Severe ROP	Total
High-Oxygen	314	68	382
Low-Oxygen	325	31	356
Total	639	99	738

*Assumes 987 subjects enrolled and 738 survived to discharge and had retinopathy status determined
χ^2=13.118; P=0.0003

Based on the above analyses, with respect to the harmful outcome of severe ROP, a statistically significant greater incidence of harm in the high-oxygen group might have been detected after reaching just 25 percent of target subject enrollment, and almost certainly would have been detected after reaching 50 percent of target enrollment. Early termination of the study following enrollment of either one-quarter or one-half of the projected final target enrollment likely would have spared some of the subsequently enrolled infants randomized to the high-oxygen group from developing severe ROP that resulted from receiving a higher level of oxygen exposure than they would have otherwise received if they had not been enrolled in the study. We are not able to reliably estimate the number of children who would have been spared severe ROP had the study been terminated early because the study lacked a current-practice control group.

It is important to recognize that the inclusion of a plan to separately monitor for severe ROP as an important adverse outcome during the conduct of the study would not have been sufficient to

address the other fundamental flaw in the SUPPORT study design — the lack of a usual-care control group. By experimentally increasing oxygen exposure in one study group relative to current practice and lowering it in the other, the harms resulting from each experimental intervention *relative to current practice* could not be monitored for or determined, and therefore, risks to subjects were not minimized.

The SUPPORT study investigators may argue that separately monitoring for severe ROP as an adverse event could have led to premature termination of the study and prevented the detection of the higher mortality rate that was seen in the low-oxygen group, which in turn could have led to a dangerous recommendation to routinely target oxygen saturation levels at 85 to 89 percent in all extremely premature infants. (Indeed, as discussed in the next section of our letter, this thought process may explain why separate monitoring for severe ROP did not occur.) However, if the study had been stopped early based on an interim analysis showing a statistically significant higher incidence of severe ROP in the high-oxygen group, without a usual-care control group there would have been no sound basis for concluding that the lower-oxygen intervention was better than usual care. The higher incidence of severe ROP in the low-oxygen group may have been due to oxygen exposure being experimentally raised in the high-oxygen group (relative to usual care), experimentally lowered in the low oxygen group (relative to usual care), or both. The study results were ultimately uninformative in this regard given the lack of a usual-care control group. In addition, interim analyses may have revealed a non-statistically significant higher death rate in the low-oxygen group compared to the high-oxygen group, which should have precluded anyone from making recommendations to modify current practice to routinely using the lower oxygen saturation target in the clinical care of extremely premature infants.

All of these problems could have been avoided with an alternative study design that employed a usual-care control group and low-oxygen experimental group. Such a design could have informed the medical community whether oxygen could be safely lowered to prevent severe ROP without increasing the mortality rate. Moreover, because experimentally lowering oxygen was unlikely to increase the incidence of severe ROP and blindness relative to current practice, it would not have been necessary to monitor this outcome as a separate adverse event.

C. The higher mortality rate in low-oxygen group infants: *Not* a surprising finding

As noted above, for the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors.

Over the past several months, in an awkward attempt to explain why death was not identified as a risk of the research in the SUPPORT study consent forms, the study investigators have repeatedly asserted that they all had no expectation that the low-oxygen group subjects would have a higher mortality rate than the high-oxygen group subjects, and indeed some investigators

have indicated that they were surprised when the final study results revealed such an outcome.[10,11,12,13]

In contrast, the investigators in recent months have not asserted that they were surprised to find a higher rate of severe ROP in the high-oxygen group than in the low-oxygen group, and as previously noted, such a finding undoubtedly was not a surprise.

All physicians understand the well-established pathophysiologic relationship in which increasing degrees of hypoxemia result in progressively higher mortality rates. At the time of the SUPPORT study, all neonatologists knew that increasing the degree of hypoxemia in premature infants *at some point* would increase the infants' mortality rate. The exact shape of the curve for the relationship between the degree of hypoxemia and mortality and the exact threshold of oxygen exposure below which mortality will start to increase in premature infants were not known at the time the SUPPORT study was conducted and remain unknown today.

The SUPPORT study investigators may have believed that targeting oxygen saturations at 85 to 89 percent in extremely premature infants was unlikely to cross below the oxygen exposure threshold that would increase the mortality rate. However, they did not know for certain that this was the case, and the available data from the medical literature cited by the investigators in their protocol were clearly insufficient to prove that maintaining oxygen saturations at 85 to 89 percent would *not* have an adverse impact on the mortality rate of extremely premature infants. Indeed, assessing whether the lower oxygen saturation target could decrease the incidence of severe ROP in severely premature infants without increasing mortality was one of the major reasons for conducting the study.

As neonatology experts, the SUPPORT study investigators had an ethical obligation to thoroughly research the literature, to understand areas of ongoing uncertainty regarding oxygen management, and to be aware of all plausible study risks. To not have known that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study would have constituted reckless ignorance.

Investigators in New Zealand undertaking a similarly designed study (discussed below) understood that regardless of their expectations about the study outcome, it was appropriate to

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[10] Transcript for the Diane Rehm Show from WAMU and National Public Radio: Clinical trials and premature babies. April 17, 2013. http://thedianerehmshow.org/shows/2013-04-17/clinical-trials-and-premature-babies/transcript. Accessed January 20, 2014. (SUPPORT study investigator Dr. Edward Bell stated, "As a matter of fact, there was no reason for us to suspect that there would be a difference in mortality, and that was a surprising finding.")

[11] Finer NN, Bell EF, Van Meurs K. Consent forms in a clinical trial of premature babies (letter to the editor). *The New York Times*. April 18, 2013. http://www.nytimes.com/2013/04/19/opinion/consent-forms-in-a-clinical-trial-of-premature-babies.html. Accessed January 20, 2014. ("When the study was planned, the best evidence showed that lower oxygen targets — even lower than used in the study — resulted in less eye disease without a higher death rate. The finding of a higher death rate in one study group was not anticipated.")

[12] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med*. 2013;368(20):1949-1950. ("Death was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected.")

[13] D'Angio C, Finer N, Newman N, et al. Misconceptions about the SUPPORT trial. Posted September 10, 2013. http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2013-0004-0067. Accessed January 20, 2014.

explain to subjects' parents in the consent forms the well-known and previously established separate risks of death from lowering oxygen exposure, as well as ROP from raising oxygen exposure, for premature infants enrolled in the study. It is unclear why the SUPPORT study investigators in the U.S. would have lacked such an understanding.

Although the SUPPORT study investigators undoubtedly were *hopeful* at the onset of the study that the low-oxygen intervention would result in a decreased incidence in severe ROP without a concomitant increase in mortality, there is clear evidence that before initiating the study at least some of them were aware that a higher mortality rate in the low-oxygen group relative to the high-oxygen group could have been one plausible finding of their study. In particular, the SUPPORT study investigators cited in their protocol a 2003 paper by Cole et al, published in the journal *Pediatrics,* discussing the planning and design of studies comparing the low- and high-oxygen interventions that were to be used in their study[14] (see reference 55 in the SUPPORT study protocol[15]). The authors of this paper were members of the Pulse Oximetry Saturation Trial for Prevention of Retinopathy of Prematurity (POST ROP) Planning Study Group.

The POST ROP study was to be a multicenter, multinational prospective trial to evaluate different levels of oxygen in premature babies. It is our understanding that the POST ROP study comprised the Benefits of Oxygen Saturation Targeting (BOOST) II studies in the United Kingdom (UK), Australia, and New Zealand, and the Canadian-funded Canadian Oxygen Trial (COT). The SUPPORT study protocol made reference to this study as follows: "The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial…"

Of note, Dr. Waldemar Carlo at the University of Alabama at Birmingham — who was one of the lead investigators for the SUPPORT study and was on the Neonatal Research Network working group that developed and wrote the SUPPORT study protocol — was a member of the POST ROP Planning Study Group. The acknowledgements section at the end of the Cole et al paper states that Dr. Carlo was among the POST ROP Planning Study Group members who reviewed and critiqued the paper.[16]

The 2003 Cole et al paper makes clear that when the SUPPORT study and the parallel POST ROP studies were being designed, there were real concerns among neonatologists that the low-oxygen intervention could expose extremely premature infants to an increased risk of death or neurologic injury. In particular, the paper emphasized that large numbers of patients would have to be studied to address concerns about mortality risk with the low oxygen dose, noting the following:[17]

---

[14] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[15] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

[16] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[17] *Ibid.*

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

Emphasizing the need for a data and safety monitoring committee and plan for the POST ROP studies, the 2003 *Pediatrics* paper stated the following:[18]

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

Further indication of the serious concern among some neonatologists that the low-oxygen intervention could expose extremely premature infants to an increased risk of death or neurologic injury was provided in the 2005 version of the consent form used in the New Zealand BOOST II study discussed above, which included the following:[19]

> Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . The aim of this study is to determine, within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%), **whether targeting the lower end of this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision**

[18] *Ibid.*

[19] Lantos JD. OHRP and Public Citizen are wrong about neonatal research on oxygen therapy research. The Hastings Center Bioethics Forum. Posted April 18, 2013. http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blog+140. Accessed January 20, 2014. Cited as "BOOST-NZ consent form, July 2005, personal communication from Brian Darlow, principal investigator of BOOST-NZ."

> **(ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability**. [Emphasis added]

Finally, members of the data monitoring committee for the BOOST II UK study noted the following in a recent commentary article discussing the four POST-ROP studies and the SUPPORT study: [20]

> Evidence from controlled trials had shown that if the oxygen levels are relatively high there is an increased risk of the infant developing the blinding condition retinopathy of prematurity. On the other hand, observational data had suggested that keeping levels of arterial oxygen relatively low might result in increased mortality, and neurological handicap among long term survivors.
>
> During the past decade, five similar trials - in the USA, New Zealand, Canada, Australia and the UK - **were organized more or less concurrently to investigate this therapeutic dilemma.** Although they were separately organized and funded, all of them compared different oxygen tension targeting strategies intended to minimize both mortality and serious morbidity. **It was recognized at the outset that none of the five trials, individually, would have the statistical power to provide a reliable estimate of survival without serious morbidity 18 to 24 months after birth.** Indeed, two of these trials were only funded on the understanding that the data from several similar trials would be combined. [Emphasis added]

All of the above statements could not be clearer. At least some of the expert neonatologists involved in the design of the SUPPORT study and parallel studies to be conducted in other countries were well aware when designing these studies that there were real concerns within the neonatology community that the low-oxygen intervention to be used in these studies might increase the risk of death.

In view of the commentary paper authored by members of the POST ROP Planning Study Group and cited by the SUPPORT study investigators in their own protocol, it is remarkably disingenuous of the SUPPORT study investigators to now assert that because some of them were surprised to find a higher mortality rate in the low-oxygen group subjects in their study, it was not necessary to inform parents about the reasonably foreseeable risk of death for subjects assigned to the low-oxygen group. Such a finding was one reasonably foreseeable and highly plausible outcome. This undoubtedly is one of the reasons why, as noted above, death was to be monitored according to the SUPPORT study protocol and was a component of the primary outcome being studied.

The investigators certainly had hoped for a different result and perhaps had reason to be disappointed when they found the significantly higher mortality rate in the low-oxygen group, but they could not genuinely have been shocked by the fact that when they lowered oxygen exposure, the mortality rate increased in premature infants in the study. Indeed, none of the

[20] Chalmers I, Altman DG, McHaffie H, et al. Data sharing among data monitoring committees and responsibilities to patients and science. *Trials.* 2013;14:102. http://www.trialsjournal.com/content/14/1/102. Accessed January 20, 2014.

investigators at any point in discussing the results of the SUPPORT study have proposed an alternative hypothesis to explain the higher mortality rate in the low-oxygen group compared to the high-oxygen group. They implicitly recognize that the well-established pathophysiologic relationship in which decreasing oxygen exposure results in increasing hypoxemia and mortality is undoubtedly the explanation for their study findings, whether unexpected by some of the investigators or not.

Finally, we strongly suspect that the apparent failure to monitor separately for severe ROP and to have stopping criteria based on finding a difference in the incidence of severe ROP between the high- and low-oxygen groups at the time of any planned interim analyses was due to concern among the investigators that stopping the oxygen experiment early based on a statistically significant difference in ROP between groups could have resulted in a failure to detect a difference in the mortality rate between the two study groups.

D. Failure to minimize risks to subjects by not having a data and safety monitoring plan involving interim analyses of pooled data from the SUPPORT study and the four concurrent POST ROP studies

As noted above, the SUPPORT study and the four POST ROP studies were five parallel studies concurrently planned and conducted around the world using nearly identical study designs comparing high- and low-oxygen interventions in extremely premature infants. The planning and designing of these studies were coordinated,[21,22] and the investigators for each study obviously were aware of the other studies.

To minimize risks to subjects across all five studies, the protocols should have specified a mechanism for joint safety monitoring. Ideally, there should have been a formal data and safety monitoring plan involving interim analyses of pooled data from all five studies combined. At a minimum, there should have been a plan for informally sharing any troubling safety signal arising in one study with the investigators and data monitoring committees for the other studies. No such formal or informal plan was described in the SUPPORT protocol. Instead, monitoring of data and safety was conducted independently and separately across these studies. Not having pooled monitoring across all five studies, even in some informal manner, represents a troubling failure to ensure the protection of human subjects.

Disturbingly, members of the data monitoring committee for the BOOST II UK study recognized the importance of seeing interim data from the other four parallel studies, but their attempts to obtain data from the other studies, which began as early as 2006, apparently were ignored or rebuffed by the data monitoring committees for the other four parallel studies.[23] For example,

[21] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[22] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

[23] Chalmers I, Altman DG, McHaffie H, et al. Data sharing among data monitoring committees and responsibilities to patients and science. *Trials.* 2013;14:102. http://www.trialsjournal.com/content/14/1/102. Accessed January 20, 2014.

they noted the following in a recent commentary article discussing the four POST-ROP studies and the SUPPORT study:

> Accordingly, because data from the other four trials were of obvious relevance to our responsibility, the chair of our DMC wrote to the DMC chairs of the other trials in 2006, expressing the **'hope that we can help each other fulfil our respective commitments to the babies being treated in these trials'** (Emails sent 11 and 15 July 2006).
>
> **No response was received from the other DMC chairs for several years**; but consideration of the proposal became urgent when, more than three years later, in 2009, the management group of the US trial sent results, in advance of publication, to those associated with the trials that were still recruiting.

E. Conclusions and requested actions

For each of the three critical issues described above, parents of subjects enrolled in the SUPPORT study, as well as the public, deserve clear answers to the following questions:

(1) With respect to monitoring separately for difference in the incidence of severe ROP between groups:

(a) Was ROP monitored separately during the course of the trial as an important adverse event? If not, why not?

(b) If ROP was monitored separately during the course of the trial, at the time of any of the planned interim analyses, did the difference in the incidence of severe ROP between the low- and high-oxygen groups reach statistical significance? If so, when did this occur, and why wasn't the study terminated at that point?

(c) Did OHRP consider the lack of appropriate safety monitoring during the SUPPORT study and the lack of a usual-care control group when it evaluated adequacy of the SUPPORT study design?

(d) Since the SUPPORT study investigators must have recognized that the incidence of severe ROP was likely to be higher in the high-oxygen group and have voiced no surprise in finding this result, does HHS agree or disagree with OHRP's finding that the IRB-approved consent forms failed to comply with HHS regulations under 45 C.F.R. 46.116(a)(2) by not disclosing severe ROP as a risk of the research?

(2) With respect to the investigators' statements about being surprised to find a higher mortality rate in the low-oxygen group: Since the SUPPORT study investigators either knew or should have known prior to initiating the study that an increased death rate in the low-oxygen group was a foreseeably plausible outcome of the SUPPORT study, does HHS agree or disagree with OHRP's finding that the IRB-approved consent forms failed to comply with HHS regulations under 45 C.F.R. 46.116(a)(2) by not disclosing death as a risk of the research?

(3) With respect to the failure to establish a plan to monitor data pooled across the SUPPORT study and the four POST ROP studies:

(a) Why didn't the SUPPORT study protocol include a plan for joint safety monitoring with the POST ROP studies, either formally, via pooled interim analyses across all five studies, or informally, by sharing any troubling safety signals arising in one study with the investigators and data monitoring committees for the other studies?

(b) Were the SUPPORT study investigators or NIH officials aware of the BOOST II UK data monitoring committee's requests for SUPPORT study data for the purposes of pooled interim analysis? If so, what was their response to those requests? Why were the requests not granted?

We urge HHS to provide prompt answers to these important questions. We also request an opportunity to meet with you or your representative to discuss these important issues, which have critically important implications for the safety and welfare of premature infants participating in ongoing clinical trials funded by HHS.

In closing, we renew our April 10, 2013, request that you issue a formal apology 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. Such an apology is the most critical step for redressing the ethical lapses that occurred during the conduct of this study.

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

Sincerely,

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

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

cc: The Honorable Bill Corr, Deputy Secretary, HHS
The Honorable Howard K. Koh, Assistant Secretary for Health, HHS
Dr. Francis Collins, Director, NIH

Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borror, Director, Division of Compliance Oversight, OHRP

From: Juliann DiFiore
To: Gantz, Marie
Cc: Walsh, Michele; richard.martin@uhhospitals.org; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: interpolation procedures
Date: Tuesday, March 04, 2014 4:47:25 PM

Hi Marie,

I have a few questions about the quadratic and cubic spline interpolation procedures for smoothing the SpO2 histogram.

1. The latest documentation I have from you (4/13/14) states that you are using quadratic interpolation unless you get negative values. In those cases the quadratic interpolation model will be replaced by cubic hermite interpolation. Is that still the current plan? I have yet to analyze how much of a difference I will get in daily mean/median values using both vs cubic alone but I am trying to be consistent with the SUPPORT analyses.

2. I inserted your SAS code into my Matlab routines – currently only for the low target group. I thought the code lines pertaining to overshoot and monotonicity would totally eliminate the negative values from the quadratic interpolation model. I have found that the cubic spline reduced the negative values by ~75% but, in some cases, I am still getting negative values, predominantly at 94% (sometimes at both 94/95%). Since I basically cut the source code from your SAS documentation with a few syntax modifications for Matlab, I was wondering if you saw a similar result? If not I must have a glitch in the code that I haven't found yet.

I would appreciate your thoughts.

Take Care,

Julie

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

otherwise permitted.

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: SUPPORT related paper
Date: Friday, February 28, 2014 5:37:52 PM

Thanks Rose --appreciate all your help this week

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, February 28, 2014 3:28 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: SUPPORT related paper

Hi

The attached paper was just accepted by the Journal of Pediatrics. I don't have a publication date as of yet. I don't think we need a press release, but may want some talking points if asked.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: hirschfs@mail.nih.gov
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Results
Date: Friday, February 28, 2014 3:42:33 PM

Hi
Steven – see below – the SUPPORT results need to be posted before we can change the record – any time frame for us??
Thanks
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Crawford, Meg [mailto:mcrawford@rti.org]
Sent: Friday, February 28, 2014 3:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT Results

Thanks for the update. That will be the final step before I can move all records to RTI's account.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 28, 2014 3:36 PM
To: Crawford, Meg; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT Results

I asked Steven about this when I saw him at a meeting last week – he was still looking into it and told me he needed to meet with someone at clinicaltrials.gov

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
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Sent: Friday, February 28, 2014 3:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT Results

Hi Rose and Steph,

These results are still not posted.

Thanks,
Meg

Meg Crawford, CCRP
RTI International
701 13th St. NW, Ste. 750
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tel: 202-974-7837
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: hirschfs@mail.nih.gov
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Results
Date: Friday, February 28, 2014 3:36:13 PM

HI
Any follow up on the SUPPORT results being posted in clincaltrials.gov?
Thanks
Rose

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To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: SUPPORT related paper
Date: Friday, February 28, 2014 3:27:47 PM
Attachments: NIHMS571602-Breathing Outcomes.pdf

Hi
The attached paper was just accepted by the Journal of Pediatrics. I don't have a publication date as of yet. I don't think we need a press release, but may want some talking points if asked.

Thanks
Rose

Manuscript Information

Journal name:	The Journal of pediatrics
NIHMS ID:	NIHMS571602
Manuscript Title:	Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial
Principal Investigator:	
Submitter:	Author support, Elsevier (ElsevierNIHsupport@elsevier.com)

Manuscript Files

Type	Fig/Table #	Filename	Size	Uploaded
manuscript		YMPD_6740.pdf	339144	2014-02-28 07:04:47
citation		571602_cit.cit	165	2014-02-28 07:04:47

Title: Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial

Authors: Timothy P. Stevens, Neil N. Finer, Waldemar A. Carlo, Peter G. Szilagyi, Dale L. Phelps, Michele C. Walsh, Marie G. Gantz, Abbot R. Laptook, Bradley A. Yoder, Roger G. Faix, Jamie E. Newman, Abhik Das, Barbara T. Do, Kurt Schibler, Wade Rich, Nancy S. Newman, Richard A. Ehrenkranz, Myriam Peralta-Carcelen, Betty R. Vohr, Deanne E. Wilson-Costello, Kimberly Yolton, Roy J. Heyne, Patricia W. Evans, Yvonne E. Vaucher, Ira Adams-Chapman, Elisabeth C. McGowan, Anna Bodnar, Athina Pappas, Susan R. Hintz, Michael J. Acarregui, Janell Fuller, Ricki F. Goldstein, Charles R. Bauer, T.Michael O'Shea, Gary J. Myers, Rosemary D. Higgins

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Reference: YMPD/6740

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Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial

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Abbreviations:

BPD – Bronchopulmonary Dysplasia

CA - Corrected Age

CPAP – Continuous Positive Airway Pressure

NICHD - National Institute of Child Health and Human Development

NRN – NICHD Neonatal Research Network

PMA – Postmenstrual Age

ROP – Retinopathy of Prematurity

SUPPORT - Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial

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Retinopathy of prematurity (ROP)

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Intubation, endotracheal

Pulmonary surfactants/therapeutic use

Oxygen inhalation therapy/methods

Oxygen administration & dosage

Follow-up studies

* 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).

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ABSTRACT

Objective To explore the early childhood pulmonary outcomes of infants who participated in the NICHD SUPPORT Trial, using a factorial design that randomized extremely preterm infants to lower vs. higher oxygen saturation targets and delivery room CPAP vs. intubation/surfactant, found no significant difference in the primary composite outcome of death or BPD.

Study design The Breathing Outcomes Study, a prospective secondary to SUPPORT, assessed respiratory morbidity at 6 month intervals from hospital discharge to 18-22 months corrected age (CA). Two pre-specified primary outcomes, wheezing more than twice per week during the worst 2 week period and cough longer than 3 days without a cold were compared between each randomized intervention.

Results One or more interviews were completed for 918 of 922 eligible infants. The incidence of wheezing and cough were 47.9% and 31.0%, respectively, and did not differ between study arms of either randomized intervention. Infants randomized to lower vs. higher oxygen saturation targets had similar risks of death or respiratory morbidities (except for croup, treatment with oxygen or diuretics at home). Infants randomized to CPAP vs. intubation/surfactant had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p<0.05$), respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p<0.05$) and physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p<0.05$) by18-22 months CA.

Conclusion Treatment with early CPAP rather than intubation/surfactant is associated with less respiratory morbidity by 18-22 months CA. Longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions for neonates.

Extremely preterm infants are at greater risk of respiratory morbidity 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) Lung injury, which may result from mechanical ventilation and supplemental oxygen exposure in the early neonatal period, has been identified as a risk factor for development of Bronchopulmonary Dysplasia (BPD) and pulmonary morbidity in infancy, childhood and beyond.(1, 2, 9, 10) Though infants with 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 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 lower (85-89%) compared with higher (91-95%) oxygen saturation targets and early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (intubation/surfactant). Our Network previously reported results of SUPPORT demonstrating no significant differences in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants randomized to either of the two respiratory interventions.(12-14) It is important to note that although the composite incidence of death or BPD was similar, infants randomized to lower rather than higher oxygen saturation targets had significantly lower incidences of retinopathy of prematurity but significantly greater mortality at discharge.

We now report on The Breathing Outcomes Study, a sub study to the SUPPORT Trial, which compared respiratory morbidities among extremely preterm infants treated with the SUPPORT

interventions as neonates. It was hypothesized that infants randomized to lower rather than higher oxygen saturation targets or CPAP, rather than intubation and surfactant, would have a lower incidence of wheezing more than twice per week during their worst 2 week period, a lower incidence of cough lasting more than 3 days without a cold, and as a secondary outcome, less need for outpatient pulmonary care between discharge and 18-22 months' corrected age (CA, age in months following the expected date of full term delivery).

METHODS

Infants eligible for The Breathing Outcomes Study were infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. Infants (n=1316) from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009 and seen in follow-up between 2006 and 2011. As a sub study to SUPPORT, Breathing Outcomes gained approval and began recruitment after SUPPORT began enrollment. As a result not all SUPPORT patients were successfully recruited into Breathing Outcomes. Written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT or separately for those patients already enrolled in SUPPORT but not yet discharged from the hospital. The study was approved by the institutional review boards at all participating Network centers.(12, 13)

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned prior to delivery to receive CPAP after birth, followed by a limited ventilation strategy if intubation was needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age (intubation/surfactant). Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with

either an oxygen saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported.(13) Primary outcomes of SUPPORT included the incidence of death or meeting criteria for the physiologic definition of BPD and death or meeting criteria for traditional BPD, defined as receipt of supplemental oxygen at 36 weeks PMA. (15)

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 telephone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at or near 6, 12 and 18-22 months CA. 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 review the manual of operations (MOP) which included a written interview script. Interview trainees then interviewed a standardized patient simulated by the project trainers. With the aid of the MOP, 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, four interviews were conducted at approximately 6 month intervals beginning at the time of hospital discharge.(16) 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, parents 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 was designed to provide a complete respiratory history over the first 18-22 months' CA. In addition to reporting interview responses during the first 18-22 months CA (defined as the combined responses to the 6, 12, 18-22 month interviews and listed as 6-22 months in Table IV), 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.(17)

Respiratory Questionnaires:

Questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study were used to elicit the frequency and characteristics of respiratory signs, including wheezing and cough; incidence of physician-diagnosed asthma or allergy, presence of

pets in home, siblings, reactive airway disease; 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.(18, 19)

Outcomes

Primary Outcomes: Because preterm infants with or without BPD are at risk for altered airway function and greater risk of wheezing in infancy and later childhood (20-24), we chose to assess respiratory symptoms as a measure of pulmonary morbidity in infancy. Some authors have used incidence of recurrent wheezing as a primary measure of pulmonary morbidity (8, 23, 25), and others have used a combined outcome of either recurrent wheezing or chronic cough as a measure of occult wheezing in preterm infants. (1, 2, 26) To best capture overt and occult wheezing, two primary outcomes were assessed by parental report: the incidence of wheezing more than twice per week during the worst 2 week period and incidence of cough lasting more than 3 days without a cold.

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?". (18) The outcome for wheezing more than twice per week during the worst 2 week period was considered positive if the parent selected "More than two times a week" in response to the question, "during the worst 2 week period, how often has your child's chest sounded wheezy or whistling". The incidence of cough lasting more than 3 days without a cold was ascertained using the Tucson question, "Has your child had a cough for 3 days or more when he/she did not have a cold?".(18)

Secondary outcomes and covariates: Secondary outcomes included incidence of any wheezing and incidence of the combined outcome, wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold. Also assessed were parental report of respiratory signs, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, questions not validated prior to this study were added to the Tucson questionnaires to more fully elicit use of preventive therapies including palivizumab and influenza immunization; attendance at daycare, frequency of BPD exacerbation or flare-up and impact on the family including whether the parent or caregiver needed to change their plans due to their child's breathing; parental report of at least some breast milk intake on any of the 6, 12 or 18-22 month questionnaires; family history of inhaled allergies, food allergies, asthma, COPD or emphysema, other chronic respiratory illness; environmental exposure to tobacco smoke, daycare, children under 12 years old and pets; 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

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 the primary outcome of wheezing more than twice per week between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of wheezing more than twice per week of 29%.(24) 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.

The two primary analyses used the number of patients with either wheezing more than twice per week during their worst 2 week period or cough lasting more than 3 days without a cold as the numerator and the number of infants for whom that outcome was known as the denominator. Secondary responses were tabulated similarly. To assess the robustness of our findings, we calculated respiratory outcomes as a composite outcome with death and also calculated respiratory outcomes for patients with and without BPD. Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. 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. When the two adjustment models failed to converge due to low prevalence (<5%), unadjusted relative risks are reported. 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.

Given the 2x2 factorial design of our randomized trial, we considered the potential for interactions between primary outcomes of one arm on the other (CPAP vs. surfactant and lower vs higher saturation targets). Analysis by robust Poisson regression implemented in Generalized Estimating Equation (GEE) models conducted for the primary outcomes of the main trial did not identify significant interactions between the two treatment arms (p-value for interaction terms all > 0.05). For this reason, only marginal (main) effects of each randomization are reported. No

adjustments have been made for multiple comparisons. All calculations were performed using SAS software, version 9.3 (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study. The 918 subjects with at least one completed questionnaire were considered the study cohort (Figure; available at www.jpeds.com). Follow up rates at each time point are listed in the Figure.

Among the follow up cohort, the group randomized to lower compared with higher oxygen saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with BPD defined using the traditional criteria of supplemental oxygen use at 36 weeks' PMA. The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to intubation/surfactant (Table I). Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and intubation/surfactant groups (Table II; available at www.jpeds.com). Subjects with responses to all four questionnaires were similar in demographic characteristics, neonatal outcomes and home environmental exposures with the exception that those with less than four responses were more apt to have been discharged on respiratory medications (Table III; available at www.jpeds.com).

Overall in the Breathing Outcomes cohort during the first 18-22 months CA, wheezing more than twice per week during the worst 2 week period was reported in 47.9% of patients, cough

lasting more than 3 days without a cold in 31.0% and either wheezing more than twice per week or cough more than 3 days without a cold in 68.2%. Among cohort subjects, use of inhaled (26.3%) and/or systemic steroids (9.4%) was common. Cohort subjects also had high use of physician visits (63.8%), emergency room visits (46.6%) and hospitalizations for wheezing or breathing problems (31.0%).

Primary Outcomes

There was no difference in incidence of the two primary outcomes, wheezing more than twice per week during the worst 2 week period and cough lasting more than 3 days without a cold, between infants randomized to lower compared with higher oxygen saturation targets nor between infants randomized to treatment with CPAP rather than intubation/surfactant (Table IV). Analyzed as a combined outcome, the incidence of death or cough more than 3 days without a cold trended ($p=0.05$) lower among patients in the CPAP compared with intubation/surfactant study arms. The combined outcome of episodes of wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold for the overall cohort was 64.6% and did not differ significantly between infants randomized to lower rather than higher oxygen saturation target or CPAP rather than intubation/surfactant when analyzed alone or as a combined outcome with death (Tables IV and V).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months CA, infants randomized to lower compared with higher oxygen saturation targets had a lower incidence of wheezing and use of nebulized medications following NICU discharge (Table IV). Over the first 18-22 months CA, infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (Table IV). When

analyzed as composite outcomes, the lower compared with higher saturation group had a similar incidence of death or respiratory morbidities except for croup diagnosed by a doctor or treatment with a diuretic or oxygen at home) (Table V).

Early CPAP Intervention

At 6 months CA, infants randomized to treatment with CPAP and a limited ventilation strategy rather than intubation/surfactant were reported to have fewer asthma, reactive airway disease or BPD exacerbation or flare-up episodes diagnosed by a doctor since NICU discharge and a trend toward fewer hospitalizations for wheezing or breathing problems. Perhaps related to these differences, parents or primary caregivers of infants randomized to CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (Table V).

During the first 18-22 months CA, infants randomized to early CPAP versus intubation/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 exacerbation or flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, p=0.02), or wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, p<0.05). Compared with those of infants in the intubation/surfactant group, parents or guardians of infants in the CPAP group were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, p<0.05). When outcomes were analyzed as composite outcomes with death, similar findings were observed with additional differences noted in incidence of treatment with

oxygen or diuretics at home and a trend towards lower incidence of overnight hospitalization for breathing problems.

As expected, our study questionnaires were able to detect significant differences in respiratory outcomes for infants with versus without BPD (Table VI). Although the incidence of wheezing more than twice per week was different between infants with and without BPD, there was no difference in incidence of cough lasting more than 3 days as an indicator of occult wheezing. Taken together, the combined incidence of either overt (wheezing more than twice per week) or potential occult (cough lasting more than 3 days) wheezing was significantly different between infants with BPD and those without (Table VI).

DISCUSSION

We report results of the Breathing Outcomes Study, a sub study to SUPPORT, which sought to quantify respiratory morbidity by 18-22 months corrected age for extremely premature children born 24-27 weeks gestation. We found no significant differences at 18-22 months CA in the incidence of either of the two primary outcomes, wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold, between patients randomized to lower versus higher oxygen saturation targets or randomized to CPAP versus intubation/surfactant.

In secondary analyses, although extremely preterm infants randomized to low compared with high oxygen saturation targets were less likely to have wheezing or use a home nebulizer at 6 months CA and to have wheezing apart from a cold between discharge and 18-22 months CA, these differences were not seen when respiratory outcomes were analyzed as composite

outcomes with death. In fact, analyzed this way, the incidence of death or adverse respiratory outcome for some measures of morbidity were worse for patients in the low saturation group. 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, 27-29) Though patients treated with lower compared with higher saturation targets in SUPPORT had a shorter duration of oxygen exposure, they had greater mortality, similar incidence of BPD, and based on results of the Breathing Outcomes Study, survivors had a similar use of outpatient services for respiratory care and only minor differences in the incidence of respiratory signs. Based on these findings, if oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant lung injury other than targeting lower oxygen saturations will be needed. (24, 30)

Though the primary outcomes were similar, patients in the first 18-22 months CA who were randomized to CPAP and limited ventilation rather than intubation followed by surfactant administration within 1 hour had a lower incidence of several important respiratory morbidities including respiratory illnesses diagnosed by a doctor, treatment with oxygen or diuretics at home and a trend towards lower incidence of overnight hospitalization for breathing problems. Likely related to these findings was a significant reduction in the proportion of parents reporting that they needed to change their daily plans due to their child's breathing difficulties. These differences persisted whether the outcome was analyzed among survivors only or as composite outcomes with death.

Respiratory benefits of CPAP and a limited ventilation strategy were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria(15), was similar between CPAP and intubation/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 age among a 39 patient single-center sub cohort of study infants randomized to CPAP. (31, 32) These observations suggest that treatment of infants 25-27 6/7 weeks gestation at risk for RDS with a limited ventilation strategy is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone. As confirmed in our analysis of respiratory morbidity, BPD has proven to be useful surrogate to identify infants at highest risk of later morbidity. However, based upon the high incidence of respiratory morbidity among infants without BPD, it is likely, though not proven in this study, that the prevalence of respiratory morbidity in former preterm infants may be under recognized. Given the potential for respiratory therapies to improve pulmonary outcomes for infants with and without BPD, 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 signs and use of health care are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months CA. Over two-thirds of subjects in the Breathing Outcomes Study cohort reported wheezing more than twice per week during their worst 2 week period or a cough lasting more than 3 days without a cold. Treatment of these respiratory signs was not only associated with frequent use of both inhaled and systemic steroids, medications that have potential long term effects on growth and development, (33, 34) but also with frequent physician and emergency room visits and hospitalizations, health services which contribute greatly to health care costs.(8)

The strengths of this study include the large number of extremely preterm infants enrolled. 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 to assess outcome measures due to clinical and financial concerns associated with the use of invasive pulmonary testing and the 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. (16, 35)

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.(16) 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 more common use of antenatal steroids than the entire eligible cohort. (36)

In summary, we found no significant differences in the incidence of wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold at 18-22 months CA between extremely preterm survivors who were randomized at delivery to either lower versus higher oxygen saturation targets or early CPAP and a limited ventilation strategy versus intubation/surfactant. In secondary analyses, we found minor reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months CA, but an overall increase in the risk of death or respiratory morbidity (except for croup and treatment with oxygen or diuretics at home) for infants randomized to lower vs. higher oxygen saturation targets. Also in secondary analyses, we report less respiratory morbidity among survivors and lower incidence or respiratory morbidity or death among infants randomized to CPAP rather than intubation/surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over intubation/surfactant.(12-14) 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 surfactant within 1 hour is safe and may result in less respiratory morbidity during the first 18-22 months CA. Lastly, our findings demonstrate a high risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation (with or without BPD) that not only require close medical monitoring but also pose potential burdens to families as well as to society by increasing health care costs.

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Figure. CONSORT diagram including follow up rates.

Table 1. Demographic and neonatal characteristics of follow-up cohorts.

Table 2. Family and environmental exposure history of follow-up cohorts.

Table 3. Differences between those who answered all four questionnaires vs less than four.

Table 4. Respiratory outcomes for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts at the 6 month interview and for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Table 5. Combined outcomes of death or respiratory morbidity for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Table 6. Respiratory outcomes for infants with traditional BPD (oxygen requirement at 36 weeks post-menstrual age) for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

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expired infant cohort. To minimize this bias, oxygen saturation waveform data recorded 24 hours before death will be removed from the data analysis.

Sample Size:

Sample of convenience based on 237 infant deaths (130 in the low target and 107 in the high target groups) and 1079 controls.

Statistics:

Daily measurements of baseline oxygen saturation will be compared between survivors and expired infants. Cox survival regression models will be created with daily baseline oxygen saturation entered into the model as a time-dependent covariate, such that the value will be allowed to vary by infant and by day. Interactions with time can also be included as time-dependent covariates in order to assess whether the effect of daily baseline oxygen saturation on mortality changed over time (e.g., for earlier vs. later days of life). The contribution of covariates including gestational age, multiples, race, center, caffeine and gender will also be examined. These models will yield risk ratios estimating the extent to which the covariates were associated with the risk of mortality.

References:

1. Di Fiore JM, Bloom JN, Orge F, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. J Pediatr, 2010;157:69–73.
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From: Walsh, Michele
To: Juliann DiFiore; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Abhik " <adas@rti.org>, " Wrage@ndb-mr2.cc.emory.edu
Subject: RE: Data Request for IH and mortality ancillary study
Date: Wednesday, March 12, 2014 11:06:44 AM

Kristin: what is the determination- how can we get the data?

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

From: Juliann DiFiore [mailto:jmd3@case.edu]
Sent: Wednesday, March 12, 2014 10:26 AM
To: Zaterka-Baxter, Kristin; Walsh, Michele
Subject: Re: Data Request for IH and mortality ancillary study

Hi Kris,

Just following up on our conversation a month ago about the request for additional data for the IH and mortality ancillary study. Any progress?

Julie

On 2/17/2014 6:35 PM, Zaterka-Baxter, Kristin wrote:

> Hi Julie,
>
> So not ignoring you at all, just trying to determine it the additional data requested needs further approvals .... Will let you know soon.
>
> Thanks,
> Kris
>
> ---
>
> **From:** Juliann DiFiore [mailto:jmd3@case.edu]
> **Sent:** Monday, February 17, 2014 12:25 PM
> **To:** Zaterka-Baxter, Kristin
> **Cc:** Walsh, Michele
> **Subject:** Fwd: Data Request for IH and mortality ancillary study
>
> Hi Kristen,

I am following up on the data request below. When do you think you will be able to update the DUA? I am hoping we can move it through our legal dept on this end much more quickly than the last time!

Regards,

Julie

-------- Original Message --------
Subject: Data Request for IH and mortality ancillary study
Date: Fri, 07 Feb 2014 11:57:01 -0500
From: Juliann DiFiore <jmd3@case.edu>
To: Pickett, James <japickett@rti.org>, Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>, Das, Abhik <adas@rti.org>, Gantz, Marie <mgantz@rti.org>, Zaterka-Baxter, Kristin <kzaterka@rti.org>, Walsh, Michele <Michele.Walsh@uhhospitals.org>, rxm6@case.edu <rxm6@case.edu>

RE: IH and mortality ancillary study

After discussions with Michele and Richard regarding the IH and mortality study we feel we need to include additional covariates that may influence IH. Therefore, I am asking for one more amendment to the DUA (and hopefully the last). Would you please add the following:

Early Sepsis (< 72 hrs) and Late Sepsis (>= 72 hrs)
IVH: Any and Severe
NEC- any and medical vs surgical.
Cause of Death.
Thank you,
Julie

--
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

5122.31 and 3701.243 prohibit
disclosure of this information without the specific written consent
of the person to whome it pertains, or as otherwise permitted.

--
Julliann 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

Blansfield, Earl (NIH/NICHD) [E]

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 8:22 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Thanks for including me – looks like it is figured out

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:34 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Got it, thanks

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:34 PM
To: Kaeser, Lisa (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

(b)(5)

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
31 Center Drive
Building 31, Room 2A03
Bethesda, MD 20892-2425

Phone: 301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:28 PM

To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

R and I spoke earlier – we would like to recommend (b)(5)

(b)(5)

But what do you think?

Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
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Bethesda, MD 20892
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kaeserl@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 5:25 PM
To: Kaeser, Lisa (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

"However, OHRP did 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)(2): A description of any reasonably foreseeable risks and discomforts." (b)(5)

Alan

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 4:06 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Hi all – we've been asked for clearance for the Secretary's response to the most recent Carome letter. In my opinion, (b)(5)

(b)(5) We tried to revise last time, without much success.

What do you all think? Due Friday.

Thanks,

Lisa

Lisa Kaeser, J.D.

Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
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From: Ott, Sandra (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 3:30 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

Note from Exec Sec:

OS Clearance (please clear by 3:00 p.m., Friday, March 7, 2014).

Hello,

Please clear the Draft letters from the Secretary regarding the " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" located in the Draft Response folder, entitled, "Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14." The Incoming or Source Document is also located in the Draft Response folder. Please provide all comments by 3:00 p.m., Friday, March 7, 2014.

Note: NICHD, OER, and OSP are being asked to please clear.

Thank you:)
Monica Dozier

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
Sent: Wednesday, March 05, 2014 2:54 PM
To: Brown, Crystal (NIH/NICHD) [C]; EDRMS_NO_REPLY (NIH/OD); EDRMS_NO_REPLY (NIH/OD); Ott, Sandra (NIH/NICHD) [E]; EDRMS_NO_REPLY (NIH/OD); Wood, Vandora (NIH/CIT) [C]
Subject: WF 328659 - Preview Clearance Status (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

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Work Folder Information
Work Folder: WF 328659

Process: IC Clearance WF 328659
Due Date: March 07, 2014
Program Analyst: Dozier, Monica (NIH/OD) [E]
WF Subject: "The Surfactant Positive Airway Pressure and Pulse Oximertry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial -Inadequate Safety Monitoring." This is a "Follow-up letter from the Public Citizen's Health Research group regarding the NIH-funded SUPPORT study involving extremely premature infants."
IC:NICHD
From: Wolfe, Sidney;Carome, Michael;
To: Sebelius, Kathleen;
Remarks: OS Clearance (please clear by 3:00 p.m., Friday, March 7, 2014). Hello, Please clear the Draft letters from the Secretary regarding the " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" located in the Draft Response folder, entitled, "Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14." The Incoming or Source Document is also located in the Draft Response folder. Please provide all comments by 3:00 p.m., Friday, March 7, 2014. Note: NICHD, OER, and OSP are being asked to please clear. Thank you:)

From: Kaeser, Lisa (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study
Date: Wednesday, March 05, 2014 4:05:34 PM
Attachments: 328659 - Draft Response - Source Document.pdf
328659 - Draft Response - Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14.pdf

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(b)(5)
(b)(5) We tried to revise last time, without much success.

What do you all think? Due Friday.

Thanks,

Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
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31 Center Drive, MSC 2425
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From: Ott, Sandra (NIH/NICHD) [E]
Sent: Wednesday, March 05, 2014 3:30 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 328659 - Round 1 Clearance due by Friday, March 7, 2014 by 3:00 PM - SUPPORT Study

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Thank you:)
Monica Dozier

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Sent: Wednesday, March 05, 2014 2:54 PM

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Subject: WF 328659 - Preview Clearance Status (CC)

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Work Folder: WF 328659
Process: IC Clearance WF 328659
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Program Analyst: Dozier, Monica (NIH/OD) [E]
WF Subject: "The Surfactant Positive Airway Pressure and Pulse Oximertry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial -Inadequate Safety Monitoring." This is a "Follow-up letter from the Public Citizen's Health Research group regarding the NIH-funded SUPPORT study involving extremely premature infants."
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Remarks: OS Clearance (please clear by 3:00 p.m., Friday, March 7, 2014). Hello, Please clear the Draft letters from the Secretary regarding the " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial" located in the Draft Response folder, entitled, "Draft Letters from the Secreetary 021220141007 Public Citizen 1-27-14 re SUPPORT 3-3-14." The Incoming or Source Document is also located in the Draft Response folder. Please provide all comments by 3:00 p.m., Friday, March 7, 2014. Note: NICHD, OER, and OSP are being asked to please clear. Thank you:)

Page 0730 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0731 of 2000

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of the Freedom of Information and Privacy Act

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2014 FEB 3 PM 4 43

January 27, 2014

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

RE: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial – Inadequate Safety Monitoring

Dear Secretary Sebelius:

We are writing in follow-up to Public Citizen's April 10, 2013, letter and May 8, 2013, report regarding the SUPPORT study funded by the National Institutes of Health (NIH) and conducted by approximately two dozen academic medical institutions of the Neonatal Research Network.[1,2] That letter and report highlighted important and material factual omissions regarding the purpose, nature, and risks of the research in the consent forms approved by the institutional review boards (IRBs) and signed by parents of infants enrolled in the SUPPORT study, and also brought to light deficiencies in the study design that resulted in a failure to ensure that risks to subjects were minimized.

To date, the Department of Health and Human Services' (HHS's) response to the serious ethical lapses in the conduct of the SUPPORT study has been unsatisfactory. Rather than taking substantive steps to remedy these ethical lapses, HHS bowed to pressure from NIH and an academic research establishment dependent on NIH for support and stifled appropriate compliance oversight enforcement action by the Office for Human Research Protections (OHRP).

We write to you now to highlight the following additional important issues related to the SUPPORT study that have come to our attention and also have not been adequately addressed by HHS:

(1) The SUPPORT study protocol appears to have lacked a safety monitoring plan for *separately* monitoring for differences in severe retinopathy of prematurity (ROP) between the two experimental oxygen study groups. If such a plan had been

[1] Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. April 10, 2013. http://www.citizen.org/documents/2111.pdf. Accessed January 20, 2014.
[2] Carome M, Wolfe S, Macklin R. Analysis of the complete protocol and consent form for the SUPPORT study: Lack of informed consent and a failure to ensure that risks were minimized. May 8, 2013. http://www.citizen.org/documents/2124.pdf. Accessed January 20, 2014.

implemented, the study likely would have been terminated early, sparing some extremely premature infants enrolled in the study from suffering severe ROP or death.

(2) In spite of evidence we presented previously,[3] the SUPPORT study investigators — in an attempt to defend the adequacy of their study consent forms — have continued to repeatedly assert that they all had no expectation that the low-oxygen group subjects would have a higher mortality rate than the high-oxygen group subjects and indeed were surprised when the final study results revealed such an outcome. We provide below additional clear evidence that before the study began, there was an awareness among at least some of the investigators — including among the lead investigators who developed the study protocol — that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study. Moreover, as neonatology experts, the SUPPORT study investigators had an ethical obligation to thoroughly research the literature, to understand areas of ongoing uncertainty regarding oxygen management, and to be aware of all plausible study risks. To not have known that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study would have constituted reckless ignorance.

(3) The SUPPORT study was one of five concurrently planned, coordinated, and conducted studies around the world using nearly identical study designs for testing low- versus high-oxygen interventions in extremely premature infants. To minimize risks to subjects across all five studies, the protocols should have specified a mechanism for joint safety monitoring. Ideally, there should have been a formal data and safety monitoring plan involving interim analyses of pooled data from all five studies combined. At a minimum, there should have been a plan for informally sharing any troubling safety signal arising in one study with the investigators and data monitoring committees for the other studies. No such formal or informal plan was described in the SUPPORT protocol. Of note, the members of the data monitoring committee for at least one of the five studies recognized early on the need to see interim data from the other four parallel studies to ensure the safety of subjects across all trials, but their attempts to obtain data from the other studies were either ignored or rebuffed.

We describe below each of these issues in detail and conclude by asking key questions for which the parents of SUPPORT study subjects and the public deserve clear answers from HHS.

A. Background

As you are aware, the SUPPORT study involved two simultaneous complex experiments. In one experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing (ventilation of the lungs) following delivery.[4]

For the other experiment (the oxygen experiment), babies assigned to each of the two ventilation groups were further randomly divided between a low-oxygen group and a high-oxygen group.[5]

---

[3] *Ibid.*

[4] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely premature infants. *N Engl J Med.* 2010;362(21):1970-1979.

For the low-oxygen group, the SUPPORT study investigators tried to maintain the babies' blood oxygen levels in a low target range (oxygen saturation level of 85 to 89 percent), and for the high-oxygen group in a high target range (oxygen saturation level of 91 to 95 percent), regardless of the infants' clinical status.

The primary efficacy outcome measure for the oxygen experiment was a combination of severe retinopathy of prematurity (ROP, which can lead to visual impairment and blindness and often requires surgery to preserve vision), death before discharge from the hospital, or both.

For both experimental oxygen groups, oxygen monitors relied upon by the medical teams caring for the infants in the study displayed either intentionally falsely high (low-oxygen group) or intentionally falsely low (high-oxygen group) values when the infants' actual oxygen saturation levels were between 85 and 95 percent.

Premature infants enrolled in the SUPPORT study were not given the same care with respect to oxygen management that otherwise similar infants would have received at the same participating hospitals. In particular, oxygen management of enrolled infants lacked the following features of usual care:

(1) fully functional, properly operating pulse oximeters that displayed accurate oxygen saturations for use by health care providers to guide care;

(2) access to the entire range of target oxygen saturations endorsed in guidelines (85 to 95 percent) for management of premature infants, including the possibility of employing the center of this range (88 to 92 percent); and

(3) adjustment of supplemental oxygen and oxygen saturation targets based on an assessment of risks and benefits for each infant's particular characteristics. Some of the clinical factors that are often considered in individualizing oxygen management include level of prematurity; capillary refill time (a simple physical exam test to assess the adequacy of tissue perfusion); cardiopulmonary, hepatic, and renal function; hematocrit; intravascular volume; acid-base status; oxygen requirements in the toxic range; and clinical signs suggestive of impending necrotizing enterocolitis.

For the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. The low-oxygen intervention presented the foreseeable risks of neurologic injury and death.

In contrast, for the high-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 91 to 95 percent using oxygen monitors that displayed falsely *low* readings predictably caused, on average, higher levels of oxygen exposure than

[5] 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.

would have occurred under usual care using accurately reading oxygen monitors. The high-oxygen intervention presented the foreseeable risk of severe ROP.

B. Inadequate safety monitoring plan: Apparent failure to monitor for severe ROP as a separate adverse event and to terminate the study early because of harm to subjects in the high-oxygen group

Minimization of risks to research subjects requires adequate safety monitoring. Both death and severe ROP comprised the primary risks of the SUPPORT study's oxygen experiment, and each should have been monitored *separately as adverse events* during the conduct of the trial in order to minimize risks to subjects. If separate monitoring of both had been implemented, the study likely would have been terminated early, sparing some extremely premature infants enrolled in the study from suffering severe ROP or death.

However, as reflected in the following excerpts from the data and safety monitoring plan in the SUPPORT study protocol, it appears that unlike death, severe ROP was not monitored *separately as an adverse event* during the course of the trial. Instead, severe ROP apparently was monitored only in combination with death as a component of the composite primary efficacy endpoint, and the study was not terminated early. The protocol stated:[6]

> **4.4 Adverse Events**
>
> Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:
>
> 1. Air leak on admission to the NICU, or during the initial 14 days of life
> 2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
> 3. The occurrence of severe IVH (Grades 3-4, Papile)
> 4. Death
>
> These outcomes will be evaluated on a monthly basis by RTI [Research Triangle Institute], and if the incidence of any of these outcomes is determined to be 5% -10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.
>
> **4.5 Data Safety Monitoring Committee**
>
> The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome

[6] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

Monitoring of the *composite* primary efficacy endpoint of severe ROP or death before discharge during the conduct of the SUPPORT study as designed was not sufficient for monitoring safety related to the occurrence of severe ROP because of the following factors:

(1) The SUPPORT study's oxygen experiment involved only two experimental groups (the low-oxygen group and the high-oxygen group) and no usual care (or current-practice) control group; and

(2) The two components of the composite primary efficacy endpoint — death and severe ROP — were countervailing, but asymmetric, potential harms:

(a) For the high-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 91 to 95 percent using oxygen monitors that displayed falsely low readings predictably caused, on average, higher levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. As a result, the research procedures for these subjects presented a reasonably foreseeable increased risk of suffering severe ROP (a risk that was not described in 20 of 22 IRB-approved SUPPORT study consent forms as required by HHS human subjects protection regulations at 45 CFR 46.116(a)(2)).[7]

(b) For the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. As a result, the research procedures for these subjects presented a reasonably foreseeable risk of death (a risk that was not disclosed in any of 22 IRB-approved SUPPORT study consent forms).

Adequate safety monitoring of the study as designed would have required periodic checking for differences between the low-oxygen and high-oxygen groups for *both* death and retinopathy *separately*. The importance of such separate comparisons was reflected in the way the results were presented in the published paper describing the primary results of the study (see Table 1 below).[8]

[7] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed January 20, 2014.

[8] 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.

Table 1: Key Major Outcomes from SUPPORT Study

Outcome	Low-Oxygen Group *no./total no.(%)*	High-Oxygen Group *no./total no.(%)*	Adjusted Relative Risk (95% Confidence Interval)	P-value
Primary efficacy outcome: severe ROP or death before discharge	171/605 (28.3%)	198/616 (32.1%)	0.90 (0.76-1.06)	0.20
Severe ROP	41/475 (8.6%)	91/509 (17.9%)	0.52 (0.37-0.73)	<0.001
Death before discharge	130/654 (19.9%)	107/662 (16.2%)	1.27 (1.01-1.60)	0.04

Because severe ROP often requires surgery and can lead to blindness, it represented a clear potential harm to the high-oxygen group infants of significant-enough degree to require separate safety monitoring, as was done for death. Yet the protocol's data and safety monitoring plan did not indicate that it was separately monitored. Indeed, the problem of ROP in premature infants was considered such a serious health problem in premature infants that NIH spent more than $20 million on the SUPPORT study to find out whether using the low-oxygen intervention would reduce the incidence of this important adverse outcome in comparison to the high-oxygen intervention without causing an increase in mortality or brain injury.

In what obviously came as no surprise to the SUPPORT study investigators and was not an unexpected finding, the study results, after SUPPORT was concluded, demonstrated that the high-oxygen group babies had a highly significant increase in retinopathy in comparison to the low-oxygen group babies (17.9 percent versus 8.6 percent, respectively; $p<0.001$).[9]

If the incidence of severe ROP had been monitored separately as an important adverse event in the high-oxygen group at increased risk for this adverse outcome and compared to the incidence in the low-oxygen group, the trial conceivably could have been stopped early, thus preventing the occurrence of retinopathy and avoiding retinal surgery in many high-oxygen group infants.

To estimate the approximate point at which one of the planned interim analyses of study data would have demonstrated a statistically significant difference in the rate of severe ROP between the high- and low-oxygen groups, we performed a series of hypothetical interim analyses using the chi-square test based on enrollments of 25, 50, and 75 percent of the actual final enrollment (i.e., 1,316 infants). Because interim data were not available to us for these analyses, we assumed that the following factors remained constant throughout the study: the incidence of severe ROP, the proportion of high- and low-oxygen group subjects, and the proportion of subjects in each group who survived to the time of discharge and had a determination made regarding whether severe ROP had developed.

[9] *Ibid.*

The contingency tables below (Tables 2-4) summarize our analysis. Following each table is the chi-square statistic without Yates correction and two-tailed P-value (uncorrected for multiple looks):

Table 2: 25 Percent of Final Enrollment*Group	No Severe ROP	Severe ROP	Total
High-Oxygen	104	23	127
Low-Oxygen	109	10	119
Total	213	33	246

*Assumes 329 subjects enrolled and 246 survived to discharge and had retinopathy status determined
χ^2=4.984; P=0.0256

Table 3: 50 Percent of Final Enrollment*

Group	No Severe ROP	Severe ROP	Total
High-Oxygen	209	45	254
Low-Oxygen	217	21	238
Total	426	66	492

*Assumes 658 subjects enrolled and 492 survived to discharge and had retinopathy status determined
χ^2=8.366; P=0.0038

Table 4: 75 Percent of Final Enrollment*

Group	No Severe ROP	Severe ROP	Total
High-Oxygen	314	68	382
Low-Oxygen	325	31	356
Total	639	99	738

*Assumes 987 subjects enrolled and 738 survived to discharge and had retinopathy status determined
χ^2=13.118; P=0.0003

Based on the above analyses, with respect to the harmful outcome of severe ROP, a statistically significant greater incidence of harm in the high-oxygen group might have been detected after reaching just 25 percent of target subject enrollment, and almost certainly would have been detected after reaching 50 percent of target enrollment. Early termination of the study following enrollment of either one-quarter or one-half of the projected final target enrollment likely would have spared some of the subsequently enrolled infants randomized to the high-oxygen group from developing severe ROP that resulted from receiving a higher level of oxygen exposure than they would have otherwise received if they had not been enrolled in the study. We are not able to reliably estimate the number of children who would have been spared severe ROP had the study been terminated early because the study lacked a current-practice control group.

It is important to recognize that the inclusion of a plan to separately monitor for severe ROP as an important adverse outcome during the conduct of the study would not have been sufficient to

address the other fundamental flaw in the SUPPORT study design — the lack of a usual-care control group. By experimentally increasing oxygen exposure in one study group relative to current practice and lowering it in the other, the harms resulting from each experimental intervention *relative to current practice* could not be monitored for or determined, and therefore, risks to subjects were not minimized.

The SUPPORT study investigators may argue that separately monitoring for severe ROP as an adverse event could have led to premature termination of the study and prevented the detection of the higher mortality rate that was seen in the low-oxygen group, which in turn could have led to a dangerous recommendation to routinely target oxygen saturation levels at 85 to 89 percent in all extremely premature infants. (Indeed, as discussed in the next section of our letter, this thought process may explain why separate monitoring for severe ROP did not occur.) However, if the study had been stopped early based on an interim analysis showing a statistically significant higher incidence of severe ROP in the high-oxygen group, without a usual-care control group there would have been no sound basis for concluding that the lower-oxygen intervention was better than usual care. The higher incidence of severe ROP in the low-oxygen group may have been due to oxygen exposure being experimentally raised in the high-oxygen group (relative to usual care), experimentally lowered in the low oxygen group (relative to usual care), or both. The study results were ultimately uninformative in this regard given the lack of a usual-care control group. In addition, interim analyses may have revealed a non-statistically significant higher death rate in the low-oxygen group compared to the high-oxygen group, which should have precluded anyone from making recommendations to modify current practice to routinely using the lower oxygen saturation target in the clinical care of extremely premature infants.

All of these problems could have been avoided with an alternative study design that employed a usual-care control group and low-oxygen experimental group. Such a design could have informed the medical community whether oxygen could be safely lowered to prevent severe ROP without increasing the mortality rate. Moreover, because experimentally lowering oxygen was unlikely to increase the incidence of severe ROP and blindness relative to current practice, it would not have been necessary to monitor this outcome as a separate adverse event.

C. The higher mortality rate in low-oxygen group infants: *Not* a surprising finding

As noted above, for the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors.

Over the past several months, in an awkward attempt to explain why death was not identified as a risk of the research in the SUPPORT study consent forms, the study investigators have repeatedly asserted that they all had no expectation that the low-oxygen group subjects would have a higher mortality rate than the high-oxygen group subjects, and indeed some investigators

have indicated that they were surprised when the final study results revealed such an outcome.[10,11,12,13]

In contrast, the investigators in recent months have not asserted that they were surprised to find a higher rate of severe ROP in the high-oxygen group than in the low-oxygen group, and as previously noted, such a finding undoubtedly was not a surprise.

All physicians understand the well-established pathophysiologic relationship in which increasing degrees of hypoxemia result in progressively higher mortality rates. At the time of the SUPPORT study, all neonatologists knew that increasing the degree of hypoxemia in premature infants *at some point* would increase the infants' mortality rate. The exact shape of the curve for the relationship between the degree of hypoxemia and mortality and the exact threshold of oxygen exposure below which mortality will start to increase in premature infants were not known at the time the SUPPORT study was conducted and remain unknown today.

The SUPPORT study investigators may have believed that targeting oxygen saturations at 85 to 89 percent in extremely premature infants was unlikely to cross below the oxygen exposure threshold that would increase the mortality rate. However, they did not know for certain that this was the case, and the available data from the medical literature cited by the investigators in their protocol were clearly insufficient to prove that maintaining oxygen saturations at 85 to 89 percent would *not* have an adverse impact on the mortality rate of extremely premature infants. Indeed, assessing whether the lower oxygen saturation target could decrease the incidence of severe ROP in severely premature infants without increasing mortality was one of the major reasons for conducting the study.

As neonatology experts, the SUPPORT study investigators had an ethical obligation to thoroughly research the literature, to understand areas of ongoing uncertainty regarding oxygen management, and to be aware of all plausible study risks. To not have known that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study would have constituted reckless ignorance.

Investigators in New Zealand undertaking a similarly designed study (discussed below) understood that regardless of their expectations about the study outcome, it was appropriate to

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[10] Transcript for the Diane Rehm Show from WAMU and National Public Radio: Clinical trials and premature babies. April 17, 2013. http://thedianerehmshow.org/shows/2013-04-17/clinical-trials-and-premature-babies/transcript. Accessed January 20, 2014. (SUPPORT study investigator Dr. Edward Bell stated, "As a matter of fact, there was no reason for us to suspect that there would be a difference in mortality, and that was a surprising finding.")

[11] Finer NN, Bell EF, Van Meurs K. Consent forms in a clinical trial of premature babies (letter to the editor). *The New York Times*. April 18, 2013. http://www.nytimes.com/2013/04/19/opinion/consent-forms-in-a-clinical-trial-of-premature-babies.html. Accessed January 20, 2014. ("When the study was planned, the best evidence showed that lower oxygen targets — even lower than used in the study — resulted in less eye disease without a higher death rate. The finding of a higher death rate in one study group was not anticipated.")

[12] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med*. 2013;368(20):1949-1950. ("Death was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected.")

[13] D'Angio C, Finer N, Newman N, et al. Misconceptions about the SUPPORT trial. Posted September 10, 2013. http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2013-0004-0067. Accessed January 20, 2014.

explain to subjects' parents in the consent forms the well-known and previously established separate risks of death from lowering oxygen exposure, as well as ROP from raising oxygen exposure, for premature infants enrolled in the study. It is unclear why the SUPPORT study investigators in the U.S. would have lacked such an understanding.

Although the SUPPORT study investigators undoubtedly were *hopeful* at the onset of the study that the low-oxygen intervention would result in a decreased incidence in severe ROP without a concomitant increase in mortality, there is clear evidence that before initiating the study at least some of them were aware that a higher mortality rate in the low-oxygen group relative to the high-oxygen group could have been one plausible finding of their study. In particular, the SUPPORT study investigators cited in their protocol a 2003 paper by Cole et al, published in the journal *Pediatrics,* discussing the planning and design of studies comparing the low- and high-oxygen interventions that were to be used in their study[14] (see reference 55 in the SUPPORT study protocol[15]). The authors of this paper were members of the Pulse Oximetry Saturation Trial for Prevention of Retinopathy of Prematurity (POST ROP) Planning Study Group.

The POST ROP study was to be a multicenter, multinational prospective trial to evaluate different levels of oxygen in premature babies. It is our understanding that the POST ROP study comprised the Benefits of Oxygen Saturation Targeting (BOOST) II studies in the United Kingdom (UK), Australia, and New Zealand, and the Canadian-funded Canadian Oxygen Trial (COT). The SUPPORT study protocol made reference to this study as follows: "The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial…"

Of note, Dr. Waldemar Carlo at the University of Alabama at Birmingham — who was one of the lead investigators for the SUPPORT study and was on the Neonatal Research Network working group that developed and wrote the SUPPORT study protocol — was a member of the POST ROP Planning Study Group. The acknowledgements section at the end of the Cole et al paper states that Dr. Carlo was among the POST ROP Planning Study Group members who reviewed and critiqued the paper.[16]

The 2003 Cole et al paper makes clear that when the SUPPORT study and the parallel POST ROP studies were being designed, there were real concerns among neonatologists that the low-oxygen intervention could expose extremely premature infants to an increased risk of death or neurologic injury. In particular, the paper emphasized that large numbers of patients would have to be studied to address concerns about mortality risk with the low oxygen dose, noting the following:[17]

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[14] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[15] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

[16] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[17] *Ibid.*

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

Emphasizing the need for a data and safety monitoring committee and plan for the POST ROP studies, the 2003 *Pediatrics* paper stated the following:[18]

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

Further indication of the serious concern among some neonatologists that the low-oxygen intervention could expose extremely premature infants to an increased risk of death or neurologic injury was provided in the 2005 version of the consent form used in the New Zealand BOOST II study discussed above, which included the following:[19]

> Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . The aim of this study is to determine, within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%), **whether targeting the lower end of this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision**

[18] *Ibid.*

[19] Lantos JD. OHRP and Public Citizen are wrong about neonatal research on oxygen therapy research. The Hastings Center Bioethics Forum. Posted April 18, 2013. http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blog+140. Accessed January 20, 2014. Cited as "BOOST-NZ consent form, July 2005, personal communication from Brian Darlow, principal investigator of BOOST-NZ."

(ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability. [Emphasis added]

Finally, members of the data monitoring committee for the BOOST II UK study noted the following in a recent commentary article discussing the four POST-ROP studies and the SUPPORT study: [20]

> Evidence from controlled trials had shown that if the oxygen levels are relatively high there is an increased risk of the infant developing the blinding condition retinopathy of prematurity. On the other hand, observational data had suggested that keeping levels of arterial oxygen relatively low might result in increased mortality, and neurological handicap among long term survivors.
>
> During the past decade, five similar trials - in the USA, New Zealand, Canada, Australia and the UK - **were organized more or less concurrently to investigate this therapeutic dilemma**. Although they were separately organized and funded, all of them compared different oxygen tension targeting strategies intended to minimize both mortality and serious morbidity. **It was recognized at the outset that none of the five trials, individually, would have the statistical power to provide a reliable estimate of survival without serious morbidity 18 to 24 months after birth.** Indeed, two of these trials were only funded on the understanding that the data from several similar trials would be combined. [Emphasis added]

All of the above statements could not be clearer. At least some of the expert neonatologists involved in the design of the SUPPORT study and parallel studies to be conducted in other countries were well aware when designing these studies that there were real concerns within the neonatology community that the low-oxygen intervention to be used in these studies might increase the risk of death.

In view of the commentary paper authored by members of the POST ROP Planning Study Group and cited by the SUPPORT study investigators in their own protocol, it is remarkably disingenuous of the SUPPORT study investigators to now assert that because some of them were surprised to find a higher mortality rate in the low-oxygen group subjects in their study, it was not necessary to inform parents about the reasonably foreseeable risk of death for subjects assigned to the low-oxygen group. Such a finding was one reasonably foreseeable and highly plausible outcome. This undoubtedly is one of the reasons why, as noted above, death was to be monitored according to the SUPPORT study protocol and was a component of the primary outcome being studied.

The investigators certainly had hoped for a different result and perhaps had reason to be disappointed when they found the significantly higher mortality rate in the low-oxygen group, but they could not genuinely have been shocked by the fact that when they lowered oxygen exposure, the mortality rate increased in premature infants in the study. Indeed, none of the

[20] Chalmers I, Altman DG, McHaffie H, et al. Data sharing among data monitoring committees and responsibilities to patients and science. *Trials.* 2013;14:102. http://www.trialsjournal.com/content/14/1/102. Accessed January 20, 2014.

investigators at any point in discussing the results of the SUPPORT study have proposed an alternative hypothesis to explain the higher mortality rate in the low-oxygen group compared to the high-oxygen group. They implicitly recognize that the well-established pathophysiologic relationship in which decreasing oxygen exposure results in increasing hypoxemia and mortality is undoubtedly the explanation for their study findings, whether unexpected by some of the investigators or not.

Finally, we strongly suspect that the apparent failure to monitor separately for severe ROP and to have stopping criteria based on finding a difference in the incidence of severe ROP between the high- and low-oxygen groups at the time of any planned interim analyses was due to concern among the investigators that stopping the oxygen experiment early based on a statistically significant difference in ROP between groups could have resulted in a failure to detect a difference in the mortality rate between the two study groups.

D. Failure to minimize risks to subjects by not having a data and safety monitoring plan involving interim analyses of pooled data from the SUPPORT study and the four concurrent POST ROP studies

As noted above, the SUPPORT study and the four POST ROP studies were five parallel studies concurrently planned and conducted around the world using nearly identical study designs comparing high- and low-oxygen interventions in extremely premature infants. The planning and designing of these studies were coordinated,[21,22] and the investigators for each study obviously were aware of the other studies.

To minimize risks to subjects across all five studies, the protocols should have specified a mechanism for joint safety monitoring. Ideally, there should have been a formal data and safety monitoring plan involving interim analyses of pooled data from all five studies combined. At a minimum, there should have been a plan for informally sharing any troubling safety signal arising in one study with the investigators and data monitoring committees for the other studies. No such formal or informal plan was described in the SUPPORT protocol. Instead, monitoring of data and safety was conducted independently and separately across these studies. Not having pooled monitoring across all five studies, even in some informal manner, represents a troubling failure to ensure the protection of human subjects.

Disturbingly, members of the data monitoring committee for the BOOST II UK study recognized the importance of seeing interim data from the other four parallel studies, but their attempts to obtain data from the other studies, which began as early as 2006, apparently were ignored or rebuffed by the data monitoring committees for the other four parallel studies.[23] For example,

[21] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.
[22] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.
[23] Chalmers I, Altman DG, McHaffie H, et al. Data sharing among data monitoring committees and responsibilities to patients and science. *Trials.* 2013;14:102. http://www.trialsjournal.com/content/14/1/102. Accessed January 20, 2014.

they noted the following in a recent commentary article discussing the four POST-ROP studies and the SUPPORT study:

> Accordingly, because data from the other four trials were of obvious relevance to our responsibility, the chair of our DMC wrote to the DMC chairs of the other trials in 2006, expressing the **'hope that we can help each other fulfil our respective commitments to the babies being treated in these trials'** (Emails sent 11 and 15 July 2006).
>
> **No response was received from the other DMC chairs for several years**; but consideration of the proposal became urgent when, more than three years later, in 2009, the management group of the US trial sent results, in advance of publication, to those associated with the trials that were still recruiting.

E. Conclusions and requested actions

For each of the three critical issues described above, parents of subjects enrolled in the SUPPORT study, as well as the public, deserve clear answers to the following questions:

(1) With respect to monitoring separately for difference in the incidence of severe ROP between groups:

(a) Was ROP monitored separately during the course of the trial as an important adverse event? If not, why not?

(b) If ROP was monitored separately during the course of the trial, at the time of any of the planned interim analyses, did the difference in the incidence of severe ROP between the low- and high-oxygen groups reach statistical significance? If so, when did this occur, and why wasn't the study terminated at that point?

(c) Did OHRP consider the lack of appropriate safety monitoring during the SUPPORT study and the lack of a usual-care control group when it evaluated adequacy of the SUPPORT study design?

(d) Since the SUPPORT study investigators must have recognized that the incidence of severe ROP was likely to be higher in the high-oxygen group and have voiced no surprise in finding this result, does HHS agree or disagree with OHRP's finding that the IRB-approved consent forms failed to comply with HHS regulations under 45 C.F.R. 46.116(a)(2) by not disclosing severe ROP as a risk of the research?

(2) With respect to the investigators' statements about being surprised to find a higher mortality rate in the low-oxygen group: Since the SUPPORT study investigators either knew or should have known prior to initiating the study that an increased death rate in the low-oxygen group was a foreseeably plausible outcome of the SUPPORT study, does HHS agree or disagree with OHRP's finding that the IRB-approved consent forms failed to comply with HHS regulations under 45 C.F.R. 46.116(a)(2) by not disclosing death as a risk of the research?

(3) With respect to the failure to establish a plan to monitor data pooled across the SUPPORT study and the four POST ROP studies:

(a) Why didn't the SUPPORT study protocol include a plan for joint safety monitoring with the POST ROP studies, either formally, via pooled interim analyses across all five studies, or informally, by sharing any troubling safety signals arising in one study with the investigators and data monitoring committees for the other studies?

(b) Were the SUPPORT study investigators or NIH officials aware of the BOOST II UK data monitoring committee's requests for SUPPORT study data for the purposes of pooled interim analysis? If so, what was their response to those requests? Why were the requests not granted?

We urge HHS to provide prompt answers to these important questions. We also request an opportunity to meet with you or your representative to discuss these important issues, which have critically important implications for the safety and welfare of premature infants participating in ongoing clinical trials funded by HHS.

In closing, we renew our April 10, 2013, request that you issue a formal apology 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. Such an apology is the most critical step for redressing the ethical lapses that occurred during the conduct of this study.

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

Sincerely,

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

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

cc: The Honorable Bill Corr, Deputy Secretary, HHS
The Honorable Howard K. Koh, Assistant Secretary for Health, HHS
Dr. Francis Collins, Director, NIH

Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borror, Director, Division of Compliance Oversight, OHRP

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: SUPPORT related paper
Date: Friday, February 28, 2014 5:37:52 PM

Thanks Rose –appreciate all your help this week

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, February 28, 2014 3:28 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: SUPPORT related paper

Hi
The attached paper was just accepted by the Journal of Pediatrics. I don't have a publication date as of yet. I don't think we need a press release, but may want some talking points if asked.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: hirschfs@mail.nih.gov
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Results
Date: Friday, February 28, 2014 3:42:33 PM

Hi
Steven – see below – the SUPPORT results need to be posted before we can change the record – any time frame for us??
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Crawford, Meg [mailto:mcrawford@rti.org]
Sent: Friday, February 28, 2014 3:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT Results

Thanks for the update. That will be the final step before I can move all records to RTI's account.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 28, 2014 3:36 PM
To: Crawford, Meg; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT Results

I asked Steven about this when I saw him at a meeting last week – he was still looking into it and told me he needed to meet with someone at clinicaltrials.gov

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
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From: Crawford, Meg [mailto:mcrawford@rti.org]
Sent: Friday, February 28, 2014 3:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT Results

Hi Rose and Steph,

These results are still not posted.

Thanks,
Meg

Meg Crawford, CCRP
RTI International
701 13th St. NW, Ste. 750
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tel: 202-974-7837
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www.rti.org

From: Higgins, Rosemary (NIH/NICHD) [E]
To: hirschfs@mail.nih.gov
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT Results
Date: Friday, February 28, 2014 3:36:13 PM

HI
Any follow up on the SUPPORT results being posted in clincaltrials.gov?
Thanks
Rose

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Cc: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: SUPPORT related paper
Date: Friday, February 28, 2014 3:27:47 PM
Attachments: NIHMS571602-Breathing Outcomes.pdf

Hi

The attached paper was just accepted by the Journal of Pediatrics. I don't have a publication date as of yet. I don't think we need a press release, but may want some talking points if asked.

Thanks

Rose

Manuscript Information

Journal name:	The Journal of pediatrics
NIHMS ID:	NIHMS571602
Manuscript Title:	Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial
Principal Investigator:	
Submitter:	Author support, Elsevier (ElsevierNIHsupport@elsevier.com)

Manuscript Files

Type	Fig/Table #	Filename	Size	Uploaded
manuscript		YMPD_6740.pdf	339144	2014-02-28 07:04:47
citation		571602_cit.cit	165	2014-02-28 07:04:47

Title: Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial

Authors: Timothy P. Stevens, Neil N. Finer, Waldemar A. Carlo, Peter G. Szilagyi, Dale L. Phelps, Michele C. Walsh, Marie G. Gantz, Abbot R. Laptook, Bradley A. Yoder, Roger G. Faix, Jamie E. Newman, Abhik Das, Barbara T. Do, Kurt Schibler, Wade Rich, Nancy S. Newman, Richard A. Ehrenkranz, Myriam Peralta-Carcelen, Betty R. Vohr, Deanne E. Wilson-Costello, Kimberly Yolton, Roy J. Heyne, Patricia W. Evans, Yvonne E. Vaucher, Ira Adams-Chapman, Elisabeth C. McGowan, Anna Bodnar, Athina Pappas, Susan R. Hintz, Michael J. Acarregui, Janell Fuller, Ricki F. Goldstein, Charles R. Bauer, T.Michael O'Shea, Gary J. Myers, Rosemary D. Higgins

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Edited by Wright and WFB

Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial

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4-00758

MD[22] on behalf of the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network*

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Abbreviations:

BPD – Bronchopulmonary Dysplasia

CA - Corrected Age

CPAP – Continuous Positive Airway Pressure

NICHD - National Institute of Child Health and Human Development

NRN – NICHD Neonatal Research Network

PMA – Postmenstrual Age

ROP – Retinopathy of Prematurity

SUPPORT - Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial

[22]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Key Words: 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, endotracheal

Pulmonary surfactants/therapeutic use

Oxygen inhalation therapy/methods

Oxygen administration & dosage

Follow-up studies

* 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 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 (recruitment 2004-2009; follow-up 2006-2011). T.S. supported by NICHD (SUPPORT Breathing Outcomes Secondary Protocol K23 HD50646). 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.

Registered with ClinicalTrials.gov: NCT00233324

ABSTRACT

Objective To explore the early childhood pulmonary outcomes of infants who participated in the NICHD SUPPORT Trial, using a factorial design that randomized extremely preterm infants to lower vs. higher oxygen saturation targets and delivery room CPAP vs. intubation/surfactant, found no significant difference in the primary composite outcome of death or BPD.

Study design The Breathing Outcomes Study, a prospective secondary to SUPPORT, assessed respiratory morbidity at 6 month intervals from hospital discharge to 18-22 months corrected age (CA). Two pre-specified primary outcomes, wheezing more than twice per week during the worst 2 week period and cough longer than 3 days without a cold were compared between each randomized intervention.

Results One or more interviews were completed for 918 of 922 eligible infants. The incidence of wheezing and cough were 47.9% and 31.0%, respectively, and did not differ between study arms of either randomized intervention. Infants randomized to lower vs. higher oxygen saturation targets had similar risks of death or respiratory morbidities (except for croup, treatment with oxygen or diuretics at home). Infants randomized to CPAP vs. intubation/surfactant had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p<0.05$), respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p<0.05$) and physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p<0.05$) by18-22 months CA.

Conclusion Treatment with early CPAP rather than intubation/surfactant is associated with less respiratory morbidity by 18-22 months CA. Longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions for neonates.

Extremely preterm infants are at greater risk of respiratory morbidity 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) Lung injury, which may result from mechanical ventilation and supplemental oxygen exposure in the early neonatal period, has been identified as a risk factor for development of Bronchopulmonary Dysplasia (BPD) and pulmonary morbidity in infancy, childhood and beyond.(1, 2, 9, 10) Though infants with 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 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 lower (85-89%) compared with higher (91-95%) oxygen saturation targets and early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (intubation/surfactant). Our Network previously reported results of SUPPORT demonstrating no significant differences in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants randomized to either of the two respiratory interventions.(12-14) It is important to note that although the composite incidence of death or BPD was similar, infants randomized to lower rather than higher oxygen saturation targets had significantly lower incidences of retinopathy of prematurity but significantly greater mortality at discharge.

We now report on The Breathing Outcomes Study, a sub study to the SUPPORT Trial, which compared respiratory morbidities among extremely preterm infants treated with the SUPPORT

interventions as neonates. It was hypothesized that infants randomized to lower rather than higher oxygen saturation targets or CPAP, rather than intubation and surfactant, would have a lower incidence of wheezing more than twice per week during their worst 2 week period, a lower incidence of cough lasting more than 3 days without a cold, and as a secondary outcome, less need for outpatient pulmonary care between discharge and 18-22 months' corrected age (CA, age in months following the expected date of full term delivery).

METHODS

Infants eligible for The Breathing Outcomes Study were infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. Infants (n=1316) from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009 and seen in follow-up between 2006 and 2011. As a sub study to SUPPORT, Breathing Outcomes gained approval and began recruitment after SUPPORT began enrollment. As a result not all SUPPORT patients were successfully recruited into Breathing Outcomes. Written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT or separately for those patients already enrolled in SUPPORT but not yet discharged from the hospital. The study was approved by the institutional review boards at all participating Network centers.(12, 13)

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned prior to delivery to receive CPAP after birth, followed by a limited ventilation strategy if intubation was needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age (intubation/surfactant). Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with

either an oxygen saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported.(13) Primary outcomes of SUPPORT included the incidence of death or meeting criteria for the physiologic definition of BPD and death or meeting criteria for traditional BPD, defined as receipt of supplemental oxygen at 36 weeks PMA. (15)

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 telephone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at or near 6, 12 and 18-22 months CA. 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 review the manual of operations (MOP) which included a written interview script. Interview trainees then interviewed a standardized patient simulated by the project trainers. With the aid of the MOP, 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, four interviews were conducted at approximately 6 month intervals beginning at the time of hospital discharge.(16) 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, parents 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 was designed to provide a complete respiratory history over the first 18-22 months' CA. In addition to reporting interview responses during the first 18-22 months CA (defined as the combined responses to the 6, 12, 18-22 month interviews and listed as 6-22 months in Table IV), 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.(17)

Respiratory Questionnaires:

Questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study were used to elicit the frequency and characteristics of respiratory signs, including wheezing and cough; incidence of physician-diagnosed asthma or allergy, presence of

pets in home, siblings, reactive airway disease; 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.(18, 19)

Outcomes

Primary Outcomes: Because preterm infants with or without BPD are at risk for altered airway function and greater risk of wheezing in infancy and later childhood (20-24), we chose to assess respiratory symptoms as a measure of pulmonary morbidity in infancy. Some authors have used incidence of recurrent wheezing as a primary measure of pulmonary morbidity (8, 23, 25), and others have used a combined outcome of either recurrent wheezing or chronic cough as a measure of occult wheezing in preterm infants. (1, 2, 26) To best capture overt and occult wheezing, two primary outcomes were assessed by parental report: the incidence of wheezing more than twice per week during the worst 2 week period and incidence of cough lasting more than 3 days without a cold.

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?". (18) The outcome for wheezing more than twice per week during the worst 2 week period was considered positive if the parent selected "More than two times a week" in response to the question, "during the worst 2 week period, how often has your child's chest sounded wheezy or whistling". The incidence of cough lasting more than 3 days without a cold was ascertained using the Tucson question, "Has your child had a cough for 3 days or more when he/she did not have a cold?".(18)

Secondary outcomes and covariates: Secondary outcomes included incidence of any wheezing and incidence of the combined outcome, wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold. Also assessed were parental report of respiratory signs, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, questions not validated prior to this study were added to the Tucson questionnaires to more fully elicit use of preventive therapies including palivizumab and influenza immunization; attendance at daycare, frequency of BPD exacerbation or flare-up and impact on the family including whether the parent or caregiver needed to change their plans due to their child's breathing; parental report of at least some breast milk intake on any of the 6, 12 or 18-22 month questionnaires; family history of inhaled allergies, food allergies, asthma, COPD or emphysema, other chronic respiratory illness; environmental exposure to tobacco smoke, daycare, children under 12 years old and pets; 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

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 the primary outcome of wheezing more than twice per week between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of wheezing more than twice per week of 29%.(24) 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.

The two primary analyses used the number of patients with either wheezing more than twice per week during their worst 2 week period or cough lasting more than 3 days without a cold as the numerator and the number of infants for whom that outcome was known as the denominator. Secondary responses were tabulated similarly. To assess the robustness of our findings, we calculated respiratory outcomes as a composite outcome with death and also calculated respiratory outcomes for patients with and without BPD. Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. 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. When the two adjustment models failed to converge due to low prevalence (<5%), unadjusted relative risks are reported. 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.

Given the 2x2 factorial design of our randomized trial, we considered the potential for interactions between primary outcomes of one arm on the other (CPAP vs. surfactant and lower vs higher saturation targets). Analysis by robust Poisson regression implemented in Generalized Estimating Equation (GEE) models conducted for the primary outcomes of the main trial did not identify significant interactions between the two treatment arms (p-value for interaction terms all > 0.05). For this reason, only marginal (main) effects of each randomization are reported. No

adjustments have been made for multiple comparisons. All calculations were performed using SAS software, version 9.3 (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study. The 918 subjects with at least one completed questionnaire were considered the study cohort (Figure; available at www.jpeds.com). Follow up rates at each time point are listed in the Figure.

Among the follow up cohort, the group randomized to lower compared with higher oxygen saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with BPD defined using the traditional criteria of supplemental oxygen use at 36 weeks' PMA. The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to intubation/surfactant (Table I). Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and intubation/surfactant groups (Table II; available at www.jpeds.com). Subjects with responses to all four questionnaires were similar in demographic characteristics, neonatal outcomes and home environmental exposures with the exception that those with less than four responses were more apt to have been discharged on respiratory medications (Table III; available at www.jpeds.com).

Overall in the Breathing Outcomes cohort during the first 18-22 months CA, wheezing more than twice per week during the worst 2 week period was reported in 47.9% of patients, cough

lasting more than 3 days without a cold in 31.0% and either wheezing more than twice per week or cough more than 3 days without a cold in 68.2%. Among cohort subjects, use of inhaled (26.3%) and/or systemic steroids (9.4%) was common. Cohort subjects also had high use of physician visits (63.8%), emergency room visits (46.6%) and hospitalizations for wheezing or breathing problems (31.0%).

Primary Outcomes

There was no difference in incidence of the two primary outcomes, wheezing more than twice per week during the worst 2 week period and cough lasting more than 3 days without a cold, between infants randomized to lower compared with higher oxygen saturation targets nor between infants randomized to treatment with CPAP rather than intubation/surfactant (Table IV). Analyzed as a combined outcome, the incidence of death or cough more than 3 days without a cold trended ($p=0.05$) lower among patients in the CPAP compared with intubation/surfactant study arms. The combined outcome of episodes of wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold for the overall cohort was 64.6% and did not differ significantly between infants randomized to lower rather than higher oxygen saturation target or CPAP rather than intubation/surfactant when analyzed alone or as a combined outcome with death (Tables IV and V).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months CA, infants randomized to lower compared with higher oxygen saturation targets had a lower incidence of wheezing and use of nebulized medications following NICU discharge (Table IV). Over the first 18-22 months CA, infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (Table IV). When

analyzed as composite outcomes, the lower compared with higher saturation group had a similar incidence of death or respiratory morbidities except for croup diagnosed by a doctor or treatment with a diuretic or oxygen at home) (Table V).

Early CPAP Intervention

At 6 months CA, infants randomized to treatment with CPAP and a limited ventilation strategy rather than intubation/surfactant were reported to have fewer asthma, reactive airway disease or BPD exacerbation or flare-up episodes diagnosed by a doctor since NICU discharge and a trend toward fewer hospitalizations for wheezing or breathing problems. Perhaps related to these differences, parents or primary caregivers of infants randomized to CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (Table V).

During the first 18-22 months CA, infants randomized to early CPAP versus intubation/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 exacerbation or flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, p=0.02), or wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, $p<0.05$). Compared with those of infants in the intubation/surfactant group, parents or guardians of infants in the CPAP group were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, $p<0.05$). When outcomes were analyzed as composite outcomes with death, similar findings were observed with additional differences noted in incidence of treatment with

oxygen or diuretics at home and a trend towards lower incidence of overnight hospitalization for breathing problems.

As expected, our study questionnaires were able to detect significant differences in respiratory outcomes for infants with versus without BPD (Table VI). Although the incidence of wheezing more than twice per week was different between infants with and without BPD, there was no difference in incidence of cough lasting more than 3 days as an indicator of occult wheezing. Taken together, the combined incidence of either overt (wheezing more than twice per week) or potential occult (cough lasting more than 3 days) wheezing was significantly different between infants with BPD and those without (Table VI).

DISCUSSION

We report results of the Breathing Outcomes Study, a sub study to SUPPORT, which sought to quantify respiratory morbidity by 18-22 months corrected age for extremely premature children born 24-27 weeks gestation. We found no significant differences at 18-22 months CA in the incidence of either of the two primary outcomes, wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold, between patients randomized to lower versus higher oxygen saturation targets or randomized to CPAP versus intubation/surfactant.

In secondary analyses, although extremely preterm infants randomized to low compared with high oxygen saturation targets were less likely to have wheezing or use a home nebulizer at 6 months CA and to have wheezing apart from a cold between discharge and 18-22 months CA, these differences were not seen when respiratory outcomes were analyzed as composite

outcomes with death. In fact, analyzed this way, the incidence of death or adverse respiratory outcome for some measures of morbidity were worse for patients in the low saturation group. 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, 27-29) Though patients treated with lower compared with higher saturation targets in SUPPORT had a shorter duration of oxygen exposure, they had greater mortality, similar incidence of BPD, and based on results of the Breathing Outcomes Study, survivors had a similar use of outpatient services for respiratory care and only minor differences in the incidence of respiratory signs. Based on these findings, if oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant lung injury other than targeting lower oxygen saturations will be needed. (24, 30)

Though the primary outcomes were similar, patients in the first 18-22 months CA who were randomized to CPAP and limited ventilation rather than intubation followed by surfactant administration within 1 hour had a lower incidence of several important respiratory morbidities including respiratory illnesses diagnosed by a doctor, treatment with oxygen or diuretics at home and a trend towards lower incidence of overnight hospitalization for breathing problems. Likely related to these findings was a significant reduction in the proportion of parents reporting that they needed to change their daily plans due to their child's breathing difficulties. These differences persisted whether the outcome was analyzed among survivors only or as composite outcomes with death.

Respiratory benefits of CPAP and a limited ventilation strategy were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria(15), was similar between CPAP and intubation/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 age among a 39 patient single-center sub cohort of study infants randomized to CPAP. (31, 32) These observations suggest that treatment of infants 25-27 6/7 weeks gestation at risk for RDS with a limited ventilation strategy is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone. As confirmed in our analysis of respiratory morbidity, BPD has proven to be useful surrogate to identify infants at highest risk of later morbidity. However, based upon the high incidence of respiratory morbidity among infants without BPD, it is likely, though not proven in this study, that the prevalence of respiratory morbidity in former preterm infants may be under recognized. Given the potential for respiratory therapies to improve pulmonary outcomes for infants with and without BPD, 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 signs and use of health care are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months CA. Over two-thirds of subjects in the Breathing Outcomes Study cohort reported wheezing more than twice per week during their worst 2 week period or a cough lasting more than 3 days without a cold. Treatment of these respiratory signs was not only associated with frequent use of both inhaled and systemic steroids, medications that have potential long term effects on growth and development, (33, 34) but also with frequent physician and emergency room visits and hospitalizations, health services which contribute greatly to health care costs.(8)

The strengths of this study include the large number of extremely preterm infants enrolled. 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 to assess outcome measures due to clinical and financial concerns associated with the use of invasive pulmonary testing and the 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. (16, 35)

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.(16) 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 more common use of antenatal steroids than the entire eligible cohort. (36)

In summary, we found no significant differences in the incidence of wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold at 18-22 months CA between extremely preterm survivors who were randomized at delivery to either lower versus higher oxygen saturation targets or early CPAP and a limited ventilation strategy versus intubation/surfactant. In secondary analyses, we found minor reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months CA, but an overall increase in the risk of death or respiratory morbidity (except for croup and treatment with oxygen or diuretics at home) for infants randomized to lower vs. higher oxygen saturation targets. Also in secondary analyses, we report less respiratory morbidity among survivors and lower incidence or respiratory morbidity or death among infants randomized to CPAP rather than intubation/surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over intubation/surfactant.(12-14) 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 surfactant within 1 hour is safe and may result in less respiratory morbidity during the first 18-22 months CA. Lastly, our findings demonstrate a high risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation (with or without BPD) that not only require close medical monitoring but also pose potential burdens to families as well as to society by increasing health care costs.

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Figure. CONSORT diagram including follow up rates.

Table 1. Demographic and neonatal characteristics of follow-up cohorts.

Table 2. Family and environmental exposure history of follow-up cohorts.

Table 3. Differences between those who answered all four questionnaires vs less than four.

Table 4. Respiratory outcomes for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts at the 6 month interview and for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Table 5. Combined outcomes of death or respiratory morbidity for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Table 6. Respiratory outcomes for infants with traditional BPD (oxygen requirement at 36 weeks post-menstrual age) for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

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Table 1.

Demographic and neonatal characteristics of follow-up cohorts.

	Low Sat N=439	High Sat N=479	CPAP N=474	Intubation/ Surfactant N=444
Birth Weight (g, mean ± s.d.)	858 ± 186	844 ± 190	850 ± 184	851 ± 193
Gestational Age (w, mean ± s.d.)	25.9 ± 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 (35.6)	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 (traditional definition) - 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)

* Low sat vs. high sat, $p < 0.05$
** Low sat vs. high sat, $p < 0.01$

Table 2.

Family and environmental exposure history of follow-up cohorts.

	Low Sat N=439	High Sat N=479	CPAP N=474	Intubation/ Surfactant N=444
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)
Food allergies - no. (%)	60 (14.4)	52 (11.3)	61 (13.5)	51 (11.9)
Inhaled allergies – no. (%)	140 (30.4)	129 (30.9)	136 (30.1)	133 (31.2)
Chronic Respiratory Disease no. (%)	7 (1.7)	4 (0.9)	1 (0.2)	10 (2.5)
Any breast milk - 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. (%)	181 (40.5)	177 (36.1)	187 (38.5)	171 (37.8)
Flu vaccination- no. (%)	307 (78.1)	342 (80.1)	335 (79.0)	314 (79.3)
RSV prophylaxis - no. (%)	281 (71.5)	313 (73.1)	308 (72.6)	286 (72.0)

Table 3 - Online Only

Differences between those who answered all four questionnaires vs less than four.

Label	Answered <4 questionnaires N=50	Answered all 4 questionnaires N=868	P-Value
Birth Weight	852.94+158.29	852.23+189.68	0.98
Gestational Age	25.62+1.03	25.90+1.02	0.06
24 wks 0 days - 25 wks 6 days	23(46.00)	307(35.45)	0.13
25 wks 0 days - 27 wks 6 days	27(54.00)	559(64.55)	
Male	24(48.00)	452(52.07)	0.58
Non-Hispanic Black	13(26.00)	309(35.60)	0.47¥
Non-Hispanic White	25(50.00)	365(42.05)	
Hispanic	11(22.00)	164(18.89)	
Other/unknown	1(2.00)	30(3.46)	
Length of NICU Hospitalization	109.24+49.64	98.76+37.62	0.15
BPD (supplemental O2)	22(44.00)	355(40.90)	0.66
BPD (physiological definition)	25(50.00)	329(37.90)	0.09
Home on oxygen	16(32.00)	199(23.03)	0.15
Home on respiratory medication	17(43.59)	189(26.21)	0.02
Discharged home October-March	22(44.00)	435(50.35)	0.38
Family history of COPD,emphysema, etc	2(4.00)	89(10.25)	0.22¥
First degree relative with asthma	13(26.00)	288(33.18)	0.29
Family history of allergies	6(15.38)	141(16.79)	0.82
Family history of CRD	0(0.00)	11(1.37)	0.99¥
Breast fed	16(32.00)	299(34.45)	0.72
Smoking in house	23(46.94)	352(41.27)	0.43
Spent time at daycare	21(47.73)	284(36.55)	0.14
Living with children < 12	23(52.27)	482(62.03)	0.20
Pets	23(46.00)	335(38.59)	0.30
Flu Shot	34(77.27)	615(79.25)	0.75
RSV Shot	32(72.73)	562(72.33)	0.95
CPAP	28(56.00)	446(51.38)	0.53
Oxygen Saturation	30(60.00)	449(51.73)	0.25

¥ = Fisher's exact test

Table 4. Respiratory outcomes for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts at the 6 month interview and for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Primary Outcomes	**Low Sat**	**High Sat**	**ARR (95% CI)**	**p-value**	**CPAP**	**Intubation/ Surfactant**	**ARR (95% CI)**	**p-value**
Has your child's chest sounded wheezy or whistling more than twice in one week?								
6 months	94 (22.0)	129 (27.7)	0.73 (0.53, 1.01)	0.06	107 (23.2)	116 (26.9)	0.79 (0.58, 1.09)	0.16
6-22 months	203 (46.7)	233 (49.1)	0.92 (0.70, 1.22)	0.57	224 (47.7)	212 (48.2)	0.90 (0.68, 1.19)	0.47
Has your child had a cough for more than 3 days without a cold?								
6 months	63 (16.9)	76 (19.3)	0.84 (0.57, 1.22)	0.35	63 (16.2)	76 (20.2)	0.77 (0.53, 1.12)	0.17
6-22 months	127 (30.8)	141 (31.1)	1.01 (0.75, 1.37)	0.93	127 (28.4)	141 (33.7)	0.81 (0.60, 1.10)	0.18
Secondary Outcomes								
Symptoms								
Wheezing/whistling more than twice in one week or cough more than 3 days								
6 months†	162 (43.5)	195 (49.5)	0.78 (0.58, 1.05)	0.10	178 (45.8)	179 (47.5)	0.95 (0.70, 1.28)	0.72
6-22 months	276 (66.8)	316 (69.5)	0.87 (0.65, 1.18)	0.37	303 (67.8)	289 (68.7)	0.95 (0.70, 1.29)	0.74
Has your child's chest sounded wheezy or whistling?								
6 months	135 (36.3)	171 (43.4)	0.73 (0.54, 1.00)	<0.05	151 (38.8)	155 (41.1)	0.89 (0.66, 1.21)	0.47
6-22 months	245 (59.3)	286 (62.9)	0.85 (0.64, 1.13)	0.27	269 (60.2)	262 (62.2)	0.86 (0.64, 1.15)	0.31
Has your baby's chest sounded wheezy or whistling apart from colds?								
6 months	61 (16.4)	84 (21.3)	0.73 (0.50, 1.06)	0.10	66 (17.0)	79 (21.0)	0.77 (0.53, 1.11)	0.16
6-22 months	117 (28.4)	165 (36.3)	0.67 (0.49, 0.91)	0.01	129 (28.9)	153 (36.5)	0.68 (0.50, 0.92)	0.01
Illnesses								
Has your child had asthma, reactive airway disease or BPD exacerbation or flare-up diagnosed by a doctor?								
6 months†	51 (13.7)	62 (15.7)	0.84 (0.56, 1.27)	0.41	48 (12.3)	65 (17.2)	0.66 (0.44, 1.00)	<0.05
6-22 months†	140 (33.9)	158 (35.0)	1.01 (0.75, 1.37)	0.93	144 (32.2)	154 (36.8)	0.81 (0.60, 1.09)	0.16
Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?								
6 months	72 (19.4)	78 (19.8)	0.98 (0.67, 1.41)	0.90	70 (18.0)	80 (21.2)	0.82 (0.57, 1.19)	0.30
6-22 months	161 (39.0)	183 (40.4)	0.96 (0.72, 1.28)	0.79	167 (37.4)	177 (42.2)	0.81 (0.61, 1.09)	0.17
Any of asthma, reactive airway disease, BPD exacerbation or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor								
6 months	95 (25.5)	109 (27.7)	0.91 (0.65, 1.27)	0.58	96 (24.7)	108 (28.7)	0.81 (0.58, 1.13)	0.22
6-22 months	204 (49.4)	241 (53.1)	0.91 (0.69, 1.21)	0.52	213 (47.7)	232 (55.2)	0.71 (0.53, 0.95)	0.02

Has your child had croup diagnosed by a doctor?								
6 months††	9 (2.4)	11 (2.8)	0.87 (0.36, 2.08)	0.75	7 (1.8)	13 (3.5)	0.52 (0.21, 1.30)	0.16
6-22 months†	46 (11.2)	39 (8.6)	1.35 (0.84, 2.16)	0.21	40 (9.0)	45 (10.8)	0.77 (0.49, 1.23)	0.28
Health Services								
Has your child ever had to visit the doctor or Emergency Room for breathing or wheezing problems?								
6 months	167 (44.9)	188 (47.8)	0.82 (0.60, 1.11)	0.20	173 (44.6)	182 (48.3)	0.81 (0.60, 1.10)	0.18
6-22 months	292 (70.1)	319 (70.1)	0.98 (0.72, 1.34)	0.89	304 (68.0)	307 (72.9)	0.73 (0.53, 1.00)	<0.05
Has your child had to stay in a hospital overnight?								
6 months	105 (28.2)	118 (30.0)	0.89 (0.64, 1.23)	0.47	106 (27.3)	117 (31.0)	0.79 (0.57, 1.10)	0.17
6-22 months	169 (41.0)	199 (43.7)	0.90 (0.68, 1.20)	0.48	182 (40.7)	186 (44.3)	0.87 (0.66, 1.16)	0.35
Has your child had to stay in a hospital overnight for wheezing/breathing problems?								
6 months	69 (18.6)	73 (18.6)	0.98 (0.67, 1.44)	0.93	64 (16.5)	78 (20.7)	0.72 (0.49, 1.05)	0.09
6-22 months	129 (31.3)	140 (30.8)	1.04 (0.77, 1.40)	0.80	130 (29.1)	139 (33.1)	0.82 (0.61, 1.11)	0.21
Medications								
Treated with a diuretic medication?								
6 months†	27 (6.3)	24 (5.2)	1.29 (0.72, 2.32)	0.39	23 (5.0)	28 (6.5)	0.72 (0.40, 1.29)	0.27
6-22 months†	31 (7.1)	24 (5.0)	1.50 (0.85, 2.64)	0.16	24 (5.1)	31 (7.0)	0.68 (0.39, 1.20)	0.18
Treated with an inhaled steroid medication?								
6 months	51 (11.9)	53 (11.4)	1.12 (0.73, 1.71)	0.61	54 (11.7)	50 (11.6)	1.00 (0.66, 1.53)	0.99
6-22 months	112 (25.6)	129 (26.9)	0.97 (0.71, 1.32)	0.82	128 (27.1)	113 (25.5)	1.10 (0.80, 1.50)	0.56
Treated with a nebulized medication?								
6 months††	5 (1.2)	18 (3.9)	0.30 (0.11, 0.81)	0.02	13 (2.8)	10 (2.3)	1.22 (0.54, 2.75)	0.63
6-22 months†	29 (6.6)	42 (8.8)	0.73 (0.44, 1.22)	0.23	39 (8.3)	32 (7.2)	1.11 (0.67, 1.84)	0.69
Treated with a systemic steroid medication?								
6 months††	11 (2.6)	8 (1.7)	1.50 (0.61, 3.70)	0.38	12 (2.6)	7 (1.6)	1.61 (0.64, 4.04)	0.31
6-22 months	44 (10.1)	42 (8.8)	1.13 (0.71, 1.80)	0.62	48 (10.2)	38 (8.6)	1.22 (0.77, 1.95)	0.40
Treated with oxygen at home?								
6 months†	90 (24.3)	80 (20.3)	1.22 (0.83, 1.79)	0.31	80 (20.6)	90 (23.9)	0.82 (0.56, 1.21)	0.32
6-22 months	104 (25.2)	96 (21.1)	1.31 (0.92, 1.88)	0.14	94 (21.0)	106 (25.3)	0.80 (0.56, 1.15)	0.23
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	50 (12.9)	77 (20.4)	0.58 (0.39, 0.87)	<0.01
6-22 months	139 (33.7)	170 (37.4)	0.87 (0.65, 1.17)	0.36	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 (†). If the two adjustment model failed to converge, unadjusted relative risks are reported (††).

Table 5. Combined outcomes of death or respiratory morbidity for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

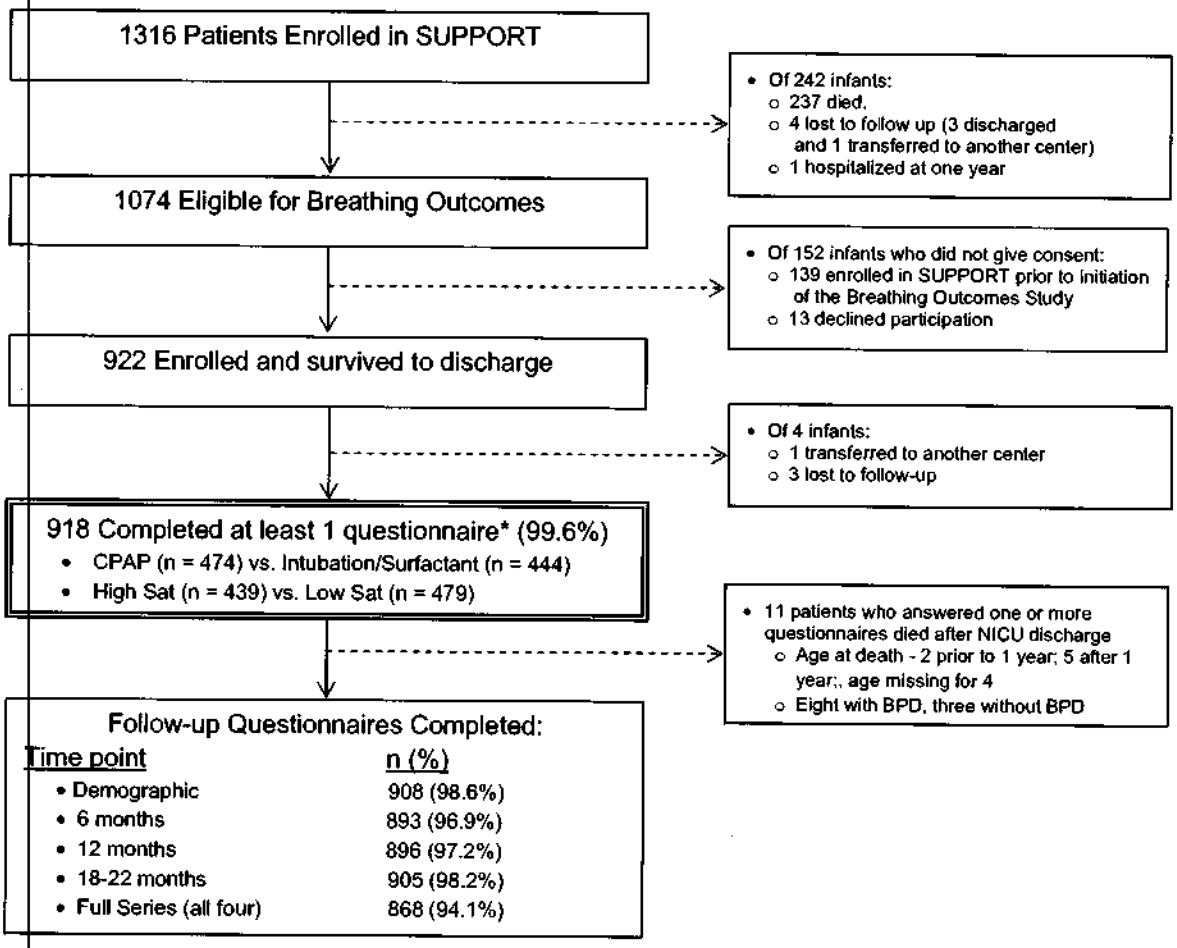
Outcomes with Death	Low Sat N=586	High Sat N=569	ARR (95% CI)	P-value	CPAP N=583	Intubation/ Surfactant N=572	ARR (95% CI)	P-value
Primary Outcomes								
Has your child's chest sounded wheezy or whistling more than twice in one week?	337 (59.5)	344 (59.0)	1.06 (0.83, 1.37)	0.62	337 (58.0)	344 (60.6)	0.86 (0.67, 1.11)	0.26
Has your child had a cough for more than 3 days without a cold	262 (47.9)	254 (45.0)	1.18 (0.91, 1.51)	0.21	240 (42.9)	276 (49.9)	0.78 (0.60, 1.00)	0.05
Secondary Outcomes								
Wheezing/whistling more than twice in one week or cough more than 3 days	410 (75.0)	425 (75.2)	0.99 (0.74, 1.32)	0.96	414(74.1)	421 (76.1)	0.92 (0.69, 1.23)	0.56
Has your child's chest sounded wheezy or whistling?	379 (69.3)	395 (69.9)	0.98 (0.75, 1.29)	0.9	380 (68.0)	394 (71.2)	0.84 (0.64, 1.10)	0.21
Has your baby's chest sounded wheezy or whistling apart from colds?	252 (46.1)	275 (48.7)	0.91 (0.71, 1.17)	0.48	241 (43.1)	286 (51.7)	0.70 (0.54, 0.90)	<0.01*
Has your child had asthma, reactive airway disease or BPD exacerbation or flare-up diagnosed by a doctor?	274 (50.1)	270 (47.9)	1.17 (0.91, 1.50)	0.23	256 (45.8)	288 (52.2)	0.76 (0.59, 0.98)	0.03*
Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?	295 (53.9)	295 (52.3)	1.12 (0.87, 1.44)	0.39	279 (49.9)	311 (56.3)	0.78 (0.60, 1.00)	0.05
Any of asthma, reactive airway disease, BPD exacerbation or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor	339 (62.0)	351 (62.2)	1.05 (0.81, 1.36)	0.71	326 (58.3)	364 (65.9)	0.71 (0.54, 0.92)	<0.01*
Has your child had croup diagnosed by a doctor?	180 (32.9)	153 (27.1)	1.35 (1.03, 1.77)	0.03*	154 (27.5)	179 (32.4)	0.78 (0.60, 1.03)	0.08
Has your child ever had to visit the doctor or Emergency Room for breathing or wheezing problems?	427 (78.1)	430 (76.1)	1.11 (0.82, 1.50)	0.49	417 (74.6)	440 (79.6)	0.73 (0.54, 0.99)	<0.05*
Has your child had to stay in a hospital overnight?	303 (55.5)	310 (54.9)	1.06 (0.82, 1.37)	0.64	294 (52.6)	319 (57.8)	0.84 (0.65, 1.08)	0.17
Has your child had to stay in a hospital overnight for wheezing/breathing problems?	263 (48.2)	252 (44.6)	1.20 (0.93, 1.54)	0.17	242 (43.3)	273 (49.5)	0.78 (0.61, 1.01)	0.06
Treated with a diuretic medication?	165 (29.0)	137 (23.4)	1.42 (1.07, 1.88)	0.02*	137 (23.5)	165 (28.8)	0.74 (0.56, 0.98)	0.04*
Treated with an inhaled steroid medication?	246 (43.2)	240 (41.0)	1.15 (0.89, 1.47)	0.29	241 (41.3)	245 (42.8)	0.96 (0.75, 1.24)	0.76
Treated with a nebulized medication?	163(28.6)	155 (26.5)	1.15 (0.87, 1.52)	0.33	152 (26.1)	166 (29.0)	0.85 (0.64, 1.13)	0.27
Treated with a systemic steroid medication?	178 (31.3)	156 (26.6)	1.28 (0.98, 1.68)	0.07	162 (27.8)	172 (30.1)	0.88 (0.68, 1.16)	0.38
Treated with oxygen at home?	238 (43.5)	206 (36.5)	1.46 (1.11, 1.91)	<0.01*	206 (36.9)	238 (43.1)	0.76 (0.58, 1.00)	0.05*
Have you had to change your plans because of your child's breathing problems?	273 (49.9)	281 (49.7)	1.04 (0.81, 1.34)	0.74	257 (46.0)	297 (53.7)	0.72 (0.56, 0.92)	0.01*

* p <0.05

Table 6. Primary Outcomes	Traditional BPD N=377	Not Traditional BPD N=539	ARR (95% CI)	P-Value
Has your child's chest sounded wheezy or whistling more than twice in one week?	194 (52.0)	242 (45.1)	1.52 (1.15, 2.01)	<0.01
Has your child had a cough for more than 3 days without a cold?	119 (33.7)	149 (29.0)	1.17 (0.86, 1.60)	0.314
Secondary Outcomes				
Symptoms				
Wheezing/whistling more than twice in one week or cough more than 3 days	262 (74.2)	330 (64.1)	1.76 (1.27, 2.43)	<0.01
Has your child's chest sounded wheezy or whistling?	231 (65.4)	300 (58.3)	1.61 (1.17, 2.21)	<0.01
Has your baby's chest sounded wheezy or whistling apart from colds?	129 (36.8)	153 (29.7)	1.57 (1.16, 2.13)	<0.01
Illnesses				
Has your child had asthma, reactive airway disease or BPD flare-up diagnosed by a doctor?	133 (38.0)	165 (32.0)	1.58 (1.17, 2.13)	<0.01
Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?	152 (43.2)	192 (37.4)	1.34 (1.00, 1.80)	0.05
Any of asthma, reactive airway disease, BPD flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	195 (55.4)	250 (48.5)	1.47 (1.08, 2.00)	0.01
Has your child had croup diagnosed by a doctor?	29 (8.2)	56 (10.9)	0.78 (0.46, 1.33)	0.36
Health Services				
Has your child ever had to visit the doctor or Emergency Room for breathing or wheezing problems?	267 (75.6)	344 (66.8)	1.56 (1.08, 2.25)	0.02
Has your child had to stay in a hospital overnight?	186 (52.7)	182 (35.4)	2.22 (1.64, 3.02)	<.0001
Has your child had to stay in a hospital overnight for wheezing/breathing problems?	136 (38.5)	133 (25.9)	1.89 (1.40, 2.57)	<.0001
Medications				
Treated with a diuretic medication?†	47 (12.5)	8 (1.5)	11.86 (5.28, 26.62)	<.0001
Treated with an inhaled steroid medication?	135 (35.8)	106 (19.7)	2.40 (1.75, 3.29)	<.0001
Treated with a nebulized medication?†	35 (9.3)	36 (6.7)	1.53 (0.88, 2.67)	0.14
Treated with a systemic steroid medication?	40 (10.6)	46 (8.5)	1.45 (0.93, 2.26)	0.10
Treated with oxygen at home?	164 (46.5)	36 (7.0)	9.18 (5.81, 14.52)	<.0001
Family				
Have you had to change your plans because of your child's breathing problems?	143 (40.5)	166 (32.2)	1.34 (1.00, 1.79)	< 0.05

Where models did not converge, adjustments are limited to center and gestational age (†).

Figure 1. Consort diagram including follow up rates.



* Follow-up Cohort

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:

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To: "Stevens, Timothy"; Newman, Jamie <newman@rti.org> (newman@rti.org); Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131439R1 submitted to JPediatr
Date: Friday, February 28, 2014 2:35:16 PM

Can I get a copy of the accepted version and the anticipated publication date?

Thanks
Rose

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Subject: FW: Your Manuscript # 20131439R1 submitted to JPediatr

Our revised manuscript has been accepted!

Thanks to all for your contributions!

Tim

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Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial The Journal of Pediatrics

Dear Dr. Stevens,

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To: Spong, Catherine (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: FW: CBS News request

Hi Cathy—BTW - -as Kerri reminded me – (b)(5) compare what we sent agreed to send out to what Renate was suggesting that they first send out – see email below!

We got them to agree to let us do the analysis, that would be based on publicly available data, in a straightforward and usable way to answer their questions –

Mona

Mona Jaffe Rowe, M.C.P.
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National Institutes of Health, DHHS
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Hi Bob:

Per our discussion, see Kim's questions below. I did a search on reporter putting "Neonatal Research Network" in the search box, checking the title box only, and selecting all years. The search result can be found here:
http://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=10E0CD0F4685C0DE7598B8961CAA4A01A2FFCEB861BF

I've also exported it into an excel file which is attached. The point of this exercise is to be able to say that NIH makes all information about its grants publicly available on NIH Reporter.

Here would be the proposed response:

(b)(5)

(b)(5)

You can run these responses through the traps.

Thanks,
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Wednesday, February 26, 2014 5:17 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Renate,

Thank you for the information. Two follow ups:

1. I guess what we need from you is the cost of the SUPPORT study, or your best estimate. But you seem to be saying that NIH has no idea how much this study cost taxpayers. I would think that, in terms of oversight, that this is a figure that NIH should be able to put its finger on. If you can't for some reason, please just give us **the total federal funding provided to NRN during the years of the SUPPORT study** and we'll have to use the total and say that the study was some subset of the total, but that NIH doesn't know how much.
2. On the consent forms: did the NIH staff scientist or steering committee object to or disapprove of the consent form general template?

Thanks again.

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
410-591-9567 cell
skeenk@cbsnews.com

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Wednesday, February 26, 2014 10:42 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Again, apologies for the delay! Here are responses to your two questions attributable to NIH.

Please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. We were told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc.

NIH did not approve the SUPPORT study consent forms. The study was conducted as a part of a cooperative agreement, and is overseen by a steering committee. An NIH staff scientist sits on the steering committee that reviewed the general template for the consent form but final approval lies with the local Institutional Review Boards (IRB). The consent form was tailored by each research institution to meet local needs, and meet the approval standards of local IRBs.

Please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars.

We cannot confirm the figure you cite. The NICHD does not allocate funding to the Neonatal Research Network (NRN) on a per trial (or per study) basis. Rather, funding is allocated annually for the entirety of the NRN's operations. These operations include not only the cost of conducting a study, but also for such expenses as equipment use and administrative tasks. Typically, Network researchers conduct numerous neonatal studies (in addition to SUPPORT) during the course of a year. Funding for the Network varies from year to year, depending on the amount allocated for the NIH budget and other factors.

Best,
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Tuesday, February 25, 2014 11:20 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Do you have confirmation on the SUPPORT study cost figure: $20.8 million in federal tax dollars? If not, when will we get that information? Thanks.

From: Skeen, Kim
Sent: Monday, February 24, 2014 11:51 AM
To: 'Myles, Renate (NIH/OD) [E]'
Subject: RE: CBS News request

Got it. We're told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc. Please let me know if that is NOT correct. Thank you!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:55 AM
To: Skeen, Kim
Subject: RE: CBS News request

Sorry, working from BB: only institutions conducting the study would have their IRBs review and approve the consent form. NIH did not carry out the study.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:53 AM

To: 'Skeen, Kim'
Subject: RE: CBS News request

No, only institutions conducting research would have their IRBs review and approve the consent form. NIH did not carry the out the study.

From: Skeen,]
Sent: Monday, February 24, 2014 10:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Yes you did confirm the 24 IRB's figure some time ago—just double checking that NIH was one of the IRB's. Thanks again.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:49 AM
To: Skeen, Kim
Subject: RE: CBS News request

I confirmed that with you quite some time ago. I'll dig it up and resend.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:48 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
410-591-9567 cell
skeenk@cbsnews.com

<NRN Funding on NIH Reporter.csv>

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, February 28, 2014 12:28 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: Interview request: SUPPORT Study

Never mind! ☺

From: Dreyfuss, Ira (HHS/ASPA)
Sent: Friday, February 28, 2014 12:03 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); Daniels, Carla (HHS/ASPA/News Division); HHS/OS Interviews
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Akinso, Woleola (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]
Subject: Re: Interview request: SUPPORT Study

Ok
Ira

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Friday, February 28, 2014 11:51 AM
To: Sye, Tait (OS/ASPA); Daniels, Carla (HHS/ASPA/News Division); Dreyfuss, Ira (HHS/ASPA); OS - Interviews
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Akinso, Woleola (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL) <ODOCPLInterviews@mail.nih.gov>; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview request: SUPPORT Study

ADD
Deadline: today

Kim had a few follow up questions.

1. **I guess what we need from you is the cost of the SUPPORT study, or your best estimate. But you seem to be saying that NIH has no idea how much this study cost taxpayers. I would think that, in terms of oversight, that this is a figure that NIH should be able to put its finger on. If you can't for some reason, please just give us the total federal funding provided to NRN during the years of the SUPPORT study and we'll have to use the total and say that the study was some subset of the total, but that NIH doesn't know how much.**

(b)(5)

2. **On the consent forms: did the NIH staff scientist or steering committee object to or disapprove of the consent form general template?**

(b)(5)

From: Sye, Tait (OS/ASPA)
Sent: Wednesday, February 26, 2014 11:19 AM
To: Daniels, Carla (HHS/ASPA/News Division); Myles, Renate (NIH/OD) [E]; Dreyfuss, Ira (HHS/ASPA); HHS/OS Interviews
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Akinso, Woleola (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview request: SUPPORT Study

No concerns here.

From: Daniels, Carla (HHS/ASPA/News Division)
Sent: Wednesday, February 26, 2014 10:03 AM
To: Myles, Renate (NIH/OD) [E]; Dreyfuss, Ira (HHS/ASPA); Sye, Tait (OS/ASPA); OS - Interviews
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Akinso, Woleola (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview request: SUPPORT Study

Ok, Tait do you have any concerns?

Carla L. Daniels
Public Affairs Specialist
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs
Washington, DC
Office: 202-690-4595
Cell: (b)(6)
www.hhs.gov/news

From: Daniels, Carla (HHS/ASPA/News Division)
Sent: Wednesday, February 26, 2014 9:56 AM
To: Myles, Renate (NIH/OD) [E]; Dreyfuss, Ira (HHS/ASPA); Sye, Tait (OS/ASPA); OS - Interviews
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Akinso, Woleola (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview request: SUPPORT Study

Carla L. Daniels
Public Affairs Specialist
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs
Washington, DC
Office: 202-690-4595
Cell: (b)(6)
www.hhs.gov/news

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Wednesday, February 26, 2014 9:46 AM

To: Dreyfuss, Ira (HHS/ASPA); Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Akinso, Woleola (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview request: SUPPORT Study

ADD

Kim Skeen
CBS News
Deadline: today

Additional information: We worked with Kim late last year and provided responses to her many questions. The story was put on hold and Kim is back to confirm a few points. Her questions and our responses are listed below.

Please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. We were told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc.

(b)(5)

Please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars.

(b)(5)

From: Dreyfuss, Ira (HHS/ASPA)
Sent: Thursday, October 24, 2013 5:06 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

Ok
Ira

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Thursday, October 24, 2013 5:04 PM
To: Sye, Tait (OS/ASPA); Dreyfuss, Ira (HHS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

ADD

Kim Skeen had additional questions

Deadline: today

Were reports generated from these interim data checks? Please provide copies of these reports.

(b)(5)

How many interim data checks were done during the SUPPORT study? What were the results?

(b)(5)

Were reports generated from these interim data checks? Please provide copies of these reports.

(b)(5)

Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?

(b)(5)

During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

(b)(5)

From: Sye, Tait (OS/ASPA)
Sent: Monday, September 09, 2013 9:15 PM
To: Myles, Renate (NIH/OD) [E]; Dreyfuss, Ira (HHS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ok

From: Myles, Renate (NIH/OD) [E] [mylesr@od.nih.gov]
Sent: Monday, September 09, 2013 9:08 PM
To: Dreyfuss, Ira (HHS/ASPA); Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)

Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

Hi Ira:

See change highlighted in yellow below.

Thanks,
Renate

From: Dreyfuss, Ira (HHS/ASPA)
Sent: Monday, September 09, 2013 8:03 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: Re: Interview request: SUPPORT Study (Deadline: immediate)

Ok
Ira

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, September 09, 2013 06:47 PM
To: Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL) <ODOCPLInterviews@mail.nih.gov>; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ADD

Kim Skeen had additional questions:
Deadline: tomorrow

We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?

(b)(5)

With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

(b)(5)

Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

(b)(5)

From: Sye, Tait (OS/ASPA)
Sent: Friday, September 06, 2013 9:29 AM
To: Myles, Renate (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ok

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Friday, September 06, 2013 9:27 AM
To: Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)
Importance: High

ADD

Kim Skeen
CBS Sunday Morning
Deadline: immediate

Kim had follow up questions. NIH responses are below:

1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

(b)(5)

2. **What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

(b)(5)

3. **How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

(b)(5)

(b)(5)

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, August 29, 2013 11:23 AM
To: Sye, Tait (OS/ASPA); Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

Yes and Yes.

From: Sye, Tait (OS/ASPA)
Sent: Thursday, August 29, 2013 11:22 AM
To: Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

Who would do interview? Dr. Guttmacher?

Ok, so long as he sticks to TPs.

Talking Points:

*HHS is holding this public meeting so we can hear from the public and gather feedback on the important issue of protection of human subjects in research, specifically standard of care in clinical research.

*The public comment period will remain open until September 9, so members of the public who were unable to attend today's meeting can still submit comments.

*Our next step is to review and consider all the comments. This is an important issue that deserves thoughtful deliberation.

Hot Button QA:

Q: When will OHRP release updated guidance regarding standard of care research?

A: The first step is to solicit comments and feedback from the public. After that, HHS will thoughtfully review the comments. There is no timetable set for releasing the updated guidance.

Q: Last week, Public Citizen raised concerns similar to SUPPORT in another NIH supported study, the Transfusion of Premature (TOP) trial. Do you think that trial should be suspended until new guidance is released?

A: HHS is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. Per OHRP's letter to UAB in June of this year, OHRP is postponing actions on studies involving similar designs to SUPPORT (standard of care in clinical research) until the process of producing appropriate guidance is completed.

From: Fine, Amanda (NIH/OD) [E] [mailto:amanda.fine@nih.gov]
Sent: Thursday, August 29, 2013 11:20 AM
To: OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

ADD
Arthur Allen (Freelancer)
Science
SUPPORT TRIAL
arthurallenw@apl.com

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, August 21, 2013 12:23 PM
To: Myles, Renate (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Fritz, Craig (NIH/OD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: Interview request: (insert subject of interview only)

Producer: Kim Skeen, for Sharyl Attkison (reporter)
Organization: CBS Sunday morning
Phone: 202-457-4383
Subject: SUPPORT Trial
Deadline: Today
Spokesperson: Alan E. Guttmacher, M.D., Director, NICHD
Expected place of publication: CBS Sunday morning
Expected date of publication/airing: Sunday, September 1
Expected prominence: news feature

Skeen called and asked if Dr. Guttmacher would be available for a taping next week to discuss the NIH's views on the SUPPORT trial ruling. The feeling at our institute is (b)(5)

(b)(5)

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, February 28, 2014 11:09 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: FOR YOUR REVIEW: CBS News request on SUPPORT

Probably 8 mpnths from now. ☺ No, she did not but I'll definitely ask.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, February 28, 2014 10:34 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: FOR YOUR REVIEW: CBS News request on SUPPORT

Yeah, Rose is good with it too. She didn't give us an ETA on when it will air, did she?

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, February 28, 2014 10:21 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: FOR YOUR REVIEW: CBS News request on SUPPORT

Look okay to you?

From: Myles, Renate (NIH/OD) [E]
Sent: Friday, February 28, 2014 9:30 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: FOR YOUR REVIEW: CBS News request on SUPPORT
Importance: High

Kathy approved; look okay to you?

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 5:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: FOR YOUR REVIEW: CBS News request on SUPPORT
Importance: High

Hi all:

Kim has more questions following up from the information I provided to her. Proposed responses vetted through NIHCD (Rose and Cathy Spong) are below. Please let me know if you have any concerns with these before I send to HHS for clearance.

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From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
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Subject: RE: CBS News request

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Kim
Producer
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202-457-4383 office
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skeenk@cbsnews.com

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Blansfield, Earl (NIH/NICHD) [E]

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Friday, February 28, 2014 10:55 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: FOR YOUR REVIEW: CBS News request on SUPPORT

Importance: High

Just fyi – I want you to be aware of point #1 in the email below dated "Wednesday, February 26, 2014 5:17 PM"
I discussed at length with Mona and can fill you in if you want to discuss.
cathy

From: Bock, Robert (NIH/NICHD) [E]
Sent: Friday, February 28, 2014 10:21 AM
To: Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
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To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: FOR YOUR REVIEW: CBS News request on SUPPORT
Date: Friday, February 28, 2014 10:32:56 AM

Not yet. I'm guessing it will be tied with OHRP's release of the guidelines.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, February 28, 2014 10:22 AM
To: Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: FOR YOUR REVIEW: CBS News request on SUPPORT

I am fine with these responses? Do we have a date that this will air on TV?

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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)
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To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Do you have confirmation on the SUPPORT study cost figure: $20.8 million in federal tax dollars? If not, when will we get that information? Thanks.

From: Skeen, Kim
Sent: Monday, February 24, 2014 11:51 AM
To: 'Myles, Renate (NIH/OD) [E]'
Subject: RE: CBS News request

Got it. We're told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc. Please let me know if that is NOT correct. Thank you!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:55 AM
To: Skeen, Kim
Subject: RE: CBS News request

Sorry, working from BB: only institutions conducting the study would have their IRBs review and approve the consent form. NIH did not carry out the study.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:53 AM
To: 'Skeen, Kim'
Subject: RE: CBS News request

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From: Skeen,]
Sent: Monday, February 24, 2014 10:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Yes you did confirm the 24 IRB's figure some time ago—just double checking that NIH was one of the IRB's. Thanks again.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:49 AM
To: Skeen, Kim
Subject: RE: CBS News request

I confirmed that with you quite some time ago. I'll dig it up and resend.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:48 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Locke, Belinda (NIH/NICHD) [E]; Underwood, Brenda (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: Heads-Up
Date: Thursday, February 27, 2014 6:51:25 PM

Thanks.

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

On Feb 27, 2014, at 5:47 PM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

> Just a heads up—in case you hear from Kathy H. As you may know, CBS Sunday Morning has been planning to do a story for a while on the SUPPORT trial and they keep coming back with questions. Not sure when anything will actually air. There's been lots of activity answering questions through Renate.
>
> Today, we spent a lot of time trying determine the best way to answer the question on how much we spent on the SUPPORT trial -- as the number doesn't exist and there are many underlying complexities. So we came up with this answer below, which provides "insights" into ballpark costs, using basically publically available data... without developing a specific number
>
> (b)(5)
>
> Lots of folks contributed advice and data – Belinda, Brenda, Stephanie, Cathy S, and Rose, Renate, Bob, and Kerri
>
> *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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Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

 

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 5:47 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Locke, Belinda (NIH/NICHD) [E]; Underwood, Brenda (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: Heads-Up

Just a heads up—in case you hear from Kathy H. As you may know, CBS Sunday Morning has been planning to do a story for a while on the SUPPORT trial and they keep coming back with questions. Not sure when anything will actually air. There's been lots of activity answering questions through Renate.

Today, we spent a lot of time trying determine the best way to answer the question on how much we spent on the SUPPORT trial -- as the number doesn't exist and there are many underlying complexities. So we came up with this answer below, which provides "insights" into ballpark costs, using basically publically available data... without developing a specific number

> Essentially, funding is provided to the centers making up the Neonatal Research Network, and is not allocated on a per study basis. The Neonatal Research Network is funded through individual grants to the Network centers and the data coordinating center. The average funding for the Neonatal Research Network at the time of the SUPPORT trial was roughly $10.8 million per year. This funded 6-11 different research studies per year, including SUPPORT, over the four-year course of the main SUPPORT study.

Lots of folks contributed advice and data – Belinda, Brenda, Stephanie, Cathy S, and Rose, Renate, Bob, and Kerri

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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Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 5:23 PM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: what we think we will go with

No problem – team effort – Rose, Stephanie, and Belinda so helpful – as you know the complexities involved –even naming the number of centers over the course of the study in any one year – is variable – we wanted something accurate, based on relatively public data, easily understandable, etc etc ..sometimes the "simplest" things take the most time ☺

Mona

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Analysis and Communication
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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: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 5:14 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: what we think we will go with

Looks good, thanks for all of the work on this!

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:58 PM
To: Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Locke, Belinda (NIH/NICHD) [E]; Underwood, Brenda (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: what we think we will go with

Revised wording as of 4:58 PM – this has been a fun day—thanks to everyone's contribution—really ☺

(b)(5)

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
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Child Health and Human Development
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Email: rowem@mail.nih.gov

<< OLE Object: Picture (Device Independent Bitmap) >> << OLE Object: Picture (Device Independent Bitmap) >>

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:48 PM
To: spongc@dc49.nichd.nih.gov; higginsr@mail.nih.gov; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov)
Cc: rajut@mail.nih.gov; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: what we think we will go with

(b)(5)

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
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Email: rowem@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:54 PM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

Looks Ok to me – Bob?

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
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Email: rowem@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 4:53 PM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

I actually meant the first reference to it, which I've removed. Does this look okay?

(b)(5)

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:50 PM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

It was meant that the (b)(5)

(b)(5)

Mona

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Associate Director for Science Policy,
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Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 4:48 PM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

Actually, I have one more question. It says the (b)(5)
(b)(5)

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:47 PM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

☺☺☺☺

Mona

Mona Jaffe Rowe, M.C.P.
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Email: rowem@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 4:46 PM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

Got it!

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:45 PM
To: Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]
Subject: RE: SUPPORT Study Figures

HOLD THE PRESSES see below use (b)(5) instead

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
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Email: rowem@mail.nih.gov

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:43 PM
To: Myles, Renate (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

I might say (b)(5)

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 4:42 PM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

Hi Mona and Bob:

Okay with these changes?

Renate

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:20 PM
To: Myles, Renate (NIH/OD) [E]
Subject: SUPPORT Study Figures

(b)(5)

Bob Bock
Press Officer
Eunice Kennedy Shriver
National Institute of Child Health and
Human Development
National Institutes of Health
Tel. 301-496-5133
bockr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 4:44 PM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

Fine by me.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:43 PM
To: Myles, Renate (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

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To: Myles, Renate (NIH/OD) [E]
Subject: SUPPORT Study Figures

(b)(5)

Bob Bock
Press Officer
Eunice Kennedy Shriver
National Institute of Child Health and
Human Development
National Institutes of Health
Tel. 301-496-5133
bockr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:37 PM
To: Myles, Renate (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: RE: SUPPORT Study Figures

Sorry. I meant to cc Mona and Kerri.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 4:20 PM
To: Myles, Renate (NIH/OD) [E]
Subject: SUPPORT Study Figures

(b)(5)

Bob Bock
Press Officer
Eunice Kennedy Shriver
National Institute of Child Health and
Human Development
National Institutes of Health
Tel. 301-496-5133
bockr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 1:53 PM
To: Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: Re: CBS News request

Hi Bob:

Any development on this? I don't want to be too long in responding to Kim.

Thanks,
Renate

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, February 26, 2014 06:21 PM
To: Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: FW: CBS News request

Hi Bob:

Per our discussion, see Kim's questions below. I did a search on reporter putting "Neonatal Research Network" in the search box, checking the title box only, and selecting all years. The search result can be found here: http://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=10E0CD0F4685C0DE7598B8961CAA4A01A2FFCEB861BF

I've also exported it into an excel file which is attached. The point of this exercise is to be able to say that NIH makes all information about its grants publicly available on NIH Reporter.

Here would be the proposed response:

(b)(5)

You can run these responses through the traps.

Thanks,
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Wednesday, February 26, 2014 5:17 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Renate,

Thank you for the information. Two follow ups:

1. I guess what we need from you is the cost of the SUPPORT study, or your best estimate. But you seem to be saying that NIH has no idea how much this study cost taxpayers. I would think that, in terms of oversight, that this is a figure that NIH should be able to put its finger on. If you can't for some reason, please just give us **the total federal funding provided to NRN during the years of the SUPPORT study** and we'll have to use the total and say that the study was some subset of the total, but that NIH doesn't know how much.
2. On the consent forms: did the NIH staff scientist or steering committee object to or disapprove of the consent form general template?

Thanks again.

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Wednesday, February 26, 2014 10:42 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Again, apologies for the delay! Here are responses to your two questions attributable to NIH.

Please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. We were told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc.

NIH did not approve the SUPPORT study consent forms. The study was conducted as a part of a cooperative agreement, and is overseen by a steering committee. An NIH staff scientist sits on the steering committee that reviewed the general template for the consent form but final approval lies with the local Institutional Review Boards (IRB). The consent form was tailored by each research institution to meet local needs, and meet the approval standards of local IRBs.

Please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars.

We cannot confirm the figure you cite. The NICHD does not allocate funding to the Neonatal Research Network (NRN) on a per trial (or per study) basis. Rather, funding is allocated annually for the entirety of the NRN's operations. These operations include not only the cost of conducting a study, but also for such expenses as equipment use and administrative tasks. Typically, Network researchers conduct numerous neonatal studies (in addition to SUPPORT) during the course of a year. Funding for the Network varies from year to year, depending on the amount allocated for the NIH budget and other factors.

Best,

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Tuesday, February 25, 2014 11:20 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Do you have confirmation on the SUPPORT study cost figure: $20.8 million in federal tax dollars? If not, when will we get that information? Thanks.

From: Skeen, Kim
Sent: Monday, February 24, 2014 11:51 AM
To: 'Myles, Renate (NIH/OD) [E]'
Subject: RE: CBS News request

Got it. We're told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc. Please let me know if that is NOT correct. Thank you!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:55 AM
To: Skeen, Kim
Subject: RE: CBS News request

Sorry, working from BB: only institutions conducting the study would have their IRBs review and approve the consent form. NIH did not carry out the study.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:53 AM
To: 'Skeen, Kim'
Subject: RE: CBS News request

No, only institutions conducting research would have their IRBs review and approve the consent form. NIH did not carry the out the study.

From: Skeen,]
Sent: Monday, February 24, 2014 10:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Yes you did confirm the 24 IRB's figure some time ago—just double checking that NIH was one of the IRB's. Thanks again.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:49 AM
To: Skeen, Kim
Subject: RE: CBS News request

I confirmed that with you quite some time ago. I'll dig it up and resend.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:48 AM

To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

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Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 12:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: CBS News request

Never said thank s

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
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: Thursday, February 27, 2014 9:33 AM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: Re: CBS News request

Just tried to call - I was told you are available at 10 ET and will call back

Rose

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 27, 2014, at 6:19 AM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

HI Rose is it possible to give me a call at 301-496-1877? Thanks!!

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
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
<image001.png> <image002.png>

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 6:24 AM
To: Rowe, Mona (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: Re: CBS News request

I recognize we are trying to (b)(5)
(b)(5) Might Sarah's group be able to help us figure this out?

Kerri Childress
Director of Communications
Eunice Shriver National Institute of Child Health and Human Development

On Feb 26, 2014, at 6:21 PM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

> Hi Bob:
>
> Per our discussion, see Kim's questions below. I did a search on reporter putting "Neonatal Research Network" in the search box, checking the title box only, and selecting all years. The search result can be found here:
> http://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=10E0CD0F4685C0DE7598B8961CAA4A01A2FFCEB861BF
>
> I've also exported it into an excel file which is attached. The point of this exercise is to be able to say that NIH makes all information about its grants publicly available on NIH Reporter.
>
> Here would be the proposed response:

(b)(5)

(b)(5)

You can run these responses through the traps.

Thanks,
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Wednesday, February 26, 2014 5:17 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Renate,

Thank you for the information. Two follow ups:

1. I guess what we need from you is the cost of the SUPPORT study, or your best estimate. But you seem to be saying that NIH has no idea how much this study cost taxpayers. I would think that, in terms of oversight, that this is a figure that NIH should be able to put its finger on. If you can't for some reason, please just give us **the total federal funding provided to NRN during the years of the SUPPORT study** and we'll have to use the total and say that the study was some subset of the total, but that NIH doesn't know how much.
2. On the consent forms: did the NIH staff scientist or steering committee object to or disapprove of the consent form general template?

Thanks again.

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Wednesday, February 26, 2014 10:42 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Again, apologies for the delay! Here are responses to your two questions attributable to NIH.

Please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. We were told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc.

NIH did not approve the SUPPORT study consent forms. The study was conducted as a part of a cooperative agreement, and is overseen by a steering committee. An NIH staff scientist sits on the steering committee that reviewed the general template for the consent form but final approval lies with the local Institutional Review Boards (IRB). The consent form was tailored by each research institution to meet local needs, and meet the approval standards of local IRBs.

Please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars.

We cannot confirm the figure you cite. The NICHD does not allocate funding to the Neonatal Research Network (NRN) on a per trial (or per study) basis. Rather, funding is allocated annually for the entirety of the NRN's operations. These operations include not only the cost of conducting a study, but also for such expenses as equipment use and administrative tasks. Typically, Network researchers conduct numerous neonatal studies (in addition to SUPPORT) during the course of a year. Funding for the Network varies from year to year, depending on the amount allocated for the NIH budget and other factors.

Best,
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Tuesday, February 25, 2014 11:20 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Do you have confirmation on the SUPPORT study cost figure: $20.8 million in federal tax dollars? If not, when will we get that information? Thanks.

From: Skeen, Kim
Sent: Monday, February 24, 2014 11:51 AM
To: 'Myles, Renate (NIH/OD) [E]'
Subject: RE: CBS News request

Got it. We're told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc. Please let me know if that is NOT correct. Thank you!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:55 AM
To: Skeen, Kim
Subject: RE: CBS News request

Sorry, working from BB: only institutions conducting the study would have their IRBs review and approve the consent form. NIH did not carry out the study.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:53 AM
To: 'Skeen, Kim'
Subject: RE: CBS News request

No, only institutions conducting research would have their IRBs review and approve the consent form. NIH did not carry the out the study.

From: Skeen,]
Sent: Monday, February 24, 2014 10:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Yes you did confirm the 24 IRB's figure some time ago—just double checking that NIH was one of the IRB's. Thanks again.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:49 AM
To: Skeen, Kim
Subject: RE: CBS News request

I confirmed that with you quite some time ago. I'll dig it up and resend.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:48 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer

CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

<NRN Funding on NIH Reporter.csv>

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 8:56 AM
To: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: CBS News request

Sorry, give me 5 minutes. Just getting out of a meeting.

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 08:54 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: CBS News request

Did we miss your call? Can you try again?

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 8:45 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: CBS News request

Just tried to call. Can you call me? 301-496-5135

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, February 27, 2014 8:39 AM
To: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: CBS News request

Hi Kerri:

I wasn't planning on sending anything until the info has been vetted. That said, what are you getting estimates on? NRN or SUPPORT? I get that we want to be helpful but we do not do custom analysis and (b)(5)
(b)(5) Let's discuss before you set anything in motion.

Thanks,
Renate

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 27, 2014 08:23 AM
To: Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: CBS News request

Renate: Please hold off sending this. We are working to see if we can come up with at least an estimate and a better explanation on why it's just an estimate. The answer below (b)(5)

(b)(5) Please give us a little time to work on this. Will do our best to get back with you today. Thanks so much, Kerri

On Feb 26, 2014, at 6:21 PM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Hi Bob:

Per our discussion, see Kim's questions below. I did a search on reporter putting "Neonatal Research Network" in the search box, checking the title box only, and selecting all years. The search result can be found here:
http://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=10E0CD0F4685C0DE7598B8961CAA4A01A2FFCEB8615F

I've also exported it into an excel file which is attached. The point of this exercise is to be able to say that NIH makes all information about its grants publicly available on NIH Reporter.

Here would be the proposed response:

(b)(5)

You can run these responses through the traps.

Thanks,
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Wednesday, February 26, 2014 5:17 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Renate,

Thank you for the information. Two follow ups:

1. I guess what we need from you is the cost of the SUPPORT study, or your best estimate. But you seem to be saying that NIH has no idea how much this study cost taxpayers. I would think that,

in terms of oversight, that this is a figure that NIH should be able to put its finger on. If you can't for some reason, please just give us **the total federal funding provided to NRN during the years of the SUPPORT study** and we'll have to use the total and say that the study was some subset of the total, but that NIH doesn't know how much.

2. On the consent forms: did the NIH staff scientist or steering committee object to or disapprove of the consent form general template?

Thanks again.

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Wednesday, February 26, 2014 10:42 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Again, apologies for the delay! Here are responses to your two questions attributable to NIH.

Please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. We were told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc.

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Please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars.

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Best,
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Tuesday, February 25, 2014 11:20 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Do you have confirmation on the SUPPORT study cost figure: $20.8 million in federal tax dollars? If not, when will we get that information? Thanks.

From: Skeen, Kim
Sent: Monday, February 24, 2014 11:51 AM
To: 'Myles, Renate (NIH/OD) [E]'
Subject: RE: CBS News request

Got it. We're told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc. Please let me know if that is NOT correct. Thank you!

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Sent: Monday, February 24, 2014 10:55 AM
To: Skeen, Kim
Subject: RE: CBS News request

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Sent: Monday, February 24, 2014 10:53 AM
To: 'Skeen, Kim'
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From: Skeen,]
Sent: Monday, February 24, 2014 10:51 AM
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Sent: Monday, February 24, 2014 10:49 AM
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Subject: RE: CBS News request

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Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM

To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
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To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

<NRN Funding on NIH Reporter.csv>

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, February 26, 2014 9:44 AM
To: Myles, Renate (NIH/OD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: Statement for Kim Skeen

Yes.

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, February 26, 2014 9:43 AM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: Statement for Kim Skeen

Hi Bob:

Are you okay with adding the highlighted words below? I just want to be perfectly clear that the NRN are doing studies other than SUPPORT. Kathy Hudson does not want us to do a custom analysis of funding to SUPPORT so we're going to go with this general response.

(b)(5)

Thanks,
Renate

From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, February 25, 2014 10:26 AM
To: Myles, Renate (NIH/OD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: Statement for Kim Skeen

OK.

BTW, I Non Responsive

From: Myles, Renate (NIH/OD) [E]
Sent: Tuesday, February 25, 2014 10:25 AM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: Statement for Kim Skeen

Great, thanks Bob. I'm still waiting to hear back from Kathy H and then will send it up.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, February 25, 2014 10:24 AM
To: Myles, Renate (NIH/OD) [E]

Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: FW: Statement for Kim Skeen

Hi Renate. I heard back from Cathy and Stephanie last night. They thought it would be a good idea to (b)(5) (b)(5) Per there comments, I changed "(b)(5) in the statement I wrote for you, below.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 6:56 PM
To: Myles, Renate (NIH/OD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: Statement for Kim Skeen

Hi Renate. Rose has approved the statement below. I think (b)(5) (b)(5) (b)(5)

But, if we can't go that route, we can (b)(5) (b)(5)

(b)(5)

Bob Bock
Press Officer
Eunice Kennedy Shriver
National Institute of Child Health and
Human Development
National Institutes of Health
Tel. 301-496-5133
bockr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

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Sent: Tuesday, February 25, 2014 10:24 AM
To: Myles, Renate (NIH/OD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: FW: Statement for Kim Skeen

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Bob Bock
Press Officer
Eunice Kennedy Shriver
National Institute of Child Health and
Human Development
National Institutes of Health
Tel. 301-496-5133
bockr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, February 25, 2014 8:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Request Accuracy Check-- funding for NRN
Attachments: Timeline of Protocols, NRN, 2013-05-23.jpg

Probably don't need (b)(5) but looking at the study timeline (attached):

- During SUPPORT recruitment
  - 9 studies enrolling
  - 6 doing FU
- During SUPPORT FU
  - 11 studies enrolling
  - 3 in FU

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 25, 2014 7:46 AM
To: Spong, Catherine (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: Request Accuracy Check-- funding for NRN

Typically there at 5-10 other studies. SUPPORT spanned from 2005-2009 with follow up through 2011 so difficult to say exactly how many studies at any given point

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 6:02 PM, "Spong, Catherine (NIH/NICHD) [E]" <spongc@dir49.nichd.nih.gov> wrote:

I suggest you include that (b)(5)
(b)(5) (Rose will give correct #)

Catherine Y Spong MD
Associate Director for Extramural Research
Director, Division of Extramural Research
NICHD, NIH
6100 Executive Blvd Rm 4A05A Bethesda MD 20892
Spongc@mail.nih.gov
Phone 301 435 6894

On Feb 24, 2014, at 6:44 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> This is correct
>
> Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 3:29 PM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

Hi all. I'm working with Renate in Building 1, to respond to a request to the request for funding for the SUPPORT Trial from CBS Producer Kim Skeen. In the draft response below, we explain that (b)(5)

(b)(5)

(b)(5) Anyway, if you could check the parts highlighted in yellow and let me know if I've got it great, that would be great. Thank you.

(b)(5)

Bob Bock
Press Officer
Eunice Kennedy Shriver
National Institute of Child Health and
Human Development
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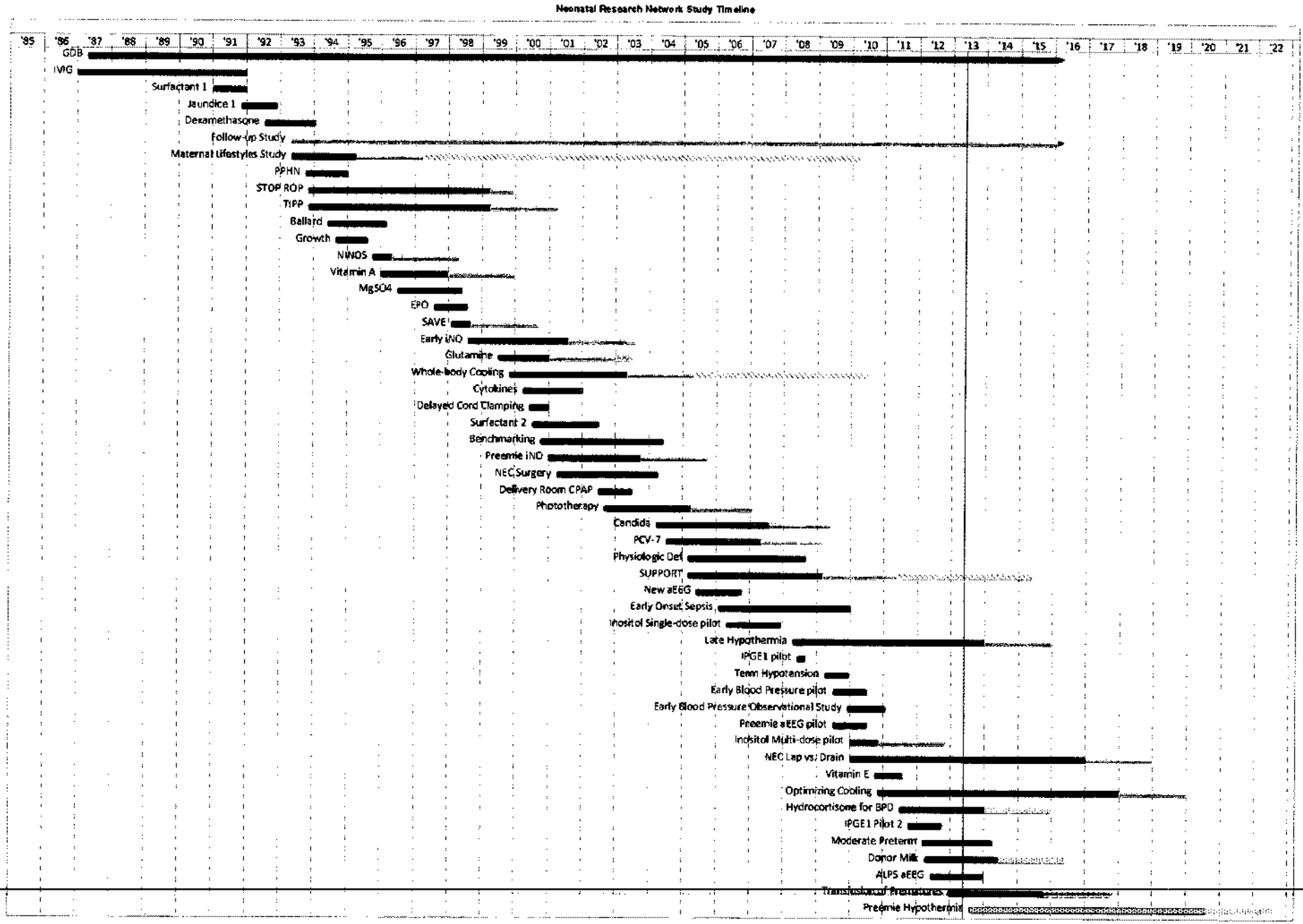
<image001.png> <image002.png>


Neonatal Research Network Study Timeline
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IVIG
Surfactant 1
Jaundice 1
Dexamethasone
Follow-up Study
Maternal Lifestyles Study
PPHN
STOP ROP
TIPP
Ballard
Growth
NNOS
Vitamin A
MgSO4
EPO
SAVE
Early iNO
Glutamine
Whole-body Cooling
Cytokines
Delayed Cord Clamping
Surfactant 2
Benchmarking
Preemie iND
NEC Surgery
Delivery Room CPAP
Phototherapy
Candida
PCV-7
Physiologic Def
SUPPORT
New aEEG
Early Onset Sepsis
Inositol Single-dose pilot
Late Hypothermia
iPGE1 pilot
Term Hypotension
Early Blood Pressure pilot
Early Blood Pressure Observational Study
Preemie aEEG pilot
Inositol Multi-dose pilot
NEC Lap vs. Drain
Vitamin E
Optimizing Cooling
Hydrocortisone for BPD
iPGE1 Pilot 2
Moderate Preterm
Donor Milk
ALPS aEEG
Preemie Hypothermia

4-00861

From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Request Accuracy Check-- funding for NRN
Date: Monday, February 24, 2014 6:51:13 PM

Thanks, Rose.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 6:44 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: Request Accuracy Check-- funding for NRN

This is correct

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 3:29 PM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

Hi all. I'm working with Renate in Building 1, to respond to a request to the request for funding for the SUPPORT Trial from CBS Producer Kim Skeen. In the draft response below, we explain that

(b)(5)

(b)(5) Anyway, if you could check the parts highlighted in yellow and let me know if I've got it great, that would be great. Thank you.

(b)(5)

Bob Bock
Press Officer
Eunice Kennedy Shriver
National Institute of Child Health and
Human Development
National Institutes of Health
Tel. 301-496-5133
bockr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 2:11 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

OK. Here's what I would send her in response to her question:

(b)(5)

Both list maximum funding amounts.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 12:09 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

Okay, thanks. She said she saw $28 million on the website. What's that figure? I haven't looked for it.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 11:56 AM
To: Myles, Renate (NIH/OD) [E]
Subject: FW: Interview request: SUPPORT Study (Deadline: today)

Funding data we've already given her, from the correspondence listed below:

3. **How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

Total NICHD funding for FY 2012 for the Neonatal Research Network was $11,886,753. This covers the 10 studies currently under way in the network. Of the $11,886,753 total, the network sites received $5,577,976. The Data Coordinating Center received $6,308,777. Of this $6,308,777 figure, approximately $3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of $5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

From: Dreyfuss, Ira (HHS/ASPA)
Sent: Thursday, October 24, 2013 5:06 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

Ok
Ira

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Thursday, October 24, 2013 5:04 PM
To: Sye, Tait (OS/ASPA); Dreyfuss, Ira (HHS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

ADD

Kim Skeen had additional questions
Deadline: today

Were reports generated from these interim data checks? Please provide copies of these reports.

(b)(5)

How many interim data checks were done during the SUPPORT study? What were the results?

(b)(5)

Were reports generated from these interim data checks? Please provide copies of these reports.

(b)(5)

Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?

(b)(5)

During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

(b)(5)

From: Sye, Tait (OS/ASPA)
Sent: Monday, September 09, 2013 9:15 PM
To: Myles, Renate (NIH/OD) [E]; Dreyfuss, Ira (HHS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ok

From: Myles, Renate (NIH/OD) [E] [mylesr@od.nih.gov]
Sent: Monday, September 09, 2013 9:08 PM
To: Dreyfuss, Ira (HHS/ASPA); Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

Hi Ira:

See change highlighted in yellow below.

Thanks,
Renate

From: Dreyfuss, Ira (HHS/ASPA)
Sent: Monday, September 09, 2013 8:03 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: Re: Interview request: SUPPORT Study (Deadline: immediate)

Ok
Ira

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, September 09, 2013 06:47 PM

To: Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL) <ODOCPLInterviews@mail.nih.gov>; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ADD

Kim Skeen had additional questions:
Deadline: tomorrow

We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?

(b)(5)

With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

(b)(5)

Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

(b)(5)

From: Sye, Tait (OS/ASPA)
Sent: Friday, September 06, 2013 9:29 AM
To: Myles, Renate (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ok

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Friday, September 06, 2013 9:27 AM
To: Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]

Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)
Importance: High

ADD

Kim Skeen
CBS Sunday Morning
Deadline: immediate

Kim had follow up questions. NIH responses are below:

1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

(b)(5)

2. **What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

(b)(5)

3. **How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

(b)(5)

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, August 29, 2013 11:23 AM
To: Sye, Tait (OS/ASPA); Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

Yes and Yes.

From: Sye, Tait (OS/ASPA)
Sent: Thursday, August 29, 2013 11:22 AM
To: Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

Who would do interview? Dr. Guttmacher?

Ok, so long as he sticks to TPs.

Talking Points:

*HHS is holding this public meeting so we can hear from the public and gather feedback on the important issue of protection of human subjects in research, specifically standard of care in clinical research.

*The public comment period will remain open until September 9, so members of the public who were unable to attend today's meeting can still submit comments.

*Our next step is to review and consider all the comments. This is an important issue that deserves thoughtful deliberation.

Hot Button QAs

Q: When will OHRP release updated guidance regarding standard of care research?

A: The first step is to solicit comments and feedback from the public. After that, HHS will thoughtfully review the comments. There is no timetable set for releasing the updated guidance.

Q: Last week, Public Citizen raised concerns similar to SUPPORT in another NIH supported study, the Transfusion of Premature (TOP) trial. Do you think that trial should be suspended until new guidance is released?

A: HHS is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. Per OHRP's letter to UAB in June of this year, OHRP is postponing actions on studies involving similar designs to SUPPORT (standard of care in clinical research) until the process of producing appropriate guidance is completed.

From: Fine, Amanda (NIH/OD) [E] [mailto:amanda.fine@nih.gov]
Sent: Thursday, August 29, 2013 11:20 AM
To: OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

ADD
Arthur Allen (Freelancer)
Science
SUPPORT TRIAL
arthurallenw@aol.com

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, August 21, 2013 12:23 PM
To: Myles, Renate (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Fritz, Craig (NIH/OD) [E]

Cc: Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: Interview request: (insert subject of interview only)

Producer: Kim Skeen, for Sharyl Attkison (reporter)
Organization: CBS Sunday morning
Phone: 202-457-4383
Subject: SUPPORT Trial
Deadline: Today
Spokesperson: Alan E. Guttmacher, M.D., Director, NICHD
Expected place of publication: CBS Sunday morning
Expected date of publication/airing: Sunday, September 1
Expected prominence: news feature

Skeen called and asked if Dr. Guttmacher would be available for a taping next week, to discuss the NIH's views on the SUPPORT trial ruling. The feeling at our institute is that NIH's view was well represented in the NEJM Perspectives piece last June, and that there really isn't anything new to add. If he is able to find time for a taping, Dr. Guttmacher would reiterate the points made in the Perspectives article.

From: Bock, Robert (NIH/NICHD) [E]
To: Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for Accuracy Check: CBS News SUPPORT request
Date: Monday, February 24, 2014 1:35:24 PM

Thanks Tonse. Sorry—we were able to respond to the review question. Right now, we're looking to respond only to her funding question.

From: Raju, Tonse (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 1:27 PM
To: Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for Accuracy Check: CBS News SUPPORT request

Hi Bob, I don't know the dollar amount. But, NICHD review board, to the best of my knowledge (b)(5)
I will get a confirmation on this soon.
Tonse

Tonse N.K. Raju, MD, DCH
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Phone: 301-402-1872, Fax: 301-496-3790
raju@mail.nih.gov

From: Bock, Robert (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 1:25 PM
To: Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Request for Accuracy Check: CBS News SUPPORT request

Hi all. Sorry to bother you again. Rose is on a plane now, so I'm sending this to you in hopes you can check my response.

Kim Skeen, the producer with CBS news, is back with another question about the SUPPORT study. Kim's request appears at the bottom of this e-mail message, my proposed response, highlighted in yellow, appears above it.

Thanks.

(b)(5)

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:44 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: CBS News request

FYI; I told we'd get her something as soon as we could.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 12:22 PM
To: Myles, Renate (NIH/OD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: Re: CBS News request

Perfect
Thanks
Rose

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 11:21 AM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Yes, that is better. See update:

(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 12:15 PM
To: Myles, Renate (NIH/OD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: Re: CBS News request

You may want to (b)(5)

(b)(5)

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 11:07 AM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Hi Rose!

So here's what I plan to share to be (b)(5)

(b)(5)

Renate

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 12:02 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Myles, Renate (NIH/OD) [E]
Subject: Re: CBS News request

CORRECT

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 11:00 AM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

HI Rose. Please see Renate's question—NIH never approved the consent forms, correct?

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 11:57 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: CBS News request

Hi Bob:

See Kim's additional question below. We don't approve it even as a federal agency, right? I found the relevant QA. Does Rose's role on the steering committee that reviewed and approved the general template for the consent form count as NIH approving the consent form?

What was NIH's role in the design and approval of the consent form?

(b)(5)

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 11:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Got it. We're told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc. Please let me know if that is NOT correct. Thank you!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:55 AM
To: Skeen, Kim
Subject: RE: CBS News request

Sorry, working from BB: only institutions conducting the study would have their IRBs review and approve the consent form. NIH did not carry out the study.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:53 AM

To: 'Skeen, Kim'
Subject: RE: CBS News request

No, only institutions conducting research would have their IRBs review and approve the consent form. NIH did not carry the out the study.

From: Skeen,]
Sent: Monday, February 24, 2014 10:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Yes you did confirm the 24 IRB's figure some time ago—just double checking that NIH was one of the IRB's. Thanks again.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:49 AM
To: Skeen, Kim
Subject: RE: CBS News request

I confirmed that with you quite some time ago. I'll dig it up and resend.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:48 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

Blansfield, Earl (NIH/NICHD) [E]

From: Bock, Robert (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 12:09 PM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

Which web site? Ask her for a link.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 12:09 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

Okay, thanks. She said she saw $28 million on the website. What's that figure? I haven't looked for it.

From: Bock, Robert (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 11:56 AM
To: Myles, Renate (NIH/OD) [E]
Subject: FW: Interview request: SUPPORT Study (Deadline: today)

Funding data we've already given her, from the correspondence listed below:
3. **How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

Total NICHD funding for FY 2012 for the Neonatal Research Network was $11,886,753. This covers the 10 studies currently under way in the network. Of the $11,886,753 total, the network sites received $5,577,976. The Data Coordinating Center received $6,308,777. Of this $6,308,777 figure, approximately $3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of $5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

From: Dreyfuss, Ira (HHS/ASPA)
Sent: Thursday, October 24, 2013 5:06 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: today)

Ok
Ira

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Subject: RE: Interview request: SUPPORT Study (Deadline: today)

ADD

Kim Skeen had additional questions
Deadline: today

Were reports generated from these interim data checks? Please provide copies of these reports.

(b)(5)

How many interim data checks were done during the SUPPORT study? What were the results?

(b)(5)

Were reports generated from these interim data checks? Please provide copies of these reports.

(b)(5)

Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?

(b)(5)

During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

(b)(5)

From: Sye, Tait (OS/ASPA)
Sent: Monday, September 09, 2013 9:15 PM
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Division)
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Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

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Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

Hi Ira:

See change highlighted in yellow below.

Thanks,
Renate

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Sent: Monday, September 09, 2013 8:03 PM
To: Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
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Subject: Re: Interview request: SUPPORT Study (Deadline: immediate)

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From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, September 09, 2013 06:47 PM
To: Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL) <ODOCPLInterviews@mail.nih.gov>; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ADD

Kim Skeen had additional questions:
Deadline: tomorrow

We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?

(b)(5)

(b)(5)

With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

(b)(5)

Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

(b)(5)

From: Sye, Tait (OS/ASPA)
Sent: Friday, September 06, 2013 9:29 AM
To: Myles, Renate (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)

ok

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Friday, September 06, 2013 9:27 AM
To: Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]
Subject: RE: Interview request: SUPPORT Study (Deadline: immediate)
Importance: High

ADD

Kim Skeen
CBS Sunday Morning
Deadline: immediate

Kim had follow up questions. NIH responses are below:

1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

   (b)(5)

2. **What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

(b)(5)

3. **How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

(b)(5)

From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, August 29, 2013 11:23 AM
To: Sye, Tait (OS/ASPA); Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

Yes and Yes.

From: Sye, Tait (OS/ASPA)
Sent: Thursday, August 29, 2013 11:22 AM
To: Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

Who would do interview? Dr. Guttmacher?

Ok, so long as he sticks to TPs.

Talking Points:

*HHS is holding this public meeting so we can hear from the public and gather feedback on the important issue of protection of human subjects in research, specifically standard of care in clinical research.

*The public comment period will remain open until September 9, so members of the public who were unable to attend today's meeting can still submit comments.

*Our next step is to review and consider all the comments. This is an important issue that deserves thoughtful deliberation.

Hot Button QA:

Q: When will OHRP release updated guidance regarding standard of care research?

A: The first step is to solicit comments and feedback from the public. After that, HHS will thoughtfully review the comments. There is no timetable set for releasing the updated guidance.

Q: Last week, Public Citizen raised concerns similar to SUPPORT in another NIH supported study, the Transfusion of Premature (TOP) trial. Do you think that trial should be suspended until new guidance is released?

A: HHS is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. Per OHRP's letter to UAB in June of this year, OHRP is postponing actions on studies involving similar designs to SUPPORT (standard of care in clinical research) until the process of producing appropriate guidance is completed.

From: Fine, Amanda (NIH/OD) [E] [mailto:amanda.fine@nih.gov]
Sent: Thursday, August 29, 2013 11:20 AM
To: OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)
Cc: Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: Interview request: (insert subject of interview only)

ADD
Arthur Allen (Freelancer)
Science
SUPPORT TRIAL
arthurallenw@aol.com

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, August 21, 2013 12:23 PM
To: Myles, Renate (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL); Fritz, Craig (NIH/OD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: Interview request: (insert subject of interview only)

Producer: Kim Skeen, for Sharyl Attkison (reporter)
Organization: CBS Sunday morning
Phone: 202-457-4383
Subject: SUPPORT Trial
Deadline: Today
Spokesperson: Alan E. Guttmacher, M.D., Director, NICHD
Expected place of publication: CBS Sunday morning
Expected date of publication/airing: Sunday, September 1
Expected prominence: news feature

Skeen called and asked if Dr. Guttmacher would be available for a taping next week, to discuss the NIH's views on the SUPPORT trial ruling. The feeling at our institute is that NIH's view was well represented in the NEJM Perspectives piece last June, and that there really isn't anything new to add. If he is able to find time for a taping, Dr. Guttmacher would reiterate the points made in the Perspectives article.

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 12:04 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: CBS News request

Am currently in the Non Responsive do have email for at least 20 minutes or so

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 11:00 AM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

HI Rose. Please see Renate's question—NIH never approved the consent forms, correct?

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 11:57 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: CBS News request

Hi Bob:

See Kim's additional question below. We don't approve it even as a federal agency, right? I found the relevant QA. Does Rose's role on the steering committee that reviewed and approved the general template for the consent form count as NIH approving the consent form?

What was NIH's role in the design and approval of the consent form?
The study was conducted as a part of a cooperative agreement, and is overseen by a steering committee. An NIH staff scientist sits on the steering committee that reviewed and approved the general template for the consent form. The consent form was tailored by each research institution to meet local needs, and meet the approval standards of local Institutional Review Boards.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 11:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Got it. We're told that NIH approved the consent form (I guess not as an IRB, just as a federal agency), as it was submitted as part of the study prior to receiving government funding etc. Please let me know if that is NOT correct. Thank you!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:55 AM
To: Skeen, Kim
Subject: RE: CBS News request

Sorry, working from BB: only institutions conducting the study would have their IRBs review and approve the consent form. NIH did not carry out the study.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:53 AM
To: 'Skeen, Kim'
Subject: RE: CBS News request

No, only institutions conducting research would have their IRBs review and approve the consent form. NIH did not carry the out the study.

From: Skeen, [redacted]
Sent: Monday, February 24, 2014 10:51 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Yes you did confirm the 24 IRB's figure some time ago—just double checking that NIH was one of the IRB's. Thanks again.

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:49 AM
To: Skeen, Kim
Subject: RE: CBS News request

I confirmed that with you quite some time ago. I'll dig it up and resend.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:48 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request
Date: Monday, February 24, 2014 12:02:26 PM

Thanks, Rose.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 12:02 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: CBS News request

Yes
Very difficult to determine actual costs. The $20 million number us coming from the latest letter from public citizen, but I do not recall ever (b)(5)

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 10:59 AM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

Right. I remember us (b)(5)
(b)(5) (Sorry to bother you when you're away.)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 11:59 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: CBS News request

Bob
The NIH irb did not review the study. As for the costs, I don't recall (b)(5) NHLBI provided $5.2 million in capitation and NICHD provided the base infrastructure over the course of the study - very hard to determine actual costs for an individual study. You may want to check with
(b)(5)

(b)(5)

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 10:51 AM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

Hi Rose. Please see request from Renate, below. I'm not sure where she got this figure from. I know we visited this issue with her before. I've been checking files and back e-mails for an hour, and can't find anything. Do you recall what we might have told her before?

I seem to remember (b)(5) I think I remember you explaining that (b)(5)

(b)(5)

Thanks.

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:44 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: CBS News request

FYI, I told we'd get her something as soon as we could.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(6) cell
skeenk@cbsnews.com

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Next Steps and Impact of Controversy on SoC Research
Date: Monday, February 24, 2014 11:27:19 AM

Thanks, Rose!

Alan

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 24, 2014 11:23 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Patterson, Amy (NIH/OD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: Re: Next Steps and Impact of Controversy on SoC Research

This study has not yet started. We are working through the FDA IDE process for the cooling blanket. We anticipate a start date of late spring or early summer if all goes well with the FDA. Let me know if there are other questions.

Rose

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 24, 2014, at 10:09 AM, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov> wrote:

No, but I suspect Rose can. Rose?

Alan

From: Patterson, Amy (NIH/OD) [E]
Sent: Monday, February 24, 2014 11:08 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: Next Steps and Impact of Controversy on SoC Research

Thanks again, Alan, for this sum-up of the effects on the NRN studies.

If I'm not mistaken, a seventh study was identified by Public Citizen.

Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Hypoxic-Ischemic Encephalopathy in Premature Infants 33-35 Weeks Gestational Age

Can you give me an update on its status?

From: Guttmacher, Alan (NIH/NICHD) [E]

Sent: Thursday, February 20, 2014 8:09 AM
To: Patterson, Amy (NIH/OD) [E]; Shurin, Susan (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Bernard, Marie A. (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]
Subject: RE: Next Steps and Impact of Controversy on SoC Research

Amy –

Besides these points already made nicely by Susan and Josie, a couple of other observations.

First, we see the same issues in our varied groups of clinical researchers.

Second, re the Network from which SUPPORT came: Six interventional trials were ongoing in the Neonatal Research Network at the time the controversy over comparative effectiveness studies arose. All six were put on hold by one or more of the 18 NRN centers for varying periods of time, while investigators and IBRs reviewed the studies. The TOP trial (compares a high versus low transfusion threshold for babies < 1000 grams at birth) was suspended at eight centers for a loss of 516 days for recruitment. One TOP site remains inactive (due to the continuing attacks by Public Citizen regarding TOP and SUPPORT and OHRP's previous response regarding SUPPORT), declining participation in the TOP trial pending HHS provision of clarity on standards for this type of research design. The other five interventional trials were suspended at three centers each. The controversy has significantly affected recruitment into much needed neonatal clinical trials to provide evidence for which clinical practice can be improved. Details about all this can be found in the attached.

Alan

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

From: Patterson, Amy (NIH/OD) [E]
Sent: Wednesday, February 19, 2014 1:04 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Shurin, Susan (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Bernard, Marie A. (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]
Subject: Next Steps and Impact of Controversy on SoC Research

All:

At his next one on one with the Deputy Secretary, Francis wi (b)(5)

(b)(5)

Francis would also like to give the Deputy Secretary a sense of (b)(5)

(b)(5)

(b)(5) Alan, can you remind me whether any of the other neonatal research network studies have been affected?

Could you get back to me before noon tomorrow?

Thanks,

Amy

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Monday, February 24, 2014 10:49 AM
To: Bock, Robert (NIH/NICHD) [E]
Subject: FW: CBS News request

PS: we answered the IRB question a long time ago. I'll dig it up and resend it.

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:48 AM
To: Myles, Renate (NIH/OD) [E]
Subject: RE: CBS News request

Thanks. Please add the IRB question, which we didn't discuss on Friday but do want to confirm. Thanks again!

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]
Sent: Monday, February 24, 2014 10:44 AM
To: Skeen, Kim
Subject: RE: CBS News request

Hi Kim:

Yep, I asked NICHD on Friday. We spoke late in the day and I'm sure they have several other requests they're working on so we'll get you something ASAP.

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]
Sent: Monday, February 24, 2014 10:43 AM
To: Myles, Renate (NIH/OD) [E]
Subject: CBS News request

Hi Renate,

As we discussed last week, please confirm this figure for the total cost of the SUPPORT study: $20.8 million in federal tax dollars. Also please confirm that an NIH Institutional Review Board was one of the 24 IRB's that approved the SUPPORT study. Thank you.

Regards,

Kim
Producer
CBS News Washington Bureau
202-457-4383 office
(b)(5) cell
skeenk@cbsnews.com

After reading these, I couldn't figure out why Seetha didn't also publish the 2-year outcomes in the first paper; I would assume that Michele plans to only write one hypercarbia manuscript including both the acute and the 2 yr outcomes.

I would vote for 2 papers – but think that it is imperative that the same statistician do both analyses and would strongly urge Seetha and Michele to submit to the same journal in tandem. The Network needs to try to avoid the potential accusation that we are publishing the least publishable unit. If only one paper is submitted, then Michele should definitely be the lead author.

From: Bock, Robert (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: USA Today story -- bullets for CSPAN
Date: Thursday, February 20, 2014 2:14:45 PM

Yes. Now you have both options.

-----Original Message-----
From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 2:14 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: USA Today story -- bullets for CSPAN

Agree, but enjoy having a few factoids on hand. Thanks.

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

> On Feb 20, 2014, at 1:31 PM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:
>
> Once again, Rose Higgins to the rescue. She sent the attached papers and I took the liberty of excerpting the charts she referred to and pasting them here.
>
> But I think you might be well served by (b)(5)
(b)(5)
>
> For example, for the question about (b)(5)
(b)(5)

>
>
> From: Higgins, Rosemary (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 1:04 PM
> To: Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E];
> Signore, Caroline (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]
> Cc: Raju, Tonse (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]
> Subject: RE: USA Today story -- bullets for CSPAN
>
> Hi
> See Figure 1 in the Fanaroff paper for survival over time by birth weight.
> [Bock, Robert (NIH/NICHD) [E]]
> [cid:image001.jpg@01CF2E3E.332FE2A0]
>
> From the Stoll paper, table 3 gives survival by week of gestation -- note once you get to 26-27 weeks, most of the mortality is attributable to congenital anomalies.
> [Bock, Robert (NIH/NICHD) [E]]
> [cid:image002.jpg@01CF2E3E.332FE2A0]
> Figure 1 shows survival by gestational age.
> [cid:image003.jpg@01CF2E3E.9C82EDB0]

> Let me know if this helps or you want more information
>
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal
> Research Network Pregnancy and Perinatology Branch 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<mailto:higginsr@mail.nih.gov>
>
> From: Bock, Robert (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 12:41 PM
> To: Spong, Catherine (NIH/NICHD) [E]; Signore, Caroline (NIH/NICHD)
> [E]; Reddy, Uma (NIH/NICHD) [E]
> Cc: Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E];
> Ilekis, John (NIH/NICHD) [E]
> Subject: FW: USA Today story -- bullets for CSPAN
>
> Please see request from Dr. G., regarding information on preterm survival rates.
>
> I did a search, and came up empty. So, when in doubt I believe in asking a profession.
>
> Would any of you be aware of a source for what he's looking for?
>
> From: Guttmacher, Alan (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 12:33 PM
> To: Childress, Kerri (NIH/NICHD) [E]
> Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush,
> Katie (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
> Subject: RE: USA Today story -- bullets for CSPAN
>
>
> For "Impact of research on preterm birth survival?", can someone give me survival rates over past few decades at one or more gestational ages?
>
>
> From: Childress, Kerri (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 12:15 PM
> To: Guttmacher, Alan (NIH/NICHD) [E]
> Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush,
> Katie (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
> Subject: FW: USA Today story -- bullets for CSPAN
>
> Dr. G: Below are my bullets, which Dr. Reddy approved. In the first
> email are Dr. Reddy's bullets, too. Hope this works. Kerri
>
>
> · In the past 15 years, C-sections have climbed to more than 60%
>
>
> · Although C-sections are safer than ever before, they are still not without risk

>
> o Death rate is 3 times higher in mothers who undergo C-Sections than those who deliver naturally
>
> o Risks increase with each C-section
>
> o Increase risk in respiratory problems with babies, as contractions help to squeeze extra fluid out of newborn's lungs
>
>
> American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine are both saying that it's important to reduce the number of C-sections in first-time moms
>
> o Babies who are breech may not need to be delivered C-section. There is a procedure to turn the baby to present head down.
>
> o Babies who are large should not automatically be delivered C-section
>
> o Long labors, may actually not be that long after all, research shows
>
>
> Of course, if the baby or mother's life is endangered, C-section may be the best choice.
>
>
> From: Reddy, Uma (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 10:21 AM
> To: Childress, Kerri (NIH/NICHD) [E]
> Cc: Bock, Robert (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
> Subject: RE: USA Today story
>
> How's this. Please feel free to rearrange, edit or ask me questions.
>
> This ACOG document is important and provides important strategies to reduce the high C- section rate:
>
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> 1) Being more patient with labor- active phase (accelerated dilation) starts at 6 cm so women should not have a C-section for failure to progress before 6 cm. This is based on NICHD funded Consortium on Safe Labor (CSL) study. Need to wait more time in second stage of labor as well. At least 2 hours of pushing in multips and 3 hours in nullips. CSL data shows OB providers performing C-sections before these threshholds are reached and could avoid unnecessary CS
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> 2) Variability in fetal heart rate interpretation – need better standardization
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> 3) Appropriate indications- document points out that doctors performing C-sections for reasons that are not accepted indications- suspected macrosomia, twins where first one is vertex
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> 4) Appropriate counseling about risks of multiple C-sections/ encourage a trial of labor after CS
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> 5) We need to prevent first C-section because once a women has 1 C-section the rate of performing a repeat C-section is high and primary cesareans account for the majority of CS.
>
>
> Uma M. Reddy, MD, MPH
> Medical Officer
> Pregnancy and Perinatology Branch
> Eunice Kennedy Shriver National Institute of Child Health and Human
> Development National Institutes of Health
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> email: reddyu@mail.nih.gov<mailto:reddyu@mail.nih.gov>
> From: Childress, Kerri (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 7:57 AM
> To: Reddy, Uma (NIH/NICHD) [E]
> Cc: Bock, Robert (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
> Subject: FW: USA Today story
> Importance: High
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> Uma: No good deed goes unpunished. Can you do me a big favor and send us 4 or 5 key talking points about C-Sections, just in case Dr. Guttmacher gets a question tomorrow during his CSPAN interview?
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> Thanks so very much – it's very early tomorrow morning, so the sooner
> the better. Very brief and easy to understand. Thanks so so so very
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> From: Guttmacher, Alan (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 7:54 AM
> To: Childress, Kerri (NIH/NICHD) [E]
> Cc: Bock, Robert (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
> Subject: RE: USA Today story
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> Please make up a talking point set on the for C-SPAN. Thanks
>
> Alan E. Guttmacher, M.D.
> Director
> Eunice Kennedy Shriver National Institute of Child Health and Human
> Development National Institutes of Health
> 31 Center Drive
> Building 31, Room 2A03
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> url: nichd.nih.gov<http://www.nichd.nih.gov>
>
> From: Childress, Kerri (NIH/NICHD) [E]
> Sent: Thursday, February 20, 2014 7:45 AM
> To: Reddy, Uma (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Bock,
> Robert (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox,
> Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona
> (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]; Underwood, Brenda
> (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary
> (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Koso-Thomas, Marion
> (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Ilekis, John
> (NIH/NICHD) [E]; Signore, Caroline (NIH/NICHD) [E]
> Cc: Kim Callinan
> (KCallinan@iqsolutions.com<mailto:KCallinan@iqsolutions.com>)
> Subject: USA Today story
>
> Excellent job to all. Please let me echo Katie's thanks Uma, we
> couldn't have done this without you. USA Today has the largest
> readership of any newspaper in the US. Kudos for a wonderful

> interview and great coverage for NICHD. Kerri
>
> From: Reddy, Uma (NIH/NICHD) [E]
> Sent: Wednesday, February 19, 2014 11:30 PM
> To: Rush, Katie (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
> Cc: Childress, Kerri (NIH/NICHD) [E]
> Subject: RE: C-sections
>
> Katie, Thanks for the positive feedback and your nice email. Happy to help, especially this time since NICHD has played a key role in performing the research to support the recommendations.
> Uma
> From: Rush, Katie (NIH/NICHD) [E]
> Sent: Wednesday, February 19, 2014 10:56 PM
> To: Reddy, Uma (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
> Cc: Childress, Kerri (NIH/NICHD) [E]
> Subject: RE: C-sections
>
> Wonderful, Uma, thanks for sharing! I'm glad the interview went well and the story came out so nicely.
>
> We really appreciate your willingness to speak with the media. I know the requests are usually last-minute, and you're busy enough as it is. But it helps us so much in building good bridges with reporters and getting NICHD's name and research info. out there. Thank you, thank you for making yourself available, even on a day when you were seeing patients.
>
> And thanks again for the follow-up!
>
> K
>
> Katie Rush
> _____
> From: Reddy, Uma (NIH/NICHD) [E]
> Sent: Wednesday, February 19, 2014 10:39 PM
> To: Bock, Robert (NIH/NICHD) [E]
> Cc: Rush, Katie (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
> Subject: RE: C-sections
> Liz Szabo was very nice and remembered talking to me before. Here's the link for the story in case:
> http://www.usatoday.com/story/news/nation/2014/02/19/reducing-cesarean
> -sections/5608139/
>
> Uma M. Reddy, MD, MPH
> <Panaroff, Trends in neonatal morbidity and mortality, Am J Ob & Gyn,
> 02-2007.pdf> <Stoll, GDB 2010.pdf> <image001.jpg> <image002.jpg>
> <image003.jpg>

From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: USA Today story -- bullets for CSPAN
Date: Thursday, February 20, 2014 1:43:06 PM

Thanks, Rose.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 1:29 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: USA Today story -- bullets for CSPAN

He was born at 34.5 weeks gestation (a little over a month early)

http://en.wikipedia.org/wiki/Patrick_Bouvier_Kennedy
Patrick Bouvier Kennedy was born by emergency caesarean section five and a half weeks early at the Otis Air Force Base Hospital in Bourne, Massachusetts. His birth weight was 4 pounds 10 $^{1}/_{2}$ ounces (2.11 kg).[1] Shortly after birth he developed symptoms of Hyaline Membrane Disease, also called Infant Respiratory Distress Syndrome (IRDS). He was transferred to Boston Children's Hospital where he died two days later, following treatment in a hyperbaric chamber.[2] His obituary in *The New York Times* stated that, at that time, all that could be done for a baby with Hyaline Membrane Disease was to "monitor the infant's blood chemistry and to try to keep it near normal levels."

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From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 1:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Signore, Caroline (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]
Subject: RE: USA Today story -- bullets for CSPAN

Thank you, Rose!

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 1:04 PM
To: Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Signore, Caroline (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]

Subject: RE: USA Today story -- bullets for CSPAN

Hi
See Figure 1 in the Fanaroff paper for survival over time by birth weight.

From the Stoll paper, table 3 gives survival by week of gestation – note once you get to 26-27 weeks, most of the mortality is attributable to congenital anomalies. Figure 1 shows survival by gestational age.

Let me know if this helps or you want more information

Rose

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From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 12:41 PM
To: Spong, Catherine (NIH/NICHD) [E]; Signore, Caroline (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]
Subject: FW: USA Today story -- bullets for CSPAN

Please see request from Dr. G., regarding information on preterm survival rates.

I did a search, and came up empty. So, when in doubt I believe in asking a profession.

Would any of you be aware of a source for what he's looking for?

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 12:33 PM
To: Childress, Kerri (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: USA Today story -- bullets for CSPAN

For "Impact of research on preterm birth survival?", can someone give me survival rates over past few decades at one or more gestational ages?

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 12:15 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: FW: USA Today story -- bullets for CSPAN

Dr. G: Below are my bullets, which Dr. Reddy approved. In the first email are Dr. Reddy's bullets, too. Hope this works. Kerri

- In the past 15 years, C-sections have climbed to more than 60%

- Although C-sections are safer than ever before, they are still not without risk
  - Death rate is 3 times higher in mothers who undergo C-Sections than those who deliver naturally
  - Risks increase with each C-section
  - Increase risk in respiratory problems with babies, as contractions help to squeeze extra fluid out of newborn's lungs

- American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine are both saying that it's important to reduce the number of C-sections in first-time moms
  - Babies who are breech may not need to be delivered C-section. There is a procedure to turn the baby to present head down.
  - Babies who are large should not automatically be delivered C-section
  - Long labors, may actually not be that long after all, research shows

- Of course, if the baby or mother's life is endangered, C-section may be the best choice.

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Cc: Kim Callinan (KCallinan@iqsolutions.com)
Subject: USA Today story

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Katie Rush

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Uma M. Reddy, MD, MPH

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To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Caldeira, Kent (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: USA Today story -- bullets for CSPAN
Date: Thursday, February 20, 2014 1:31:49 PM
Attachments: Fanaroff. Trends in neonatal morbidity and mortality. Am J Obs & Gyn. 02-2007.pdf
Stoll. JPM 2010.pdf

Once again, Rose Higgins to the rescue. She sent the attached papers and I took the liberty of excerpting the charts she referred to and pasting them here.

But I think you might be well served by a (b)(5)

For example, for the question abou (b)(5)

(b)(5)

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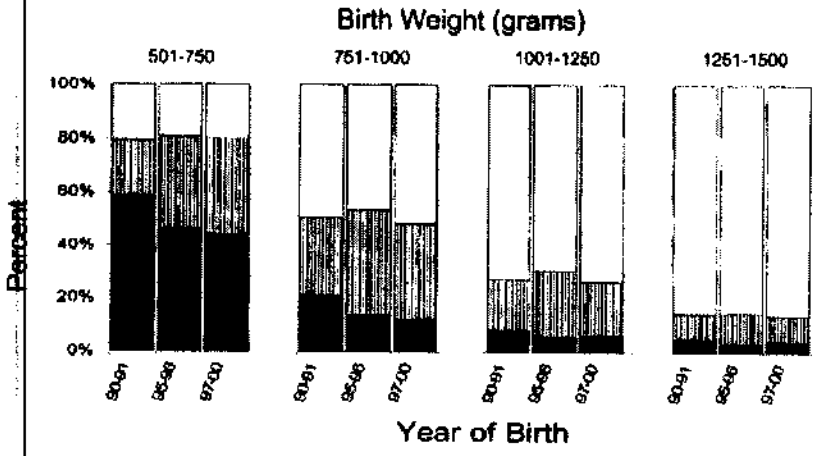
Cc: Raju, Tonse (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]
Subject: RE: USA Today story -- bullets for CSPAN

Hi
See Figure 1 in the Fanaroff paper for survival over time by birth weight.
[Bock, Robert (NIH/NICHD) [E]]

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.

From the stoll paper, table 3 gives survival by week of gestation note once you get to 26-27 weeks, most of the mortality is attributable to congenital anomalies.
[Bock, Robert (NIH/NICHD) [E]]

TABLE 3 Mortality Rates According to GA for VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007

	% (Range)							
	22 wk (*N* = 421)	23 wk (*N* = 871)	24 wk (*N* = 1370)	25 wk (*N* = 1498)	26 wk (*N* = 1576)	27 wk (*N* = 1538)	28 wk (*N* = 2001)	Total (*N* = 9575)
Survived	6 (0–50)	26 (2–53)	55 (20–100)	72 (50–90)	84 (61–100)	85 (75–100)	92 (88–100)	72 (55–95)
Died	94 (50–100)	74 (47–98)	45 (0–80)	28 (10–50)	16 (0–39)	12 (0–24)	8 (0–12)	28 (5–45)
Time of death[a]								
≤ 12 h	85 (0–100)	43 (0–90)	11 (0–44)	5 (0–19)	3 (0–11)	3 (0–5)	2 (0–7)	11 (1–25)
> 12–24 h	2 (0–6)	5 (0–7)	2 (0–6)	<1 (0–5)	<1 (0–2)	<1 (0–2)	<1 (0–1)	1 (0–2)
> 1–3 d	1 (0–8)	9 (0–30)	6 (0–11)	3 (0–25)	2 (0–8)	1 (0–6)	<1 (0–4)	3 (0–7)
4–7 d	2 (0–23)	4 (0–20)	4 (0–11)	3 (0–7)	1 (0–8)	1 (0–6)	<1 (0–2)	2 (0–5)
8–14 d	2 (0–50)	5 (0–50)	5 (0–20)	3 (0–9)	2 (0–6)	2 (0–19)	<1 (0–5)	3 (1–8)
15–28 d	1 (0–15)	4 (0–16)	7 (0–15)	4 (0–8)	5 (0–11)	2 (0–5)	2 (0–7)	3 (0–8)
> 28 d	1 (0–8)	6 (0–17)	10 (0–30)	8 (0–15)	5 (0–10)	4 (0–9)	2 (0–5)	5 (1–8)
Survived	*N* = 25	*N* = 226	*N* = 748	*N* = 1078	*N* = 1319	*N* = 1316	*N* = 1847	*N* = 6859
Survived without morbidity[b]	0 (0–0)	3 (0–14)	9 (0–18)	20 (0–43)	34 (0–49)	44 (19–65)	57 (6–74)	37 (7–50)
Died	*N* = 396	*N* = 645	*N* = 622	*N* = 420	*N* = 257	*N* = 222	*N* = 154	*N* = 2716
Respiratory support withheld/withdrawn before death[c]	82 (40–100)	77 (0–100)	68 (21–96)	68 (0–100)	73 (42–100)	66 (20–100)	69 (0–100)	72 (29–95)
Died at ≤ 12 h	*N* = 359	*N* = 575	*N* = 447	*N* = 72	*N* = 48	*N* = 27	*N* = 34	*N* = 1009
Respiratory support withheld/withdrawn before death[d]	85 (40–100)	85 (43–100)	79 (0–100)	86 (0–100)	76 (0–100)	85 (0–100)	79 (25–100)	84 (53–100)

Ranges are across all participating NRN centers.
[a] Proportions among all infants including survivors.
[b] Proportions among infants who survived. Morbidities included severe IVH, PVL, BPD, necrotizing enterocolitis, infections, and ROP stage ≥ 3.
[c] Proportions among infants who died. Data on respiratory support withheld/withdrawn were missing for 52 infants.
[d] Proportions among infants who died within 12 hours. Data on respiratory support withheld/withdrawn were missing for 2 infants.

Figure 1 shows survival by gestational age.

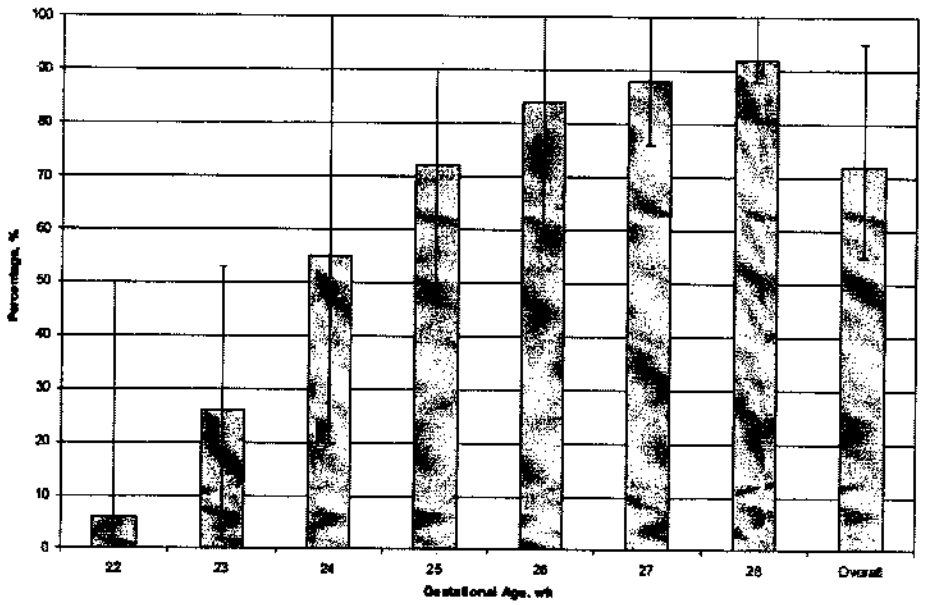


FIGURE 1
Survival to discharge according to GA among 9575 VLBW infants born in NICHD NRN centers between January 1, 2003, and December 31, 2007. The thin lines indicate ranges across centers.

Let me know if this helps or you want more information.

Rose

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Subject: FW: USA Today story -- bullets for CSPAN

Please see request from Dr. G., regarding information on preterm survival rates

I did a search, and came up empty. So, when in doubt I believe in asking a profession.

Would any of you be aware of a source for what he's looking for?

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 12:33 PM
To: Childress, Kerri (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: USA Today story -- bullets for CSPAN

For "Impact of research on preterm birth survival?", can someone give me survival rates over past few decades at one or more gestational ages?

From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 12:15 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: FW: USA Today story -- bullets for CSPAN

Dr. G: Follow are my bullets, which Dr. Reddy approved. In the first email are Dr. Reddy's bullets, too. Hope this works. Kerri

- In the past 15 years, C-sections have climbed to more than 60%
- Although C-sections are safer than ever before, they are still not without risk
  - Death rate is 3 times higher in mothers who undergo C-Sections than those who deliver naturally
  - Risks increase with each C-section
  - Increase risk in respiratory problems with babies, as contractions help to squeeze extra fluid out of newborn's lungs
- American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine are both saying that it's important to reduce the number of C-sections in first-time moms
  - Babies who are breech may not need to be delivered C-section. There is a procedure to turn the baby to present head down.
  - Babies who are large should not automatically be delivered C-section
  - Long labors, may actually not be that long after all, research shows
- Of course, if the baby or mother's life is endangered, C-section may be the best choice.

From: Reddy, Uma (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 10:21 AM
To: Childress, Kerri (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: USA Today story

How's this. Please feel free to rearrange, edit or ask me questions.

This ACOG document is important and provides important strategies to reduce the high C section rate-

1) Being more patient with labor - active phase (accelerated dilation) starts at 6 cm so women should not have a C-section for failure to progress before 6 cm. This is based on NICHD funded Consortium on Safe Labor (CSL) study. Need to wait more time in second stage of labor as well. At least 2 hours of pushing in multips and 3 hours in nullips. CSL data shows OB providers performing C-sections before these thresholds are reached and could avoid unnecessary CS
2) Variability in fetal heart rate interpretation need better standardization
3) Appropriate indications- document points out that doctors performing C-sections for reasons that are not accepted indications- suspected macrosomia twins where first one is vertex
4) Appropriate counseling about risks of multiple C-sections/ encourage a trial of labor after CS
5) We need to prevent first C-section because once a women has 1 C-section the rate of performing a repeat C-section is high and primary cesareans account for the majority of CS.

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From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 7:57 AM
To: Reddy, Uma (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: FW: USA Today story
Importance: High

Uma: No good deed goes unpunished. Can you do me a big favor and send us 4 or 5 key talking points about C-Sections, just in case Dr. Guttmacher gets a question tomorrow during his CSPAN interview?

Thanks so very much – it's very early tomorrow morning, so the sooner the better. Very brief and easy to understand. Thanks so so so very much, Kerri

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 7:54 AM
To: Childress, Kerri (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]
Subject: RE: USA Today story

Please make up a talking point set on the for C-SPAN. Thanks

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From: Childress, Kerri (NIH/NICHD) [E]
Sent: Thursday, February 20, 2014 7:45 AM
To: Reddy, Uma (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]; Underwood, Brenda (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Signore, Caroline (NIH/NICHD) [E]
Cc: Kim Callinan (KCallinan@lipsolutions.com)
Subject: USA Today story

Excellent job to all. Please let me echo Katie's thanks Uma, we couldn't have done this without you. USA Today has the largest readership of any newspaper in the US. Kudos for a wonderful interview and great coverage for NICHD. Kerri

From: Reddy, Uma (NIH/NICHD) [E]
Sent: Wednesday, February 19, 2014 11:30 PM
To: Rush, Katie (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: C-sections

Katie. Thanks for the positive feedback and your nice email. Happy to help, especially this time since NICHD has played a key role in performing the research to support the recommendations.
Uma

From: Rush, Katie (NIH/NICHD) [E]
Sent: Wednesday, February 19, 2014 10:56 PM
To: Reddy, Uma (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Childress, Kerri (NIH/NICHD) [E]
Subject: RE: C-sections

Wonderful, Uma, thanks for sharing! I'm glad the interview went well and the story came out so nicely.

We really appreciate your willingness to speak with the media. I know the requests are usually last-minute, and you're busy enough as it is. But it helps us so much in building good bridges with reporters and getting NICHD's name and research info. out there. Thank you, thank you for making yourself available, even on a day when you were seeing patients.

And thanks again for the follow-up!

K.

Katie Rush

From: Reddy, Uma (NIH/NICHD) [E]
Sent: Wednesday, February 19, 2014 10:39 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rush, Katie (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: RE: C-sections

Liz Szabo was very nice and remembered talking to me before. Here's the link for the story in case:
http://yidor.usatoday.com/story/news/nation/2014/02/19/reducing-cesarean-sections/5508139/

Uma M. Reddy, MD, MPH

OBSTETRICS

Trends in neonatal morbidity and mortality for very low birthweight infants

Avroy A. Fanaroff, MD; Barbara J. Stoll, MD; Linda L. Wright, MD; Waldemar A. Carlo, MD; Richard A. Ehrenkranz, MD; Ann R. Stark, MD; Charles R. Bauer, MD; Edward F. Donovan, MD; Sheldon B. Korones, MD; Abbot R. Laptook, MD; James A. Lemons, MD; William Oh, MD; Lu-Ann Papile, MD; Seetha Shankaran, MD; David K. Stevenson, MD; Jon E. Tyson, MD, MPH; W. Kenneth Poole, PhD; for the NICHD Neonatal Research Network

OBJECTIVE: To document the mortality and morbidity of infants weighing 501-1500 g at birth according to gestational age, birthweight, and sex.

STUDY DESIGN: Prospective collection of perinatal events and neonatal course to 120 days of life, discharge, or death from January 1990 through December 2002 for infants born at 16 participating centers of the National Institute of Child Health & Human Development Neonatal Research Network.

RESULTS: Compared with 1995-1996, for 1997-2002 the survival of infants with birthweight of 501-1500 g increased by 1 percentage point (from 84% to 85%). Survival without major neonatal morbidity remained static, at 70%; this includes bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC). Survival increased for multiple births (26%, up from 22%), antenatal corticosteroid use (79%, up from 71%), and maternal antibiotics (70%, up from 62%) ($P < .05$). From 1997 to 2002, birthweight-specific survival was 55% for infants weighing 501-750 g, 88% for 751-1000 g, 94% for 1001-1250 g, and 96% for 1251–1500 g. More females survived. The incidence of NEC (7%), severe IVH (12%), and late-onset septicemia (22%) remained essentially unchanged, but BPD decreased slightly, from 23% to 22%. The use of postnatal corticosteroids declined from 20% in 1997-2000 to 12% in 2001-2002. Growth failure (weight <10th percentile) at 36 weeks' postmenstrual age decreased from 97% in 1995-1996 to 91% in 1997-2002.

CONCLUSION: There have been no significant increases in survival without neonatal and long-term morbidity among VLBW infants between 1997 and 2002. We speculate that to improve survival without morbidity requires determining, disseminating, and applying best practices using therapies currently available, and also identifying new strategies and interventions.

Key words: limits of viability, morbidity, mortality, NICHD Neonatal Research Network, prematurity, preterm delivery, very low birthweight

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Advances in perinatal care, including antenatal corticosteroid therapy and postnatal surfactant administration, ensure that most babies born before term in the United States now survive.[1-6] Nonetheless, disorders relating to short gestation and low birthweight continue to contribute significantly to infant deaths in the United States.[7-9] Indeed the infant mortality rate rose to 7.0 per 1000 live births in 2002, from 6.8 in 2001, marking the first increase in this rate in more than 4 decades. Increases were distributed fairly widely across age, racial/ethnic groups, and geographic areas. The rise in infant mortality was attributed to increased births in both singleton and multiple deliveries with birthweight <750 g.[9] In addition, despite better predictors of preterm birth,[10,11] efforts to reduce preterm births have failed, so that prematurity continues to contribute disproportionately to neonatal morbidity and subsequent physical and neurodevelopmental disabilities.[12-15]

Determining the prognosis for survival, neurodevelopmental outcome, and resource utilization of premature infants born at the threshold of viability (between 22 and 25 completed weeks of gestation) remains a major challenge and concern.[16-18]

Our objective was to use the Neonatal Research Network very low birthweight (VLBW) registry of the National Institute of Child Health and Human Development (NICHD) to determine factors contributing to mortality and significant short-term morbidity among infants with birthweights between 501 and 1500 g from 1997 to 2002. These outcomes were compared with two prior cohorts, to document changes over the full 13-year period (1990-2002) and to examine the borders of viability.

MATERIALS AND METHODS

The present study compared perinatal information, morbidities, and mortality for 3 cohorts of infants born at participating centers (hereafter called "inborn infants"), all with birthweights between 501 and 1500 g. Cohort I comprises births in 1990 and 1991, the immediate postsurfactant era. Cohort II, comprising births in 1995 and 1996, reflects the sharp increase in antenatal corticosteroid use. Cohort III, with 18,153 infants, covers the period from 1997 to 2002.

All the infants were part of the NICHD Neonatal Research Network VLBW registry, wherein maternal and infant data were collected using common definitions developed by the investigators (with Institutional Review Board approval) and described in the study *Manual of Operations* and in previous publications.[1-5]

Bronchopulmonary dysplasia (BPD), formerly called chronic lung disease (CLD), was defined by supplemental O_2 at 36 weeks' postmenstrual age as determined by the best obstetric estimate of gestational age at birth.[19,20] In-hospital morbidity was defined by the presence of any intraventricular hemorrhage (IVH), Bell's stage 2 or greater necrotizing enterocolitis (NEC), and/or BPD.[21] Mortality includes all in-hospital deaths prior to 120 days of age. Intrauterine growth restriction and postnatal growth failure were defined by weight below the 10th percentile according to the national reference data of Alexander et al.[22]

Statistical comparisons between the different birth-year cohorts were made by logistic regression for binary outcomes (adjusting for the birthweight and center, unless indicated otherwise). The Cochran-Armitage trend test for contingency tables was used to test the overall trends in survival and morbidity by birthweight and gestational age.

RESULTS

Survival and morbidity

Mortality and selected morbidities among VLBW infants were compared for the 3 cohorts (1990-1991, 1995-1996, and 1997-2002), using data only from the 12 centers that had participated in the Network throughout this period. Mortality for the entire cohort declined from 20% in the 1990-1991 cohort to 16% (relative decline 20%, $P < .0001$) in the 1995-1996 cohort, and 15% (relative decline 6%, $P = .9117$) in the 1997-2002 cohort. Most deaths occurred within 7 days of birth, and 87% of VLBW infants who died did so by 28 days.

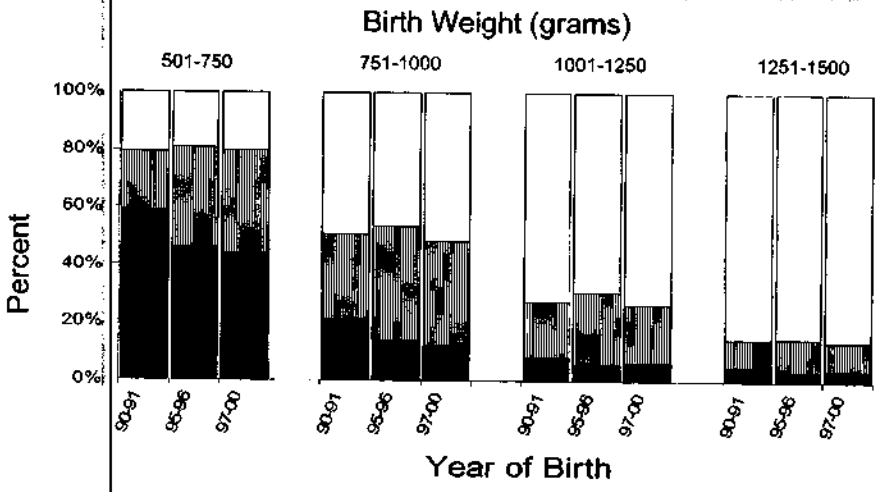
The change in mortality over time for each 250-g birthweight category is evident in Figure 1. For the lowest birthweight group, 501-750 g, mortality decreased from 59% in the 1990-1991 cohort to 46% in the 1995-1996 cohort, a relative decline of 22% ($P < .0001$), and reached 45% in the 1997-2002 cohort, a further 4% improvement ($P = .6585$). For infants with birthweight of 751-1000 g, mortality fell from 19% in the 1990-1991 cohort to 14% in the 1995-1996 cohort, a relative decline of 21% ($P < .0001$), and it reached 12% in the 1997-2002 cohort (a further 14% decline, $P = .3911$). For the next group, 1001-1250 g, mortality fell from 7.7% in the 1990-1991 cohort to 6% in the 1995-1996 cohort, a relative decline of 21% ($P < .05$); mortality was unchanged in the 1997-2002 cohort. For the heaviest of these VLBW groups, 1251-1500 g, mortality decreased from 5% to 3% between the 1990-1991 cohort and the 1995-1996 cohort, then rose to 4% in the 1997-2002 cohort.

Figure 1 reveals that morbidity (in terms of IVH, NEC, and BPD) according to birthweight increased between the 1990-1991 and 1995-1996 cohorts, and was sustained at that level for the 1997-2002 cohort. Combining the data for all birthweights, survival with the various morbidities (BPD, severe IVH, NEC, and all combinations thereof) increased slightly, from 29% to 30%, between the 1995-1996 cohort and the 1997-2002 cohort ($P = .0476$), with the exception of BPD alone, which increased from 15% to 17% ($P = .0004$). This translates into a slight improvement (71% vs 70%) in the percentage of infants who survived without significant neonatal morbidity.

Perinatal parameters for 1997-2002 are given in Table 1. Because there was little difference in the change from 1997-1998 in either 1999-2000 or 2001-2002, the combined numbers (1999-2002) were used for comparison with previous reports. The variability across participating centers (termed *center variability*) is obvious from the wide range of each parameter. Compared with the 1995-1996 cohort,[5] antenatal corticosteroid use increased from 71% to 79% ($P < .0001$), and maternal antibiotic administration

4-00908

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.

increased from 62% to 70% ($P < .0001$). There was also a 4% increase in multiple births ($P < .0001$) and a 7% decrease in endotracheal intubation in the delivery room ($P < .0001$). Other parameters remained stable.

The lower cesarean section rates (49% vs 64%) and high rates of vaginal breech delivery (14% vs 4%) for infants with birthweight of 500-749 g, compared with 751-1000 g (Table 1), suggest a less aggressive obstetrical approach for the most immature infants.

Selected morbidities, therapies, and mortalities for inborn infants are given in Tables 2 and 3. For the 1997-2002 cohort, compared with the 1995-1996 cohort, respiratory distress syndrome was reduced (44% vs 50%, $P < .0001$), but surfactant use increased (58% vs 52%, $P < .0001$), and a similar number of cases of patent ductus arteriosus required treatment (29% vs 30%) (Table 2).

There was not much change in other major morbidities, including BPD, NEC, grade III-IV IVH, periventricular leukomalacia (5% vs 3%), late-onset septicema (24% vs 22%), and growth failure (97% vs 91%).[5,22,25] Postnatal corticosteroids were given to 12% of infants in the years 2001-2002, compared with 20% of all the infants in the years 1997-2000 and 23% in the 1995-1996 cohort ($P < .0001$). Survival data, with and without selected neonatal morbidities according to birthweight, are given in Table 3.

Influence of sex, birthweight, and gestational age on mortality

Separate logistic regression[23] models of mortality by birthweight and gestational age were developed for VLBW (401-1500 g) inborn singleton infants by sex for the 1997-2002 cohort. All models included birthweight, gestational age by best obstetric measures, and an interaction term between birthweight and gestational age. The plots are presented in Figure 2 for the cohort of infants older than 21 weeks and between the 5th and 95th percentiles of birthweight for each sex at each gestational age at which a lower birthweight carried a higher mortality risk.[22] Large reductions in mortality risk occur with each additional week of gestation and 100-g increase in birthweight in the mid and lower ranges of gestational age and birthweight. At higher gestational ages, comparable changes in birthweight have a smaller effect on mortality risk.

Prediction of mortality risk at the lowest birthweights is influenced by sex (risk is greater in males) and intrauterine growth rate. For both male and female infants, mortality risk contour lines generally traveled the graph from upper left to lower right, revealing a combined effect of gestational age and birthweight on risk of death. Hence, the mortality ranged from 60% for a 24-week female with a birthweight on the 5th percentile to 20% if on the 95th percentile; mortality for males of similar gestation ranged from almost 70% on the 5th percentile to 25% on the 95th percentile.

The birthweight-specific survival for all inborn infants born between 1997 and 2002 rises progressively with increasing birthweight (Figure 3). There was a striking stepwise increase in survival, from 36% at 501-600 g to 61% at 601-700 g and to 79% at 801-900 g.

COMMENT

This report summarizes the mortality and morbidity among VLBW infants born at the Neonatal Research Network centers (listed under Acknowledgments) between 1997 and 2002. Comparison of outcomes for the full period from 1990 to 2002 is restricted to the 12 centers that participated throughout the 13 years. Between January 1997 and December 2002, 85% of inborn VLBW infants survived to discharge, ranging from 55% of infants who were 501-750 g at birth to 96% for infants 1250-1500 g at birth; however, there has been little change in survival by birthweight or gestational age categories during this time period.

Compared to the 1990-1991 cohort, mortality rates fell significantly for VLBW infants, particularly for infants weighing less than 1000 g at birth (Figure 1). Respiratory distress syndrome remained the most common acute pulmonary disease, although there was a relative decrease of almost 20% in the frequency of the diagnosis, compared to a 1991 cohort.[2,3] The incidence of grade III-IV IVH declined from 15% in the 1990-1991 cohort to 12% in the 1997-2002 cohort, but there has been no improvement since 1997 (Table 2).

TABLE 1
Perinatal information for very low birthweight infants born in the NICHD Neonatal Research Network between Jan. 1, 1997, and Dec. 31, 2002

Characteristic	501-750 g (n = 4046)	751-1000 g (n = 4266)	1001-1250 g (n = 4557)	1251-1500 g (n = 5284)	501-1500 g (n = 18,153)
Birthweight, g (range)*					
Mean	635 (611-652)	878 (868-898)	1129 (1110-1136)	1379 (1370-1385)	1033 (998-1066)
Standard deviation	69.1 (64.9-72.2)	73.4 (68.1-78.1)	71.5 (68.9-75.7)	72.3 (65.1-74.2)	289 (273-295)
Other parameters, % (range)*					
Antenatal steroids	73 (38-90)	84 (50-94)	83 (52-94)	78 (47-89)	79 (47-90)
Antenatal antibiotic	71 (60-96)	70 (62-88)	71 (58-85)	69 (55-87)	70 (59-87)
Membrane rupture > 24 h†	26 (17-35)	24 (16-32)	24 (18-29)	22 (15-30)	24 (16-28)
Multiple births	24 (14-42)	24 (14-36)	27 (16-39)	29 (17-44)	26 (18-40)
Small for gestational age‡	16 (10-31)	15 (9-22)	22 (17-28)	28 (16-35)	21 (17-26)
Mode of delivery					
Vaginal vertex	38 (12-46)	32 (22-37)	35 (26-46)	42 (31-53)	37 (29-44)
Vaginal breech	14 (6-23)	4 (<1-13)	2 (0-5)	2 (<1-4)	5 (2-9)
Cesarean section	49 (34-82)	64 (57-74)	62 (49-72)	56 (45-68)	58 (50-69)
Delivery room resuscitation					
Endotracheal intubation	78 (57-98)	71 (39-93)	46 (18-69)	24 (8-39)	53 (32-68)
Resuscitation drug	10 (<1-30)	6 (<1-13)	4 (<1-11)	3 (0-8)	5 (2-14)
Apgar score					
≤3 at 1 min	54 (36-69)	31 (17-46)	21 (11-33)	13 (5-21)	28 (18-39)
≤3 at 5 min	25 (8-41)	7 (3-15)	4 (1-8)	2 (<1-6)	9 (5-12)

NICHD, National Institute of Child Health and Human Development.

* Range across all participating Neonatal Research Network centers (listed under Acknowledgments).

† Time between rupture of membranes and delivery

‡ Small for gestational age: weight < 10th percentile.

Antenatal pharmacological therapies instituted in the face of impending preterm birth include steroids to induce maturity of fetal lungs and prevent brain hemorrhage; antibiotics to treat potential chorioamnionitis, prevent early-onset group B streptococcal (GBS) disease, and prolong the latent period; and tocolytics to extend the duration of pregnancy. The marked increase in antenatal steroid use from approximately 20% in the 1990-1991 cohort to 79% in the 1997-2002 cohort may, in part, explain the reduced mortality and lower incidence of respiratory distress syndrome.[3,5]

In the 1990-1991 cohort, only 31% of women received antenatal and/or intrapartum antibiotics. This increased to 62% in the 1995-1996 cohort and reached 70% in the 1997-2002 cohort. Early-onset sepsis (EOS), proven by blood culture, declined from 19.3 per 1000 in 1991-93 to 15.4 per 1000 live births in 1998-2000.[25] Among VLBW infants, GBS sepsis declined from 5.9 per 1000 births in 1996 to 1.7 per 1000 in 2000, but *Escherichia coli* sepsis increased from 3.2 to 6.8 per 1000 births, with most *E. coli* isolates (85%) resistant to ampicillin. This reflects a worrisome change in the pathogen distribution among VLBW infants with EOS,[25] perhaps a consequence of maternal antibiotic therapy. Early-onset sepsis remains an important risk for mortality: 37% of infants with EOS died, compared to 13% of those without EOS.

Multiple births in the Network 1997-2002 accounted for 26% of VLBW deliveries (Table 1), compared with 19% in the early 1990s. Similar increases have been noted in the Vermont Oxford Network.[6] An increasing number of multiple births are due to assisted reproductive techniques. In 1997, infants conceived with assisted reproductive technology accounted for 4.3% of very low birthweight infants (<1 kg).[26] Gestational age-adjusted comparisons of outcome between singletons and multiples have shown conflicting results.[27] Comparisons correcting for relevant confounding variables show that twins and singletons have similar risks for early morbidity and mortality.[28] Second-born VLBW twins seem to be at risk for increased respiratory morbidity, even in the era of routine antenatal corticosteroids and postnatal surfactant therapy, and we observed that IVH, NEC, and/or BPD were more common in multiples than in singletons ($P = .0010$). The inci-

TABLE 2
Morbidity for very low birthweight infants born in the NICHD Neonatal Research Network between Jan. 1, 1997 and Dec. 31, 2002

	Morbidity, % (range)*				
	501-750 g (n = 4046)	751-1000 g (n = 4266)	1001-1250 g (n = 4557)	1251-1500 g (n = 5284)	501-1500 g (n = 18,153)
Respiratory distress syndrome†	71 (51-98)	55 (39-75)	37 (22-65)	23 (11-44)	44 (30-69)
Surfactant therapy	88 (67-99)	74 (50-93)	52 (32-75)	32 (17-52)	58 (42-74)
Postnatal steroids	45 (12-64)	25 (7-46)	7 (<1-16)	2 (<1-4)	17 (4-29)
Pneumothorax	13 (1-19)	6 (3-10)	3 (0-6)	2 (<1-4)	5 (1-7)
O_2 at 28 days	66 (39-90)	37 (15-70)	14 (3-32)	5 (<1-18)	25 (11-41)
Bronchopulmonary dysplasia	46 (25-81)	33 (11-62)	14 (3-46)	6 (2-23)	22 (10-50)
Patent ductus arteriosus	49 (20-83)	38 (11-60)	23 (9-48)	13 (7-33)	29 (13-50)
Indomethacin for PDA	84 (62-98)	81 (56-98)	75 (47-96)	67 (40-88)	79 (53-91)
Surgery for PDA	29 (8-53)	21 (7-53)	10 (2-30)	6 (0-16)	19 (8-35)
Growth failure‡	97 (92-100)	93 (85-100)	87 (74-96)	86 (66-98)	91 (83-98)
Discharged home on O_2	28 (<1-75)	18 (1-53)	9 (0-36)	4 (0-23)	11 (<1-37)
Sonogram done	96 (91-100)	98 (92-100)	95 (57-100)	85 (37-99)	93 (67-100)
Grade I IVH	10 (5-16)	11 (5-22)	10 (4-24)	11 (5-29)	11 (7-23)
Grade II IVH	7 (2-15)	6 (1-11)	4 (0-16)	2 (0-6)	4 (<1-11)
Grade III IVH	12 (3-19)	9 (4-22)	6 (1-9)	4 (0-9)	7 (3-11)
Grade IV IVH	12 (9-21)	5 (1-10)	3 (0-5)	1 (0-6)	5 (3-8)
Periventricular leukomalacia	4 (0-10)	3 (0-14)	2 (0-5)	1 (0-3)	3 (1-5)
NEC, proven	11 (4-25)	9 (3-18)	5 (3-9)	3 (1-8)	7 (4-11)
Late-onset septicemia	44 (29-58)	30 (16-46)	17 (8-27)	7 (1-15)	22 (12-32)

IVH, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *NICHD*, National Institute of Child Health and Human Development; *PDA*, patent ductus arteriosus.

* Range across all participating Neonatal Research Network centers (listed under Acknowledgments).

† An infant was determined to have respiratory distress syndrome if each of the following was true: required O_2 at 6 hours of life continuing to age 24 hours, demonstrated clinical features within age 24 hours, had need for respiratory support to age 24 hours, and had an abnormal chest x-ray within age 24 hours.

‡ Growth failure defined as weight < 10th percentile at 36 weeks' postconceptual age.

dence of severe disability is increased in survivors of multiple gestations.[26]

Postnatal steroid therapy has come under close scrutiny because of multiple complications, including hypertension, hyperglycemia, sepsis, gastrointestinal perforations, growth arrest, and adverse neurodevelopmental outcome.[29-31] Overall, the use of postnatal steroids declined. At 19% in the 1995-1996 cohort, use was stable for a while (20% in 1997-2000), but decreased to 12% in 2001-2002. This has been most notable for infants with a birthweight of 501-750 g, in which group the proportion decreased from 53% in 1997-2000 to 30% in 2001-2002. In response to the Committee of the Fetus and Newborn Statement from the American Academy of Pediatrics, use of postnatal steroids should be considered with care, or discouraged, in which case further declines can be expected.[32]

Although survival rates improved, the incidence of major morbidities (including BPD, IVH, and NEC) remains a serious concern. The terms BPD (initially defined as requiring O_2 at 28 days) and CLD (O_2 at 36 weeks' postmenstrual age) have been used interchangeably to refer to chronic lung disease.[2-5] A consensus workshop has recommended the term BPD, because it is clearly distinct from the multiple chronic lung diseases of later life,[33] with the use of a physiologic test confirming the necessity of supplemental O_2 at 36 weeks.[34] BPD (O_2 at 36 weeks' postmenstrual age) increased from 19% in the 1990-1991 cohort to 23% in the 1995-1996 cohort, then decreased to 22% in the 1997-2002 cohort. The improved survival rates of VLBW infants, particularly those weighing less than 1000 g, may explain, in part, the consistent rate of BPD.

The mortality and morbidity for the smallest infants remain high, with little change in survival by birthweight or gestational age between the 1995-1996 and 1997-2002 cohorts.

The female survival advantage extends through all birthweights and gestational ages; they function as if a week more mature and 100 g heavier than males.[35]

The mortality as well as the morbidity and outcome data are entirely consistent with those reported by the Vermont Ox-

TABLE 3
Survival with selected neonatal morbidity for very low birthweight infants born in the NICHD Neonatal Research Network between Jan. 1, 1997, and Dec. 31, 2002

	Survival, % (range)*				
	501-750 g (n = 4046)	751-1000 g (n = 4266)	1001-1250 g (n = 4557)	1251-1500 g (n = 5284)	501-1500 g (n = 18,153)
Survived	55 (38-76)	88 (74-94)	94 (91-97)	96 (93-99)	85 (79-93)
Survived with morbidity†					
Overall	65 (48-80)	43 (27-63)	22 (10-33)	11 (5-19)	30 (21-43)
BPD alone	42 (15-61)	25 (5-42)	11 (1-21)	4 (0-9)	17 (4-26)
Severe IVH‡	5 (0-13)	6 (2-17)	5 (<1-8)	4 (0-12)	5 (2-10)
NEC alone	3 (0-16)	3 (1-13)	3 (<1-8)	2 (0-5)	3 (<1-7)
BPD and Severe IVH	10 (3-17)	4 (2-11)	2 (0-5)	<1 (0-2)	3 (1-6)
BPD and NEC	4 (0-9)	3 (0-6)	<1 (0-2)	<1 (0-2)	2 (<1-3)
NEC and Severe IVH	<1 (0-5)	<1 (0-2)	<1 (0-1)	<1 (0-<1)	<1 (0-1)
BPD and Severe IVH and NEC	1 (0-3)	<1 (0-3)	<1 (0-<1)	<1 (0-<1)	<1 (0-<1)

BPD, bronchopulmonary dysplasia; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *NICHD*, National Institute of Child Health and Human Development.

* Range across all participating Neonatal Research Network centers (listed under Acknowledgments).

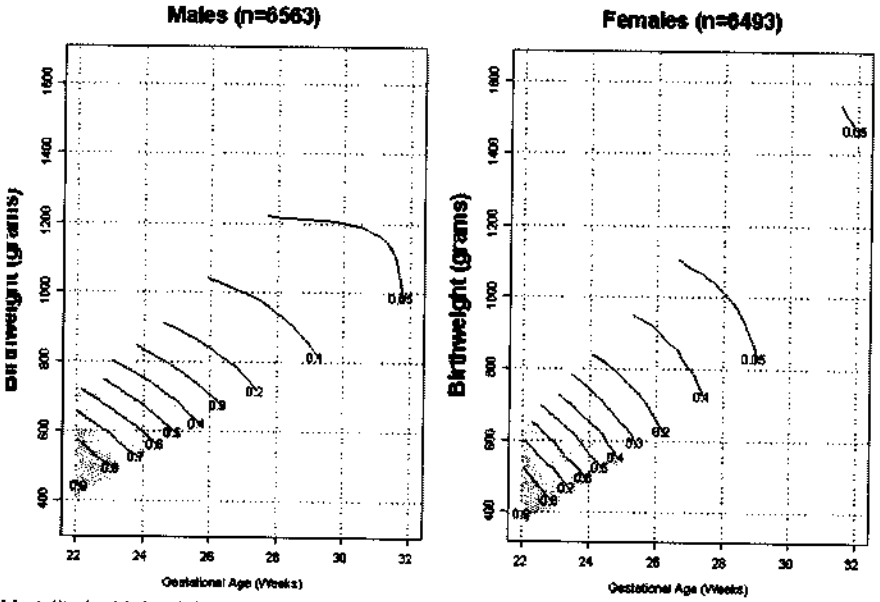
† Morbidity is defined as a diagnosis of BPD, grade III-IV IVH, or proven NEC.

‡ Severe IVH is defined as grade III (blood in the ventricles with ventriculomegaly) or IV (blood/echodensity in the parenchyma).

ford Network, who also reported the plateau in mortality in the late 1990s.[6] There are dramatic stepwise increases in survival between 23 and 25 weeks' gestation and birthweights greater than 600 g. Thus, from 23 to 24 completed weeks the survival increases from 29% to 60%, almost a 4% improvement in survival for each additional day in utero. The birthweight survival data are complementary: survival increases from 36% at 501-600 g to 61% for a birthweight of 601-700 g. Assuming an intrauterine weight gain of 15 g/day at this gestational age, this also represents improvement in survival of more than 3% for each additional day in utero. The steep curve in survival continues between 24 and 25 weeks' gestation and a birthweight of 701-800 g. These data support the concept of extending the stay in utero until there is substantial evidence that the VLBW fetus is seriously compromised.

Viability, morbidity, and resource use are the subject of much debate.[32] Both the American Academy of Pediatrics and the American College of Gynecologists have issued statements and guidelines concerning deliveries at the threshold of viability (25 or fewer completed weeks of gestation).[17,18] They concur that it is ex-

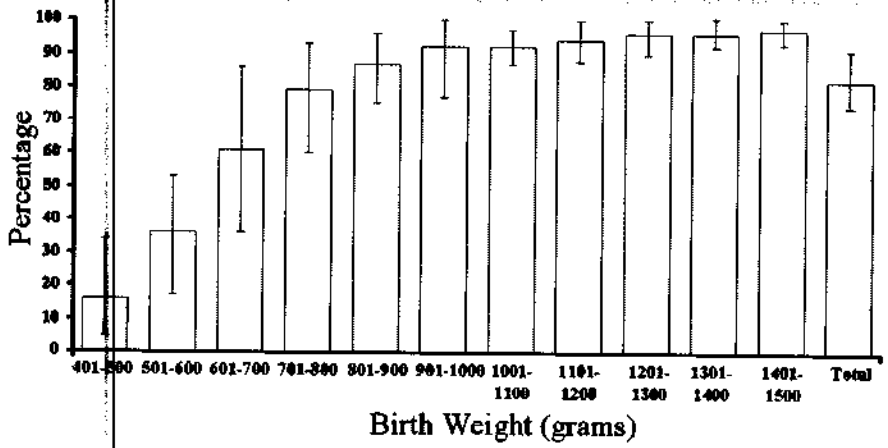
FIGURE 2
Mortality by birth weight, gestational age and gender–NICHD 1997-2002



Mortality by birthweight, gestational age, and sex. The limits of the colored area indicate the upper 95th and lower 5th percentiles of birthweight for each gestational age. The curved lines indicate combinations of birthweight and gestational age with the same estimated probability of mortality (ie, 10-90%). The gradation of color denotes the change in estimated probability of death: green indicates infants of lower gestational age and birthweight who are more likely to die; yellow indicates infants of higher gestational ages and birthweights who are less likely to die. The methods used underestimate mortality at 22 and 23 weeks with a birthweight up to 600 g.

4-00912

FIGURE 3
Survival rates by birthweight 1997-2002



Survival to discharge by birthweight in 100-g increments among infants born in NICHD Neonatal Research Network centers between Jan. 1, 1997, and Dec. 31, 2002, with center variability.

tremely difficult for physicians and families to make decisions regarding the institution and continuation of life support in such infants.

If viability is defined by a survival rate of equal to or greater than 50%, our data imply that infants delivered at 24 weeks' gestation and with a birthweight of at least 600 g are, indeed, viable. However, the definition does not take into account the considerable long-term neurodevelopmental deficits encountered at this weight and gestational age. In the EPICure Study, which included all infants born in the United Kingdom between 23 weeks and 25 weeks and 6 days of gestation, the mortality was high and fewer than half the survivors were neurologically intact.[14,15] Similar neurodevelopmental outcomes have been reported from the United States.[12,13]

To gain perspective from the 1997-2002 cohort, approximately 40% of infants delivered at 24 weeks' gestation died, and 40% of the survivors manifested significant neurodevelopmental deficit; thus, only 36% of infants delivered at 24 weeks could be expected to survive without major disability. Similar calculations from the 1995-1996 cohort at 24 weeks' gestation yielded only 30% intact survivors.

These are conservative and probably overly optimistic estimates. Substantial visual, integrative, mathematical, and other learning problems are often identified in apparently neurologically intact children of very low birthweight when they go to school.[35,36] The long-term burden of extreme preterm birth may be even greater. There remains wide center variability in survival, as well as the various short- and long-term morbidities. The group data are robust, but counseling for individual pregnancies remains extraordinarily challenging and difficult. Furthermore, one can only speculate on the outcomes and costs, if all participating units were equally aggressive (or not) in their approach to infants at the boundaries of viability.[15,34,37,38]

In summary, despite increased use of antenatal corticosteroids, antenatal antibiotics, and surfactant therapy, survival of VLBW infants changed almost imperceptibly between 1997 and 2002. There has been minimal change in the boundaries of viability and in the number of infants surviving without significant neonatal morbidity. Knowledge of birthweight, gestational age, sex, intrauterine growth rates, condition at birth, and site of delivery are needed to forecast the chances of an individual baby surviving. Long-term neurodevelopmental outcomes, still being evaluated for the most recent cohorts, will ultimately determine the true outcome of this cohort of VLBW infants. Newer strategies and interventions are needed to prevent prematurity and improve the outcome of these vulnerable infants. The wide range of mortality and morbidities among Network centers suggests that there are best practices using currently available therapies awaiting discovery. Efforts are underway to identify them.[24] ■

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Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network

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(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: The NICHD NRN has published periodic evaluations of morbidity and mortality rates for VLBW infants. Increased VLBW survival has paralleled improvements in prenatal, obsteric and neonatal care, but recent data suggest that a plateau in survival may have been reached.

WHAT THIS STUDY ADDS: This study is the first NRN study to report outcomes on the basis of GA-specific information, which should be particularly valuable to obstetricians and pediatricians as they counsel parents of high-risk infants.

OBJECTIVE: This report presents data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network on care of and morbidity and mortality rates for very low birth weight infants, according to gestational age (GA).

METHODS: Perinatal/neonatal data were collected for 9575 infants of extremely low GA (22–28 weeks) and very low birth weight (401–1500 g) who were born at network centers between January 1, 2003, and December 31, 2007.

RESULTS: Rates of survival to discharge increased with increasing GA (6% at 22 weeks and 92% at 28 weeks); 1060 infants died at ≤12 hours, with most early deaths occurring at 22 and 23 weeks (85% and 43%, respectively). Rates of prenatal steroid use (13% and 53%, respectively), cesarean section (7% and 24%, respectively), and delivery room intubation (19% and 68%, respectively) increased markedly between 22 and 23 weeks. Infants at the lowest GAs were at greatest risk for morbidities. Overall, 93% had respiratory distress syndrome, 46% patent ductus arteriosus, 16% severe intraventricular hemorrhage, 11% necrotizing enterocolitis, and 36% late-onset sepsis. The new severity-based definition of bronchopulmonary dysplasia classified more infants as having bronchopulmonary dysplasia than did the traditional definition of supplemental oxygen use at 36 weeks (68%, compared with 42%). More than one-half of infants with extremely low GAs had undetermined retinopathy status at the time of discharge. Center differences in management and outcomes were identified.

CONCLUSION: Although the majority of infants with GAs of ≥24 weeks survive, high rates of morbidity among survivors continue to be observed. *Pediatrics* 2010;126:443–456

Over the previous 2 decades, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) has monitored trends in morbidity and mortality rates among very low birth weight (VLBW) infants born at the university centers that constitute the NRN.[1–6] Increased VLBW infant survival rates have paralleled improvements in prenatal, obstetric, and neonatal care.[7,8] NRN data suggest that a plateau in VLBW infant survival rates might have been reached, despite increased use of prenatal corticosteroid treatment, prenatal antibiotic treatment, and early neonatal surfactant treatment.[5] Previous NRN reports presented patient characteristics, interventions, and outcomes according to birth weight (BW), with an upper limit of 1500 g. Such BW-specific data may be skewed by more-mature infants with growth restriction. The aim of this study was to evaluate management, hospital complications, and mortality rates among infants with gestational ages (GAs) of 22 to 28 weeks who were born at NRN centers between 2003 and 2007.

METHODS

Study Population and Clinical Outcomes

Infants born alive at NRN centers in 2003–2007 with GAs of 22⁰⁄₇ to 28⁶⁄₇ weeks and BWs of 401 to 1500 g were studied, including those with congenital anomalies. These infants were part of the NRN VLBW registry.[1–6]

Research personnel collected maternal pregnancy/delivery data soon after birth and infant data from birth to death, discharge/transfer, or 120 days of age ("status"). For infants with prolonged hospitalizations, limited information was collected up to 1 year. Definitions for maternal and infant characteristics were provided in a manual of operations. GA was determined as the best obstetric estimate by using ultrasonography and/or the date of the last menstrual period. Intrauterine growth restriction, defined as BW of <10th percentile for gender and GA, was determined by using growth charts published by Alexander et al.[9] Morbidities were defined in earlier publications,[1–6,10,11] including respiratory distress syndrome, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), early-onset and late-onset sepsis, necrotizing enterocolitis, patent ductus arteriosus, and retinopathy of prematurity (ROP). Respiratory distress syndrome was defined on the basis of clinical features and oxygen or respiratory support for ≥6 of the first 24 hours.

Three definitions of BPD were used, namely, traditional BPD (supplemental oxygen use at postmenstrual age [PMA] of 36 weeks); BPD determined by using the National Institutes of Health Workshop severity-based diagnostic criteria,[12] and BPD determined according to physiologic definition.[13] Surviving infants who were discharged or transferred before PMA of 36 weeks were classified on the basis of their status at 36 weeks, if status information was available, or oxygen use at discharge/transfer, if status information was not available. Unless noted otherwise, BPD refers to the traditional definition.

Revisions to data collection in 2006 included questions about maternal chorioamnionitis, placental pathologic conditions, nitric oxide use, and ibuprofen use and expanded data collection on birth resuscitation and neurologic, pulmonary, and ophthalmologic outcomes. In addition to ophthalmologic examination results and interventions, the following outcomes, defined in the manual of operations, were recorded: favorable in both eyes, severe ROP in either eye, or undetermined in either eye without severe ROP in either eye. Complete definitions are included in a footnote to Table 6. The registry was approved by the institutional review boards at each center.

Statistical Analyses

All infants were studied for assessment of maternal characteristics, neonatal demographic features, interventions performed soon after birth, and survival. Infants who died at ≤12 hours were excluded from analyses focused on morbidities diagnosed at >12 hours. For determination of rates of survival without morbidity, morbidity was defined as severe IVH (≥grade 3), PVL, BPD, necrotizing enterocolitis, ≥stage 3 ROP, or infection (early-onset sepsis, late-onset sepsis, or meningitis).

Statistical significance for unadjusted comparisons was determined by using χ^2 or Wilcoxon tests. Logistic or linear regression models were used to assess associations with GA, with adjustment for study center and infant BW, with statistical significance determined by using Wald χ^2 or F tests. Generalized logit regression models were used for comparisons involving categorical variables with >2 levels.

Risk of death and changes in clinical practice during the study period were assessed by using robust Poisson regression models[14] to produce correct SEs for the estimated relative risks (RRs). Additional adjustments for clustering according to center were not made because study center was treated as a fixed effect in these models, which also included effects for BW and GA. To assess linear trends, year was included as a continuous variable, with adjusted RRs for the change per year being reported. Initial models included terms for interactions between each GA and year, to assess whether yearly trends varied according to GA.

Nonsignificant interactions were removed, and the models were rerun.

Participating NRN Study Centers

The numbers of infants included from each center were as follows: University of Alabama, 805 infants; Brown University, 616 infants; University of California, San Diego, 528 infants; Case Western Reserve University, 415 infants; University of Cincinnati, 974 infants; Duke University, 426 infants; Emory University, 516 infants; Indiana University, 720 infants; University of Iowa, 99 infants; University of Miami, 515 infants; University of New Mexico, 97 infants; University of Rochester, 243 infants; Stanford University, 334 infants; University of Texas Southwestern Medical Center at Dallas, 488 infants; University of Texas Health Science Center at Houston, 765 infants; Tufts University, 137 infants; University of Utah, 269 infants; Wake Forest University, 465 infants; Wayne State University, 637 infants; Yale University, 526 infants.

RESULTS

Study Group

A total of 9575 infants with GAs of 22 to 28 weeks and BWs of 401 to 1500 g were born at NRN centers between January 1, 2003, and December 31, 2007, and are included in this study. Overall, 25% of the cohort subjects were multiple births.

Maternal and Infant Characteristics, Delivery Room Interventions, and Early Deaths

Rates of prenatal steroid use increased with increasing GA, from 13% at 22 weeks to 53% at 23 weeks and 85% to 87% at 24 to 28 weeks (Table 1). Rates of prenatal antibiotic use were lowest for mothers who delivered at 22 weeks (51%) and highest for those who delivered at 24 to 25 weeks (73%). Chorioamnionitis was documented more frequently in maternal records and confirmed more commonly by placental histologic findings at lower GAs. Overall, 59% of infants were born through cesarean section, with the steepest increase in cesarean section delivery rates between GAs of 22 and 24 weeks (7% at 22 weeks and 60% at 24 weeks).

With adjustment for center and BW, there were no differences in racial distribution according to GA (Table 2). Early neonatal interventions differed according to GA (Table 2). At 22 weeks, only 19% of infants underwent intubation and ventilation in the delivery room. Intubation rates increased to 68% at 23 weeks and 87% at 24 weeks and decreased at >24 weeks. Of 856 infants who received resuscitation drugs and/or chest compressions, 96% also underwent intubation. Rates of surfactant therapy increased from 17% at 22 weeks to 63% at 23 weeks and 90% at 24 weeks. The proportion of infants who died at ≤12 hours decreased with increasing GA, from 85% at 22 weeks to 1% to 2% at 27 to 28 weeks (Table 3). Risk of early death was significantly elevated for infants born at 22 to 24 weeks, compared with infants born at 28 weeks (22 weeks, adjusted RR: 15.76 [95% confidence interval [CI]: 10.13–24.52]; 23 weeks, adjusted RR: 9.88 [95% CI: 6.48–15.08]; 24 weeks, adjusted RR: 2.90 [95% CI: 1.90–4.43]), but not for infants born at 25 to 27 weeks.

Changes in Clinical Practices

Rates of prenatal steroid use increased by ~1% per year during the study period, and rates of cesarean section delivery increased by ~2% per year (Table 4). Rates of prenatal antibiotic use decreased by ~3% per year. These trends did not vary according to GA (year-GA interaction: for prenatal steroid therapy, $P = .47$; for cesarean section delivery, $P = .37$; for prenatal antibiotic treatment, $P = .66$). Rates of endotracheal intubation in the delivery room and surfactant therapy varied according to GA (year-GA interaction: $P < .01$ for each). Rates of intubation and surfactant therapy decreased for infants born at 28 weeks. During the study period, the proportion of infants receiving continuous positive airway pressure (CPAP) therapy at 24 hours increased among infants of ≥24 weeks, as did the proportion of infants who never underwent intubation. Although the adjusted RR for BPD decreased over time among infants who survived to PMA of 36 weeks, the change was clinically insignificant.

Neonatal Characteristics and Morbidities Among Infants Who Survived >12 Hours

Overall, 89% of infants born at GAs of 22 to 28 weeks survived >12 hours. Substantially more early survivors born at 22 to 24 weeks received resuscitation efforts (intubation, drug treatment, and/or chest compression) in the delivery room, compared with infants born at 22 to 24 weeks who died at ≤12 hours (22 weeks, 90% vs 7%; 24 weeks, 91% vs 59%). Significant differences in resuscitation efforts between those who survived >12 hours and those who did not were not seen among infants with GAs of 25 to 27 weeks. Among infants born at 28 weeks, a smaller proportion of those who survived >12 hours received resuscitation efforts in the delivery room, compared with those who died within 12 hours (48% vs 65%; $P = .05$).

Infants at the lowest GAs were at the greatest risk for morbidities of prematurity (Tables 5 and 6). Overall, 93% infants experienced respiratory distress. Rates of mechanical ventilation at 24 hours decreased from 96% at 22 weeks to 40% at 28 weeks, and rates of CPAP therapy at 24 hours increased from 0% at 22 weeks to 3% at 23 weeks, 8% at 24 weeks, and 38% at 28 weeks.

TABLE 1 Maternal Demographic Features and Perinatal Information According to GA for VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007 (Including Infants Who Died Within 12 Hours After Birth)

Characteristic	22 wk (N = 421)	23 wk (N = 871)	24 wk (N = 1370)	25 wk (N = 1498)	26 wk (N = 1576)	27 wk (N = 1838)	28 wk (N = 2001)	Total (N = 9575)
Mother's age, y[a]								
Mean (range)	27 (22–32)	27 (25–32)	27 (25–31)	27 (23–30)	27 (25–30)	27 (25–31)	27 (25–32)	27 (25–31)
SD (range)	6.9 (4.2–9.9)	6.4 (0.0–7.0)	6.5 (4.7–8.9)	6.6 (4.9–7.2)	6.5 (4.6–7.6)	6.7 (5.1–7.5)	6.8 (5.2–7.5)	6.6 (5.7–7.0)
High school degree, % (range)	68 (0–100)	69 (25–100)	72 (40–100)	70 (33–94)	72 (25–90)	70 (0–100)	72 (41–89)	71 (36–88)
Medical insurance, % (range)[b]								
Medicaid/public insurance	51 (20–100)	42 (20–100)	50 (15–71)	53 (33–69)	50 (29–71)	50 (24–81)	49 (19–78)	49 (29–69)
Private insurance	35 (0–67)	45 (0–67)	39 (9–76)	38 (6–62)	40 (5–69)	40 (3–67)	42 (4–79)	40 (6–63)
Self-pay/uninsured	13 (0–40)	13 (0–51)	11 (0–42)	8 (0–38)	9 (0–30)	9 (0–22)	8 (0–31)	9 (<1–31)
Other	<1 (0–13)	<1 (0–11)	<1 (0–10)	<1 (0–11)	<1 (0–10)	1 (0–15)	<1 (0–15)	<1 (0–13)
≥1 prenatal visit, % (range)[b]	88 (33–100)	92 (84–100)	93 (85–100)	94 (86–100)	93 (80–100)	95 (85–100)	95 (89–100)	94 (85–100)
Diabetes mellitus, % (range)[c]	3 (0–20)	3 (0–17)	3 (0–10)	4 (0–8)	5 (2–15)	5 (0–11)	6 (1–15)	5 (3–8)
Hypertension, % (range)[b]	8 (0–26)	10 (0–28)	14 (0–40)	20 (9–38)	25 (13–43)	27 (15–42)	31 (11–47)	22 (14–37)
Prepartum hemorrhage, % (range)[b]	21 (0–67)	27 (0–76)	21 (9–40)	22 (5–56)	19 (0–54)	17 (5–35)	16 (6–23)	20 (9–32)
Prenatal steroid treatment, % (range)[b]	13 (0–100)	53 (10–100)	85 (49–100)	86 (62–100)	86 (48–100)	87 (57–100)	86 (46–100)	80 (45–97)
Prenatal antibiotic treatment, % (range)[b]	51 (21–92)	65 (0–88)	73 (56–90)	73 (48–94)	68 (45–100)	66 (51–85)	64 (50–89)	67 (55–85)
ROM >24 h before delivery, % (range)[b]	22 (0–45)	22 (0–42)	25 (8–40)	26 (13–40)	28 (15–50)	25 (14–32)	24 (16–34)	25 (18–32)
Mode of delivery, % (range)[b]								
Vaginal, vertex	60 (20–100)	53 (0–75)	32 (20–56)	31 (19–44)	33 (11–43)	30 (14–44)	30 (12–48)	34 (18–43)
Vaginal, breech	32 (0–80)	23 (0–56)	7 (0–22)	4 (0–13)	3 (0–13)	2 (0–4)	2 (0–5)	6 (0–12)
Vaginal, not otherwise specified	<1 (0–33)	<1 (0–6)	0 (0–0)	<1 (0–5)	<1 (0–2)	<1 (0–1)	<1 (0–1)	<1 (0–1)
Cesarean section	7 (0–33)	24 (3–100)	60 (24–80)	65 (54–79)	65 (52–89)	68 (55–86)	68 (47–88)	59 (47–81)
Infants born in 2006–2007	N = 159	N = 321	N = 493	N = 573	N = 583	N = 732	N = 771	N = 3632
Chorioamnionitis documented in mother's medical record, % (range)[b]	28 (0–100)	26 (0–100)	20 (0–39)	19 (0–56)	19 (0–44)	15 (0–28)	14 (0–22)	18 (7–29)
Placental pathologic evaluation performed, % (range)	77 (36–100)	86 (50–100)	82 (50–100)	83 (62–100)	80 (46–100)	80 (44–100)	83 (0–100)	82 (58–100)
Placental pathologic evaluation	N = 123	N = 272	N = 401	N = 475	N = 461	N = 585	N = 634	N = 2951
Histologic chorioamnionitis, % (range)[b]	70 (25–100)	61 (0–100)	59 (0–100)	51 (25–100)	48 (0–73)	41 (23–61)	34 (8–57)	48 (26–73)

Ranges are across all participating NRN centers. Information was missing as follows: mother's age, 4 infants; mother's education, 2834 infants; mother's medical insurance, 300 infants; prenatal care, 8 infants; diabetes mellitus, 8 infants; hypertension, 10 infants; prepartum hemorrhage, 8 infants; prenatal steroid treatment, 27 infants; prenatal antibiotic treatment, 30 infants; rupture of membranes date and/or time, 228 infants; mode of delivery, 9 infants; chorioamnionitis, 9 infants; placental pathologic evaluation, 26 infants; histologic chorioamnionitis, 17 infants. P values were determined with the Wald χ^2 test for differences according to GA, with adjustment for center and BW. ROM indicates rupture of membranes.

[a] $P \leq .05$.

[b] $P \leq .001$.

[c] $P \leq .01$.

The risk of BPD was inversely related to GA at birth. Because of the inclusion of infants with mild BPD (oxygen therapy for ≥28 days but use of room air at 36 weeks), more infants were classified as having BPD with the new, severity-based, definition of BPD (new definition, 68%; traditional definition, 42%; physiologic definition, 40%).

Most infants who survived >12 hours underwent ≥1 cranial ultrasound evaluation within 28 days; 64% of results were normal (Table 6). Overall, 10% of sonograms indicated grade 1 IVH, 6% grade 2 IVH, 7% grade 3 IVH, 9% grade 4 IVH, 2% ventriculomegaly without IVH, and 2% other abnormalities. PVL was observed for 3% of infants with sonograms performed in the first 28 days and 4% with sonograms performed after 28 days. Rates of abnormal ultrasound findings decreased with increasing GA.

Sepsis was diagnosed more frequently at the lowest GA (rates of early-onset sepsis were 6% at 22 weeks and 1% at 28 weeks, and rates of late-onset sepsis were 58% at 22 weeks and 20% at 28 weeks); 11% of infants developed necrotizing enterocolitis (Table 6). Patent ductus arteriosus was diagnosed for 46% of infants, of whom 71% were treated with indomethacin, 13% ibuprofen (2006–2007), and 27% surgical closure. Among 7313 infants who were still in the hospital at 28 days, 94% underwent an ophthalmologic examination before hospital discharge, death, or transfer. Of the 6866 with examination findings, 59% were diagnosed as having ROP (96% at 22 weeks and 32% at 28 weeks), and 12% under-

TABLE 2 Infant Demographic Features and Delivery Information According to GA for VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007 (Including Infants Who Died Within 12 Hours After Birth)

Characteristic	22 wk ($N = 421$)	23 wk ($N = 871$)	24 wk ($N = 1370$)	25 wk ($N = 1498$)	26 wk ($N = 1576$)	27 wk ($N = 1838$)	28 wk ($N = 2001$)	Total ($N = 9575$)
BW, g[a]								
Mean (range)	511 (473–621)	581 (549–639)	651 (609–677)	744 (709–791)	854 (737–891)	960 (919–1009)	1082 (1022–1207)	836 (789–903)
SD (range)	66.9 (30.4–122)	92.0 (55.4–139)	105 (90.6–125)	135 (107–162)	163 (133–183)	189 (164–218)	206 (160–229)	241 (218–259)
Male, % (range)[a]	58 (0–93)	55 (43–100)	53 (40–70)	53 (46–81)	53 (45–63)	55 (37–66)	51 (36–58)	53 (47–58)
Race/ethnicity, % (range)								
Black, non-Hispanic	45 (0–100)	38 (0–81)	41 (0–85)	41 (0–81)	39 (4–86)	38 (2–89)	36 (0–87)	39 (3–84)
Black, Hispanic	0 (0–0)	1 (0–10)	<1 (0–10)	<1 (0–6)	<1 (0–5)	<1 (0–3)	<1 (0–5)	<1 (0–3)
White, non-Hispanic	30 (0–80)	37 (0–63)	34 (4–70)	34 (0–71)	36 (4–62)	40 (3–79)	41 (5–88)	37 (5–71)
White, Hispanic	19 (0–67)	20 (0–100)	18 (0–76)	19 (0–88)	19 (0–73)	18 (<1–74)	17 (0–67)	18 (1–70)
American Indian/ Alaska native	<1 (0–20)	0 (0–0)	<1 (0–40)	<1 (0–13)	<1 (0–28)	<1 (0–10)	<1 (0–30)	<1 (0–20)
Asian/Pacific islander	4 (0–43)	3 (0–54)	3 (0–37)	3 (0–23)	3 (0–21)	3 (0–19)	3 (0–23)	3 (0–27)
>1 race/other	1 (0–19)	1 (0–14)	2 (0–26)	1 (0–21)	2 (0–22)	<1 (0–9)	1 (0–11)	1 (0–17)
Intrauterine growth restriction, % (range)[a]	0 (0–0)	4 (0–16)	6 (0–30)	8 (0–14)	8 (1–20)	10 (5–15)	9 (0–15)	8 (5–10)
Multiple birth, % (range)[a]	28 (0–48)	30 (11–100)	25 (7–32)	21 (6–40)	22 (8–40)	25 (0–40)	28 (16–37)	25 (18–34)
Delivery room resuscitation, % (range)								
Endotracheal intubation[a]	19 (0–100)	68 (10–100)	87 (53–100)	82 (53–98)	75 (32–92)	65 (31–90)	47 (10–82)	67 (41–85)
Resuscitation drug[a]	3 (0–20)	8 (0–32)	9 (0–32)	6 (0–28)	5 (0–22)	4 (0–19)	2 (0–7)	5 (1–16)
Chest compression[a]	3 (0–40)	10 (0–24)	13 (0–40)	10 (1–37)	7 (0–22)	6 (0–15)	4 (0–14)	8 (2–19)
Apgar score of ≤3, % (range)[a]								
At 1 min[a]	89 (0–100)	73 (50–100)	53 (30–71)	44 (25–63)	36 (22–53)	32 (17–48)	23 (12–30)	42 (29–53)
At 5 min[a]	86 (0–100)	49 (0–89)	20 (0–40)	12 (3–25)	8 (0–22)	7 (1–14)	4 (0–9)	16 (3–25)
Admission temperature, °C[a,b]								
Mean (range)	34.7 (31.3–37.0)	35.0 (33.2–36.6)	35.4 (34.2–37.0)	35.8 (34.8–36.9)	36.1 (35.1–37.0)	36.2 (35.1–37.1)	36.2 (35.1–37.2)	35.9 (34.8–37.0)
SD (range)	1.7 (0.1–3.2)	1.7 (0.1–1.9)	1.4 (0.7–1.5)	1.1 (0.6–1.3)	1.0 (0.5–1.2)	0.9 (0.5–1.1)	0.9 (0.4–1.2)	1.2 (0.7–1.3)
Surfactant therapy, % (range)[a]	17 (0–100)	63 (10–100)	90 (58–100)	88 (72–100)	85 (56–100)	78 (43–94)	65 (41–86)	76 (58–88)

Ranges are across all participating NRN centers. Information was missing as follows: gender, 2 infants; race/ethnicity, 24 infants; intrauterine growth restriction, 2 infants; endotracheal intubation, 9 infants; resuscitation drug, 13 infants, chest compression, 13 infants; Apgar score at 1 minute, 78 infants; Apgar score at 5 minutes, 76 infants; temperature, 1097 infants.

[a] $P \leq .001$ from the Wald χ^2 test for differences according to GA, with adjustment for center and BW. Differences in BW were adjusted for center effects only. Race/ethnicity was tested as black, white, or other.

[b] Infant temperature at initial admission to the nursery for infants born in 2003–2005 and first temperature reading obtained within 60 minutes after birth for infants born in 2006–2007

went treatment for ROP (50% at 22 weeks and 2% at 28 weeks). A total of 2630 infants evaluated in 2006–2007 had ROP outcomes recorded at the time of discharge or 120 days of age. Among those infants, 39% had favorable outcomes, 7% had unfavorable outcomes with severe ROP requiring treatment, and 53% had undetermined ROP outcomes (ie, had not reached the threshold for surgery or were still immature and required further examination) (Table 6).

Survival and Morbidity Rates (All 9575 Infants)

Rates of survival to discharge increased with increasing GA, from 6% at 22 weeks to 92% at 28 weeks (72% overall) (Fig 1 and Table 3). Infants born at 22 to 23 weeks had >3 times the risk of death, compared with infants born at 28 weeks (22 weeks, adjusted RR: 3.88 [95% CI: 3.18–4.73]; 23 weeks, adjusted RR: 3.56 [95% CI: 2.95–4.30]). RRs decreased but remained significant for infants born at 24 to 27 weeks, compared with 28 weeks (24 weeks, adjusted RR: 2.52 [95% CI: 2.10–3.04]; 27 weeks, adjusted RR: 1.23 [95% CI: 1.01–1.49]). Rates of survival to discharge according to GA did not change during the study period (Table 4).

Neonatal morbidities occurred frequently among survivors. Rates of survival with morbidity decreased from 100% at 22 weeks to 92% at 23 weeks, 91% at 24 weeks, 80% at 25 weeks, 66%

TABLE 3 Mortality Rates According to GA for VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007

	% (Range)							
	22 wk ($N = 421$)	23 wk ($N = 871$)	24 wk ($N = 1370$)	25 wk ($N = 1498$)	26 wk ($N = 1576$)	27 wk ($N = 1838$)	28 wk ($N = 2001$)	Total ($N = 9575$)
Survived	6 (0–50)	26 (2–53)	55 (20–100)	72 (50–90)	84 (61–100)	88 (76–100)	92 (88–100)	72 (55–95)
Died	94 (50–100)	74 (47–98)	45 (0–80)	28 (10–50)	16 (0–39)	12 (0–24)	8 (0–12)	28 (5–45)
Time of death[a]								
≤12 h	85 (0–100)	43 (0–90)	11 (0–44)	5 (0–19)	3 (0–11)	1 (0–5)	2 (0–7)	11 (1–25)
>12–24 h	2 (0–6)	3 (0–7)	2 (0–6)	<1 (0–3)	<1 (0–2)	<1 (0–2)	<1 (0–1)	1 (0–2)
>1–3 d	1 (0–8)	9 (0–30)	6 (0–11)	3 (0–25)	2 (0–8)	1 (0–6)	<1 (0–4)	3 (0–7)
4–7 d	2 (0–23)	4 (0–20)	4 (0–11)	3 (0–7)	1 (0–8)	1 (0–6)	<1 (0–2)	2 (0–5)
8–14 d	2 (0–50)	5 (0–50)	5 (0–20)	3 (0–9)	2 (0–6)	2 (0–19)	<1 (0–5)	3 (1–8)
15–28 d	1 (0–15)	4 (0–16)	7 (0–15)	4 (0–8)	3 (0–11)	2 (0–5)	2 (0–7)	3 (0–6)
≥29 d	1 (0–8)	6 (0–17)	10 (0–30)	8 (0–15)	5 (0–10)	4 (0–8)	2 (0–5)	5 (1–9)
Survived	$N = 25$	$N = 226$	$N = 748$	$N = 1078$	$N = 1319$	$N = 1616$	$N = 1847$	$N = 6859$
Survived without morbidity[b]	0 (0–0)	8 (0–14)	9 (0–18)	20 (0–43)	34 (0–49)	44 (19–65)	57 (6–74)	37 (7–50)
Died	$N = 396$	$N = 645$	$N = 622$	$N = 420$	$N = 257$	$N = 222$	$N = 154$	$N = 2716$
Respiratory support withheld/withdrawn before death[c]	82 (40–100)	77 (0–100)	66 (21–96)	68 (0–100)	73 (42–100)	66 (20–100)	60 (0–100)	72 (29–95)
Died at ≤12 h	$N = 359$	$N = 375$	$N = 147$	$N = 72$	$N = 46$	$N = 27$	$N = 34$	$N = 1060$
Respiratory support withheld/withdrawn before death[d]	85 (40–100)	85 (43–100)	79 (0–100)	86 (0–100)	78 (0–100)	85 (0–100)	79 (25–100)	84 (53–100)

Ranges are across all participating NRN centers.

[a] Proportions among all infants including survivors.

[b] Proportions among infants who survived. Morbidities included severe IVH, PVL, BPD, necrotizing enterocolitis, infections, and ROP stage ≥3.

[c] Proportions among infants who died. Data on respiratory support withheld/withdrawn were missing for 52 infants.

[d] Proportions among infants who died within 12 hours. Data on respiratory support withheld/withdrawn were missing for 2 infants.

at 26 weeks, 56% at 27 weeks, and 43% at 28 weeks. Infection and BPD were the most-frequent morbidities. Although unadjusted rates of survival without major morbidity seemed unchanged, the adjusted RR for survival without morbidity increased over time (Table 4). The median length of hospital stay among survivors was 84 days, and lengths of stay decreased with increasing GA, from 141 days at 22 weeks to 63 days at 28 weeks ($P < .001$). PMA at discharge decreased from 42 weeks for surviving infants born at GAs of 22 weeks to 37 weeks for those born at 28 weeks (Fig 2).

DISCUSSION

Although VLBW infant mortality rates in the United States decreased substantially in the 1980s and early 1990s,[3–6,15–18] most reports, including findings for this cohort, failed to demonstrate further progress in reducing neonatal morbidity and mortality rates.[6,16–19] In contrast, a population cohort of all preterm infants born at GAs of <27 weeks in Sweden in 2004–2007 demonstrated survival rates higher than rates reported for other countries or reported previously for Sweden.[20] Our study reviewed neonatal morbidity and mortality rates for a large cohort of extremely preterm infants, to evaluate changes in clinical practice and contemporary outcomes at US academic centers. Although previous reports from the NRN used BW as the reference for morbidity and survival rates, the current study assessed outcomes according to GA. Appreciation of GA-based outcomes is particularly valuable for prenatal counseling and physician/family decision-making.

The decisions to provide active obstetric care and to initiate neonatal intensive care for the most-immature infants remain controversial. Center differences in obstetric/early neonatal interventions were identified, but we did not collect sufficiently detailed information on decision-making processes to help explain differences. In our cohort, rates of active obstetric intervention, as indicated by prenatal steroid administration and cesarean section delivery, increased markedly after 23 weeks of gestation. Prenatal steroid use was almost twice as frequent for infants born at GAs of 24 to 28 weeks, compared with infants born earlier. Similarly, rates of neonatal interventions and intensive care, measured as active resuscitation with ventilation in the delivery room, increased substantially between 22 and 23 weeks (19% vs 68%). Rates of death at ≤12 hours, which in part reflect willingness to provide intensive care to the most-immature infants, decreased with increasing GA, from 85% of infants at 22 weeks to 2% of infants at 28 weeks.

In-hospital morbidity rates remain high among extremely preterm infants, and morbidities contribute

TABLE 4 Clinical Practice Indicators and Survival Rates According to Birth Year for 9575 VLBW Infants Born in NRN Centers Between January 1, 2003, and December 31, 2007

Characteristic	Percent					Adjusted RR (95% CI)	*P*
	2003 (*N* = 1919)	2004 (*N* = 1992)	2005 (*N* = 2032)	2006 (*N* = 1900)	2007 (*N* = 1732)		
Prenatal steroid treatment, all infants	81	76	80	79	83	1.01 (1.00–1.02)	.01
Prenatal antibiotic treatment, all infants	72	68	68	63	66	0.97 (0.96–0.98)	<.001
Cesarean section, all infants	57	58	62	60	60	1.02 (1.00–1.03)	.01
Delivery room endotracheal intubation							
22 wk	17	22	21	16	19	0.98 (0.85–1.13)	.8
23 wk	69	67	67	68	67	0.99 (0.96–1.02)	.6
24 wk	89	89	88	83	86	0.98 (0.97–1.00)	04
25 wk	86	86	79	81	77	0.97 (0.95–0.99)	<.001
26 wk	83	78	68	76	69	0.95 (0.94–0.97)	<.001
27 wk	69	70	64	58	61	0.96 (0.94–0.98)	<.001
28 wk	54	58	45	41	38	0.90 (0.87–0.93)	<.001
All infants	71	72	66	63	62		
Surfactant therapy							
22 wk	18	17	21	13	18	0.97 (0.83–1.13)	.7
23 wk	65	66	63	63	59	0.98 (0.94–1.01)	.2
24 wk	91	88	89	88	93	1.00 (0.99–1.01)	.9
25 wk	89	89	85	91	87	0.99 (0.98–1.00)	.2
26 wk	89	83	84	87	82	0.99 (0.97–1.00)	.045
27 wk	78	80	75	77	78	1.00 (0.98–1.01)	.6
28 wk	73	70	61	62	59	0.94 (0.92–0.96)	<.001
All infants	78	77	74	75	74		
Survived to discharge							
22 wk	6	7	5	3	8		
23 wk	27	21	33	27	21		
24 wk	56	53	55	55	54		
25 wk	71	72	70	75	71		
26 wk	82	87	82	83	84		
27 wk	88	86	88	88	91		
28 wk	94	89	93	93	92		
All infants	72	70	71	73	72	1.00 (0.99–1.01)	.3
Survived >12 h	*N* = 1709	*N* = 1762	*N* = 1818	*N* = 1689	*N* = 1537		
Never intubated, all infants who survived >12 h[a]	8	8	10	10	11	1.12 (1.07–1.18)	<.001
Necrotizing enterocolitis, all infants who survived >12 h	9	11	11	11	12	1.04 (0.99–1.09)	.1
Survived >24 h	*N* = 1685	*N* = 1738	*N* = 1785	*N* = 1678	*N* = 1532		
CPAP therapy at 24 h							
22 wk	0	0	0	0	0		
23 wk	5	4	4	1	1	0.73 (0.51–1.05)	.09
24 wk	5	7	11	6	8	1.09 (0.95–1.24)	.2
25 wk	12	14	22	18	23	1.16 (1.07–1.25)	<.001
26 wk	27	32	32	25	34	1.01 (0.96–1.07)	.6
27 wk	32	35	35	37	40	1.05 (1.0–1.09)	.04
28 wk	36	36	36	41	40	1.04 (1.0–1.08)	.06
All infants who survived >24 h	23	25	26	27	29		
Survived >72 h	*N* = 1626	*N* = 1672	*N* = 1721	*N* = 1631	*N* = 1478		
Late-onset sepsis, all infants who survived >72 h	36	38	37	36	33	0.98 (0.96–1.0)	.1
Cranial sonography performed within 28 d after birth	*N* = 1660	*N* = 1708	*N* = 1749	*N* = 1646	*N* = 1497		
Severe IVH, all infants with sonograms	16	16	14	17	16	0.96 (0.93–1.0)	.05
Infants who underwent cranial imaging before and/or after 28 d	*N* = 1665	*N* = 1714	*N* = 1752	*N* = 1651	*N* = 1500		
PVL, all infants with imaging findings	4	5	5	4	5	0.93 (0.87–1.0)	.06
Survived to PMA of 36 wk	*N* = 1426	*N* = 1455	*N* = 1483	*N* = 1421	*N* = 1280		
BPD, infants who survived to PMA of 36 wk	43	42	40	43	43	0.94 (0.92–0.95)	<.001
Survived to discharge	*N* = 1385	*N* = 1403	*N* = 1445	*N* = 1383	*N* = 1243		
Survived without morbidity[b]							
22 wk	0	0	0	0	0		
23 wk	14	10	3	5	9		
24 wk	5	10	10	8	11		
25 wk	22	20	21	17	20		
26 wk	32	38	34	31	34		
27 wk	44	44	46	42	44		
28 wk	58	55	62	55	54		
All infants who survived to discharge	37	37	38	35	36	1.04 (1.02–1.06)	<.001

Information was missing as follows: prenatal steroid treatment, 27 infants, prenatal antibiotic treatment, 30 infants; cesarean section delivery, 9 infants; delivery room endotracheal intubation, 9 infants; surfactant therapy, 10 infants; never intubated, 3 infants; necrotizing enterocolitis, 1 infant, CPAP therapy, 14 infants; late-onset sepsis, 2 infants; severe IVH, 9 infants; PVL, 1 infant; BPD, 42 infants; survived without morbidity, 32 infants. RRs and *P* values were determined for the change per year from a modified Poisson model that included effects for study center, infant BW and GA, and year and, where significant, effects for the year-GA interaction (delivery room intubation, surfactant therapy and CPAP therapy at 24 h). RRs are shown for all infants overall in cases in which the year-GA interaction was not significant and separately for infants born at each GA in cases in which the interaction was significant. The year-GA interaction could not be assessed for the category of never intubated because of small sample sizes.

[a] Never used conventional or high-frequency ventilator or underwent nasal synchronized intermittent mandatory ventilation.

[b] Morbidities included BPD, severe IVH, PVL, necrotizing enterocolitis, ROP stage ≥3, and infections (early-onset sepsis, late-onset sepsis, or meningitis). Proportions were determined among survivors. Of the 25 surviving infants born at GA of 22 weeks, none survived without major morbidity.

TABLE 5 Pulmonary Morbidities According to GA for VLBW Infants Who Were Born in NRN Centers Between January 1, 2003, and December 31, 2007, and Survived >12 Hours After Birth

Characteristic	% (Range)							
	22 wk (*N* = 62)	23 wk (*N* = 496)	24 wk (*N* = 1223)	25 wk (*N* = 1426)	26 wk (*N* = 1530)	27 wk (*N* = 1811)	28 wk (*N* = 1967)	Total (*N* = 8515)
Respiratory distress syndrome[a]	95 (75–100)	98 (75–100)	98 (64–100)	97 (77–100)	94 (61–100)	90 (50–100)	86 (55–100)	93 (60–99)
Surfactant therapy[a]	97 (50–100)	97 (90–100)	95 (83–100)	90 (72–100)	86 (58–100)	78 (43–95)	65 (41–86)	82 (64–93)
Pneumothorax	15 (0–40)	11 (0–33)	11 (0–23)	9 (4–20)	7 (0–15)	5 (0–14)	4 (0–9)	7 (3–13)
Pulmonary hemorrhage[b]	16 (0–50)	15 (0–50)	13 (6–40)	10 (3–28)	7 (2–20)	4 (0–14)	3 (0–7)	7 (3–18)
Postnatal steroid treatment[a]	15 (0–50)	18 (0–50)	20 (0–60)	14 (0–44)	9 (0–30)	6 (0–14)	2 (0–6)	10 (0–24)
Never intubated[a,c]	0 (0–0)	<1 (0–6)	<1 (0–2)	2 (0–8)	5 (0–14)	12 (0–40)	23 (6–44)	9 (2–22)
Respiratory support at 24 h for infants who survived >24 h	*N* = 55	*N* = 471	*N* = 1192	*N* = 1414	*N* = 1520	*N* = 1804	*N* = 1962	*N* = 8418
Conventional or high-frequency ventilation[a,d]	96 (0–100)	94 (83–100)	89 (71–100)	76 (57–95)	61 (43–92)	49 (21–74)	40 (20–61)	62 (47–83)
Nasal SIMV[b,d]	0 (0–0)	<1 (0–6)	2 (0–16)	3 (0–20)	3 (0–18)	2 (0–12)	3 (0–16)	3 (0–14)
CPAP therapy[a,d]	0 (0–0)	3 (0–10)	8 (0–29)	18 (5–30)	30 (5–49)	36 (12–79)	38 (17–66)	26 (8–46)
Use of oxygen alone[a,d]	2 (0–100)	1 (0–6)	1 (0–7)	2 (0–7)	2 (0–13)	3 (0–10)	5 (0–15)	3 (<1–9)
Infants who survived to PMA of 36 wk	*N* = 27	*N* = 241	*N* = 790	*N* = 1121	*N* = 1344	*N* = 1648	*N* = 1852	*N* = 7023
BPD (oxygen use at 36 wk)[a,e]	85 (0–100)	73 (35–100)	69 (31–100)	55 (20–100)	44 (19–100)	34 (13–76)	23 (9–88)	42 (20–89)
Infants in hospital at PMA of 36 wk or discharged/transferred at 33–36 wk	*N* = 27	*N* = 231	*N* = 774	*N* = 1088	*N* = 1284	*N* = 1565	*N* = 1739	*N* = 6708
Severity-based BPD[a,f]								
Mild BPD	15 (0–100)	26 (0–50)	26 (0–67)	37 (0–62)	35 (0–58)	28 (0–52)	16 (0–35)	27 (5–38)
Moderate BPD	30 (0–100)	35 (0–100)	34 (0–68)	29 (9–70)	26 (5–71)	20 (4–55)	15 (0–57)	23 (8–60)
Severe BPD	56 (0–100)	39 (0–100)	37 (0–100)	26 (3–86)	17 (4–44)	13 (0–30)	8 (0–29)	18 (3–40)
Infants born in 2006–2007	*N* = 19	*N* = 174	*N* = 438	*N* = 547	*N* = 566	*N* = 728	*N* = 754	*N* = 3226
Inhaled nitric oxide treatment[b,g]	11 (0–50)	8 (0–50)	10 (0–54)	8 (0–27)	7 (0–25)	3 (0–12)	3 (0–14)	6 (0–19)
Infants who survived to PMA of 36 wk	*N* = 9	*N* = 83	*N* = 274	*N* = 422	*N* = 482	*N* = 650	*N* = 691	*N* = 2611
BPD by physiologic definition[a,h]	89 (50–100)	70 (0–100)	68 (0–100)	55 (19–100)	44 (6–100)	31 (0–100)	22 (0–100)	40 (15–82)

Ranges are across all participating NRN centers. Proportions are among all infants who survived >12 hours, except as noted. Information was missing as follows: respiratory distress syndrome, 5 infants; surfactant treatment, 7 infants; pulmonary hemorrhage, 2 infants; postnatal steroid treatment, 41 infants; never intubated, 3 infants; ventilator use at 24 hours, 13 infants; nasal synchronized intermittent mandatory ventilation at 24 hours, 14 infants; CPAP at 24 hours, 14 infants; oxygen alone at 24 hours, 14 infants; nitric oxide use, 1 infant. *P* values were determined with the Wald χ^2 test for differences according to GA, with adjustment for center and BW or, for nasal synchronized intermittent mandatory ventilation and inhaled nitric oxide use, with adjustment for BW only. SIMV indicates synchronized intermittent mandatory ventilation.

[a] $P \leq .001$

[b] $P \leq .05$.

[c] Never used conventional or high-frequency ventilator or underwent nasal synchronized intermittent mandatory ventilation.

[d] Proportions among infants who survived >24 hours after birth. Use of oxygen alone at 24 hours was defined as receiving supplemental oxygen without conventional or high-frequency ventilation, nasal synchronized intermittent mandatory ventilation, or CPAP therapy.

[e] Proportions among infants who survived to PMA of 36 weeks and had nonmissing outcome data (*N* values shown). BPD could not be determined for 42 infants.

[f] Proportions among infants who were still in the hospital at PMA of 36 weeks or, if discharged or transferred before 36 weeks, were in the hospital for ≥28 days and until PMA of 33 weeks. *N* values are shown for infants with nonmissing outcome data. Severity-based BPD could not be determined for 68 infants. More information about severity-based BPD is presented in the text.

[g] Proportions among infants born in 2006–2007.

[h] Proportions among infants born in 2006–2007 who survived to PMA of 36 weeks and had nonmissing outcome data (*N* values shown). BPD according to the physiologic definition could not be determined for 90 infants. Information on how BPD was determined according to the physiologic definition is presented in the text.

to adverse neurodevelopmental outcomes. The majority of infants studied experienced a major complication during the initial hospitalization, with the risk of morbidity being inversely related to GA at birth. Center differences in the proportions of infants with specific morbidities were noted. At the lowest GAs (22–24 weeks), small numbers of infants at some centers contributed to the variability. The registry does not collect data on the reasons behind the choice of interventions for individual infants and has limited data on the severity of illness at birth, information that might permit more-detailed evaluation and understanding of center differences. Reducing the high rates of in-hospital morbidity among extremely low GA infants who are provided ongoing intensive care remains a challenge for clinicians and investigators.

To reduce rates of BPD, attention is being paid to avoidance of intubation, less prophylactic use of surfactant, and alternative modes of respiratory support. Rates of endotracheal intubation in the delivery room decreased in recent years among infants of >24 weeks, with a corresponding increase in CPAP therapy use at 24 hours of life. At GA of 28 weeks, use of surfactant decreased in the most-recent years. Furthermore, the proportion of infants who survived >12 hours without ever undergoing intubation and ventilation increased with increasing GA and

TABLE 6 Rates of Infections and Other Morbidities According to GA for VLBW Infants Who Were Born in NRN Centers Between January 1, 2003, and December 31, 2007, and Survived >12 Hours After Birth

Characteristic	% (Range)							
	22 wk ($N = 62$)	23 wk ($N = 496$)	24 wk ($N = 1223$)	25 wk ($N = 1426$)	26 wk ($N = 1530$)	27 wk ($N = 1811$)	28 wk ($N = 1967$)	Total ($N = 8515$)
Early-onset sepsis[a]	6 (0–67)	4 (0–20)	4 (0–9)	2 (0–7)	2 (0–6)	2 (0–6)	1 (0–4)	2 (<1–4)
Meningitis[b]	0 (0–0)	5 (0–25)	3 (0–12)	4 (0–15)	3 (0–9)	1 (0–5)	1 (0–5)	3 (0–8)
Late-onset sepsis[a,c]	58 (0–100)	62 (0–86)	55 (29–74)	46 (24–67)	35 (14–53)	27 (15–52)	20 (4–36)	36 (18–51)
NEC[b]	5 (0–33)	12 (0–50)	15 (0–22)	13 (5–24)	9 (0–25)	10 (0–21)	8 (3–20)	11 (4–19)
NEC managed medically[d]	67 (50–100)	31 (0–100)	39 (0–100)	52 (10–100)	48 (17–100)	47 (23–75)	58 (0–100)	48 (21–100)
NEC treated surgically[d]	33 (0–50)	69 (0–100)	61 (0–100)	48 (0–90)	52 (0–83)	53 (25–77)	42 (0–100)	52 (0–79)
PDA[e]	55 (13–100)	54 (21–100)	60 (31–80)	55 (25–92)	48 (21–88)	42 (14–80)	32 (13–60)	46 (26–78)
Indomethacin therapy for PDA[e,f]	82 (0–100)	73 (0–100)	76 (25–96)	72 (29–94)	69 (7–94)	68 (37–94)	67 (31–95)	71 (33–91)
Surgical treatment of PDA[a,e]	50 (0–100)	43 (0–77)	40 (13–62)	33 (13–65)	24 (6–44)	16 (0–33)	12 (0–33)	27 (10–41)
Infants in hospital at 28 d	$N = 30$	$N = 277$	$N = 874$	$N = 1197$	$N = 1386$	$N = 1683$	$N = 1866$	$N = 7313$
ROP examination performed[a,g]	93 (50–100)	91 (71–100)	93 (50–100)	94 (78–100)	96 (67–100)	95 (87–100)	92 (68–99)	94 (82–99)
ROP diagnosed[a,h]	96 (50–100)	88 (0–100)	89 (50–100)	79 (29–94)	65 (20–81)	49 (18–75)	32 (5–56)	59 (35–75)
ROP stage ≥3[a,h]	57 (0–100)	48 (0–100)	42 (25–77)	25 (11–54)	14 (0–29)	7 (0–14)	3 (0–11)	16 (6–28)
Intervention/surgical treatment for ROP[a,h]	50 (0–100)	40 (0–100)	35 (17–58)	17 (0–40)	8 (0–21)	4 (0–9)	2 (0–7)	12 (4–22)
Infants in hospital with weight measured at PMA of 36 wk	$N = 24$	$N = 215$	$N = 736$	$N = 976$	$N = 1106$	$N = 1231$	$N = 1204$	$N = 5492$
Growth failure at 36 wk[a,i]	92 (50–100)	91 (0–100)	85 (67–100)	83 (63–100)	79 (33–98)	76 (42–98)	73 (44–96)	79 (59–97)
Cranial ultrasonography performed within 28 d after birth	85 (50–100)	92 (67–100)	95 (87–100)	97 (85–100)	98 (92–100)	98 (94–100)	98 (90–100)	97 (93–100)
Sonogram findings within 28 d[a,j]	$N = 53$	$N = 454$	$N = 1163$	$N = 1385$	$N = 1499$	$N = 1781$	$N = 1925$	$N = 8260$
Normal	32 (0–100)	41 (13–74)	49 (14–70)	57 (30–84)	65 (36–90)	70 (50–83)	77 (50–91)	64 (43–79)
IVH grade 1	13 (0–40)	9 (0–50)	11 (0–43)	9 (0–17)	11 (0–23)	10 (5–24)	10 (0–32)	10 (5–23)
IVH grade 2	13 (0–50)	9 (0–25)	9 (0–29)	8 (2–19)	5 (0–14)	5 (0–14)	4 (0–25)	6 (2–12)
IVH grade 3	8 (0–33)	15 (0–47)	12 (5–20)	8 (0–15)	7 (0–14)	6 (0–15)	4 (0–10)	7 (3–13)
IVH grade 4	30 (0–67)	21 (0–50)	14 (0–33)	13 (3–36)	7 (0–31)	5 (1–17)	3 (0–15)	9 (4–23)
Ventriculomegaly, no IVH	4 (0–33)	3 (0–13)	3 (0–6)	3 (0–6)	2 (0–9)	2 (0–6)	1 (0–5)	2 (0–4)
PVL within 28 d[b,k]	6 (0–33)	4 (0–25)	3 (0–11)	4 (0–18)	3 (0–8)	2 (0–8)	2 (0–5)	3 (<1–6)
Infants born in 2006–2007	$N = 19$	$N = 174$	$N = 438$	$N = 547$	$N = 566$	$N = 728$	$N = 754$	$N = 3226$
PDA[e,l]	53 (0–100)	52 (13–100)	56 (0–100)	55 (20–100)	51 (12–100)	43 (0–80)	34 (0–63)	47 (23–78)
Ibuprofen therapy for PDA[l]	0 (0–0)	13 (0–64)	16 (0–50)	16 (0–60)	13 (0–64)	12 (0–44)	11 (0–60)	13 (0–52)
Infants in hospital at 28 d	$N = 11$	$N = 92$	$N = 320$	$N = 471$	$N = 508$	$N = 678$	$N = 718$	$N = 2798$
ROP examination performed[f,m]	91 (50–100)	91 (71–100)	92 (50–100)	94 (75–100)	95 (67–100)	96 (82–100)	93 (68–100)	94 (82–100)
ROP outcome at status[a,n]								
Determined, favorable in both eyes	10 (0–100)	27 (0–100)	28 (0–62)	31 (0–86)	38 (0–100)	46 (0–100)	46 (5–100)	39 (8–83)
Determined, severe ROP in either eye	30 (0–100)	30 (0–100)	21 (0–67)	11 (0–38)	5 (0–25)	3 (0–9)	<1 (0–9)	7 (0–20)
Undetermined ROP status in either eye (neither had severe ROP)	60 (0–100)	43 (0–100)	51 (0–82)	58 (14–100)	57 (0–100)	51 (0–100)	53 (0–95)	53 (8–88)

Ranges are across all participating NRN centers. Proportions are among all infants who survived >12 hours, except as noted. Information was missing as follows: patent ductus arteriosus, 4 infants; indomethacin therapy for patent ductus arteriosus, 38 infants; surgical treatment for patent ductus arteriosus, 2 infants, necrotizing enterocolitis, 1 infant; early-onset sepsis, 1 infant; meningitis, 1 infant; late-onset sepsis, 2 infants; ROP examination performed, 1 infant; ROP, 1 infant, ROP stage ≥3, 7 infants; intervention/surgical treatment for ROP, 32 infants. *P* values were determined with the Wald χ^2 test for differences according to GA, with adjustment for center and BW or, for early-onset sepsis, meningitis, and ibuprofen therapy for patent ductus arteriosus, with adjustment for BW only. PDA indicates patent ductus arteriosus; NEC, necrotizing enterocolitis.

[a] $P \leq .001$.

[b] $P \leq .01$.

[c] Proportions among infants who survived >3 days after birth.

[d] Proportions among infants with necrotizing enterocolitis.

[e] Proportions among infants with patent ductus arteriosus.

[f] $P \leq .05$.

[g] Proportions among infants who were still in the hospital at 28 days of life.

[h] Proportions among infants who were still in the hospital at 28 days and underwent a ROP examination.

[i] Growth failure was defined as <10th percentile for gender at PMA of 36 weeks. Proportions were determined among infants who were alive and in the hospital at PMA of 36 weeks and who had weight measurements at PMA of 35 to 37 weeks. Among those in the hospital at 36 weeks, weight data were missing for 101 infants with other measurements taken at PMA of 36 weeks, weight was measured but not in the 35- to 37-week period for 21 infants, and growth failure could not be determined for 2 infants with missing gender information.

[j] From the sonogram with the most-severe findings. Proportions were determined among those who had sonograms performed within 28 days after birth. Categories shown are mutually exclusive. Some infants with IVH also had PVL, that is, 18 (2%) of 832 infants with grade 1 IVH, 21 (4%) of 506 infants with grade 2 IVH, 31 (5%) of 598 infants with grade 3 IVH, and 117 (16%) of 710 infants with grade 4 IVH. Ten (6%) of 173 infants with ventriculomegaly and no IVH also had PVL.

[k] Proportions indicate the proportions of infants with PVL overall, with and without IVH, among infants who had sonograms performed within 28 days after birth.

[l] Proportions were determined among infants born in 2006–2007. Ibuprofen treatment proportions are among infants who had patent ductus arteriosus. Information was missing as follows: patent ductus arteriosus, 1 infant; ibuprofen treatment, 1 infant.

[m] Proportions among infants born in 2006–2007 who were still in the hospital at 28 days of life. Information was missing for ROP examination for 1 infant.

[n] Proportions among infants born in 2006–2007 who were still in the hospital at 28 days and had ROP examinations performed. An assessment of ophthalmologic outcome at the time of status was made as follows: (1) favorable, defined as one of the following in each eye: vessels mature, vessels in zone III in 2 consecutive examinations, acute ROP of stage 1 or 2 in zone III in 2 consecutive examinations, or ROP in zone II or zone III but determined to be clearly regressing; (2) unfavorable, defined as severe ROP on the basis of one of the following in either eye: received surgical treatment for ROP, met criteria for undergoing surgery, or retinal detachment resulting from ROP; or (3) undetermined outcome, defined as one of the following in either eye: immature vessels in zone I or zone II, immature vessels reaching zone III in any single examination, stage 1 or 2 ROP in zone III at any single examination, stage 2 or 3 ROP in zone II or III not regressing, or active ROP in zone I or zone II. Data on outcome at status was missing for 13 infants.

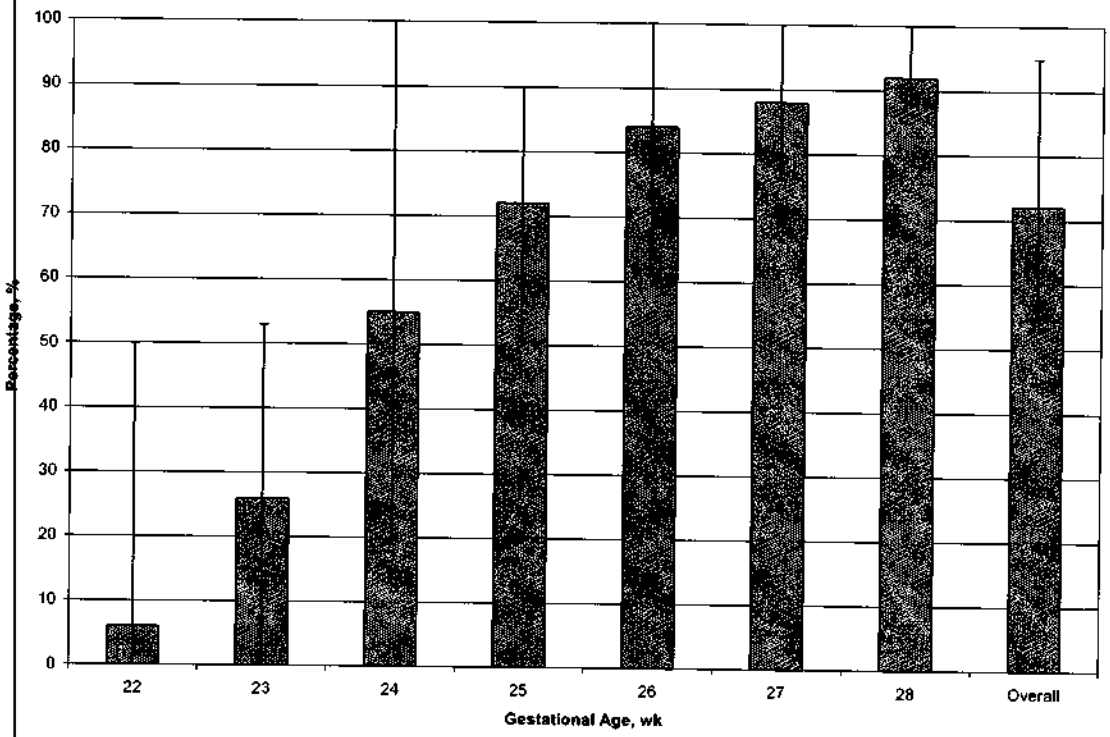
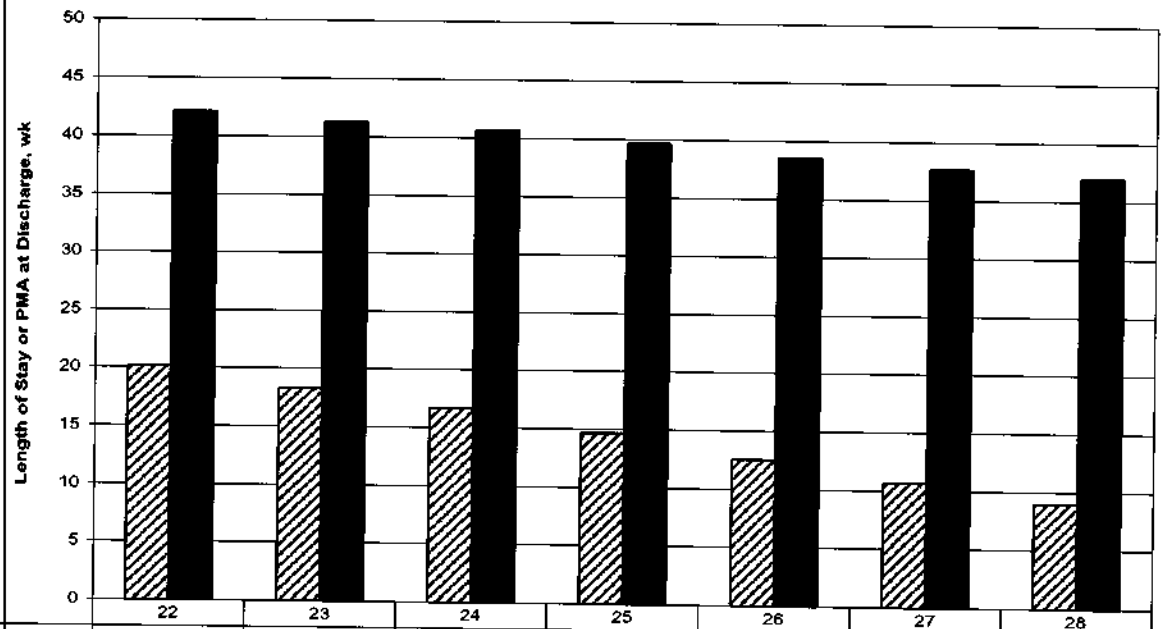


FIGURE 1
Survival to discharge according to GA among 9575 VLBW infants born in NICHD NRN centers between January 1, 2003, and December 31, 2007. The thin lines indicate ranges across centers



	22	23	24	25	26	27	28
Length of stay	20.1	18.3	16.7	14.7	12.6	10.7	9.0
PMA at discharge	42.1	41.3	40.7	39.7	38.6	37.7	37.0

FIGURE 2
Median length of hospitalization (in weeks) and median PMA at discharge (in weeks) according to GA at birth among 6859 VLBW infants who were born in NICHD NRN centers between January 1, 2003, and December 31, 2007, and survived to discharge.

more recent year of birth. With substantially increased use of CPAP therapy, it was surprising that overall rates of BPD were unchanged, although the adjusted RR for BPD decreased over the study period.

This is the first study to report ophthalmologic status as favorable, unfavorable, or undetermined at the time of the last in-hospital examination. Although 7% of all infants had severe ROP, the rate was 30% for infants with GAs of 22/23 weeks. Of concern, 53% of infants had undetermined ophthalmologic status at the last examination before discharge. This finding has implications for discharge planning and underscores the importance of a medical home, to ensure careful ophthalmologic follow-up monitoring of these vulnerable infants after discharge home or transport to a community hospital.

Although ours is not a population-based study, we included all extremely low gestation births at 20 academic centers across the United States that together represent >110 000 live births per year, an annual birth cohort equal in size to the Swedish national cohort described recently.[20] The rate of extremely low gestation birth was fivefold higher in our NRN cohort (~10 births at <27 weeks per 1000 infants) than in the Swedish cohort (2.3 births at <27 weeks per 1000 infants). This remarkable difference may be explained in part by Sweden's universal health insurance, with free prenatal care and associated social services, as well as an ethnically more homogeneous and somewhat older pregnant population. The high rates of prematurity in our cohort underscore the importance of the current health care debate in the United States. Survival rates for extremely low gestation infants born at NRN centers are lower than those reported from Sweden. For nearly all infants in the Swedish cohort, GA was estimated on the basis of ultrasound findings. The authors of the Swedish study noted that a limitation of the use of ultrasonography to determine GA is that erroneously low GAs might be estimated for infants with growth restriction. Given the decrease in mortality rates with increasing GA, underestimation of GA by as little as 1 week might explain in part the difference in mortality rates between the 2 cohorts. Greater use of prenatal steroid treatment at all GAs and of surfactant therapy at 22 to 23 weeks also might have contributed to differences between the 2 cohorts.

During the 5-year study period, there was no substantial improvement in rates of survival to discharge for extremely low gestation infants born at NRN centers. However, each additional week of GA at birth had substantial survival advantage; the most marked changes were between GAs of 22 and 25 weeks, with survival rates increasing from 6% to 72%. Furthermore, rates of survival to discharge without major morbidities increased dramatically between 22 and 25 weeks, with continued steady improvement for each additional week of gestation. PMA at discharge for VLBW infants, a proxy measure of length of stay and a reflection of the cost of care, was inversely related to GA at birth. Each additional week of GA at birth reduced PMA at discharge by almost 1 week and total length of hospital stay by ~2 weeks, a reflection of both severity of illness and complications of prematurity among these very immature infants. Although adjusted RRs for survival without morbidity increased over time, the burden of in-hospital complications remained high. Retrospective analyses of center differences and benchmarking studies to identify best performance have been unable to identify modifiable practices that consistently improve outcomes, which underscores the need for hypothesis-driven clinical trials to assess the efficacy of current neonatal interventions.[21–24] Clinicians and investigators are challenged to identify and to test currently available interventions and resources that yield consistently lower morbidity and mortality rates at some centers, so that we can improve rates of survival without major morbidities and reduce long-term neurodevelopmental impairments for all infants.

ACKNOWLEDGMENTS

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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, Pritzker School of Medicine, University of Chicago (2006–2007); Case Western Reserve University: Rainbow Babies and Children's Hospital (National Institutes of Health grants GCRC M01 RR80 and U10 HD21364): Avroy A. Fanaroff, MD; Cincinnati Children's Hospital Medical Center: University of Cincinnati Hospital and Good Samaritan Hospital (National Institutes of Health grants GCRC M01 RR8084 and U10 HD27853): Edward F. Donovan, MD; 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: University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (National Institutes of Health grants GCRC M01 RR30 and U10 HD40492): C. Michael Cotten, MD, MHS; Kathy J. Auten, MSHS; Melody B. Lohm-

eyer, RN, MSN; Emory University: Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (National Institutes of Health grants UL1RR025008 and U10 HD27851): David P. Carlton, MD; Ann M. Blackwelder, RNC, BS, MS; Michelle Tidwell, BSN; Eunice Kennedy Shriver National Institute of Child Health and Human Development: Stephanie Wilson Archer, MA; Indiana University: Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (National Institutes of Health grants GCRC M01 RR750 and U10 HD27856): James A. Lemons, MD; Diana D. Appel, RN, BSN; Dianne E. Herron, RN; Lucy C. Miller, RN, BSN, CCRC; Leslie Richard, RN; Leslie D. Wilson, BSN, CCRC; Faithe Hamer, BS; RTI International (National Institutes of Health grant U01 HD36790): W. Kenneth Poole, PhD; Betty K. Hastings; Elizabeth M. McClure, MEd; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; Kristin M. Zaterka-Baxter, RN, BSN; Stanford University: Dominican Hospital, El Camino Hospital, and Lucile Packard Children's Hospital (National Institutes of Health grants GCRC M01 RR70 and U10 HD27880): David K. Stevenson, MD; Marian M. Adams, MD; M. Bethany Ball, BS, CCRC; Melinda S. Proud, RCP; Andrew W. Palmquist, RN; Tufts Medical Center: Floating Hospital for Children (National Institutes of Health grants GCRC M01 RR54 and U10 HD53119): Brenda L. MacKinnon, RNC; Ellen Nylen, RN, BSN; University of Alabama at Birmingham: Health System and Children's Hospital of Alabama (National Institutes of Health grants GCRC M01 RR32 and U10 HD34216): Monica V. Collins, RN, BSN, MaEd; Shirley S. Cosby, RN, BSN; University of California, San Diego: Medical Center and Sharp Mary Birch Hospital for Women and Newborns (National Institutes of Health grant U10 HD40461): Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Chris Henderson, RCP, CRTT; Wade Rich, BSHS, RRT; University of Iowa: Children's Hospital (National Institutes of Health grants GCRC M01 RR59 and U10 HD53109): John A. Widness, MD; Karen J. Johnson, RN, BSN; University of Miami: Holtz Children's Hospital (National Institutes of Health grants GCRC M01 RR16587 and U10 HD21397): Ruth Everett-Thomas, RN, MSN; University of New Mexico: Health Sciences Center (National Institutes of Health grants GCRC M01 RR997 and U10 HD53089): Conra Backstrom Lacy, RN; University of Rochester: Golisano Children's Hospital at Strong (National Institutes of Health grants GCRC M01 RR44 and U10 HD40521): Linda J. Reubens, RN, CCRC; Erica Burnell, RN; University of Tennessee (National Institutes of Health grant U10 HD21415): Sheldon B. Korones, MD; University of Texas Southwestern Medical Center at Dallas: Parkland Health and Hospital System and Children's Medical Center Dallas (National Institutes of Health grants GCRC M01 RR633 and U10 HD40689): Abbot R. Laptook, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Gaynelle Hensley, RN; Melissa H. Leps, RN; Nancy A. Miller, RN; University of Texas Health Science Center at Houston: Medical School, Children's Memorial Hermann Hospital, and Lyndon Baines Johnson General Hospital/Harris County Hospital District (National Institutes of Health grant U10 HD21373): Jon E. Tyson, MD, MPH; Esther G. Akpa, RN, BSN; Patty A. Cluff, RN; Anna E. Lis, RN, BSN; Georgia E. McDavid, RN; Claudia I. Franco, RNC, MSN; Beverly Foley Harris, RN, BSN; Sarah Martin, RN, BSN; Maegan C. Simmons, RN; Patti Pierce Tate, RCP; University of Utah: University Hospital, Latter Day Saints Hospital, and Primary Children's Medical Center (National Institutes of Health grants GCRC M01 RR64 and U10 HD53124): Bradley A. Yoder, MD; Karen A. Osborne, RN, BSN, CCRC; Jennifer J. Jensen, RN, BSN; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN, BSN; Wake Forest University: Baptist Medical Center, Forsyth Medical Center, and Brenner Children's Hospital (National Institutes of Health grants GCRC M01 RR7122 and U10 HD40498): Robert G. Dillard, MD; Nancy J. Peters, RN, CCRP; Wayne State University: Hutzel Women's Hospital and Children's Hospital of Michigan (National Institutes of Health grant U10 HD21385): Rebecca Bara, RN, BSN; Geraldine Muran, RN, BSN; Women and Infants' Hospital of Rhode Island (National Institutes of Health grant U10 HD27904): William Oh, MD; Angelita M. Hensman, RN, BSN; Yale University: Yale-New Haven Children's Hospital (National Institutes of Health grants CTSA UL1 RR24139, GCRC M01 RR6022, and U10 HD27871): Patricia Gettner, RN; Monica Konstantino, RN, BSN; JoAnn Poulsen, RN; Janet Taft, RN, BSN.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. We thank Avroy Fanaroff for thoughtful review of the manuscript and Mazie Tinsley for manuscript preparation.

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(Continued from first page)

KEY WORDS
extremely low gestation, very low birth weight, morbidity, death

ABBREVIATIONS
VLBW—very low birth weight
BPD—bronchopulmonary dysplasia
BW—birth weight
CI—confidence interval
GA—gestational age
IVH—intraventricular hemorrhage
ROP—retinopathy of prematurity
RR—relative risk
NICHD—National Institute of Child Health and Human Development
NRN—Neonatal Research Network
CPAP—continuous positive airway pressure
PVL—periventricular leukomalacia
PMA—postmenstrual age

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network

Barbara J. Stoll, Nellie I. Hansen, Edward F. Bell, Seetha Shankaran, Abbot R. Laptook, Michele C. Walsh, Ellen C. Hale, Nancy S. Newman, Kurt Schibler, Waldemar A. Carlo, Kathleen A. Kennedy, Brenda B. Poindexter, Neil N. Finer, Richard A. Ehrenkranz, Shahnaz Duara, Pablo J. Sánchez, T. Michael O'Shea, Ronald N. Goldberg, Krisa P. Van Meurs, Roger G. Faix, Dale L. Phelps, Ivan D. Frantz, III, Kristi L. Watterberg, Shampa Saha, Abhik Das, Rosemary D. Higgins and for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

Pediatrics 2010;126;443-456; originally published online Aug 23, 2010;
DOI: 10.1542/peds.2009-2959

From: Namasivayam Ambalavanan
To: "Shankaran, Seetha"; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
Subject: RE: PaCO2 manuscript : Rejection from Pediatrics
Date: Wednesday, February 19, 2014 9:25:24 AM

Agree - will try J Peds. I will try to modify the presentation of the results to simplify them, and balance comprehensiveness/complexity with a user-friendly/simpler/less detailed results.
Ambal

-----Original Message-----
From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Wednesday, February 19, 2014 7:54 AM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
Subject: RE: PaCO2 manuscript : Rejection from Pediatrics

Hi Ambal
Try J Peds---but I would also suggest that the comments of the reviewers need to be addressed. Other option would be Archives or Ped Research?
All the best
Seetha

-----Original Message-----
From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Tuesday, February 18, 2014 10:09 PM
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
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Ambal

18-Feb-2014

RE: MS ID 2014-0061

PaCO2 and outcomes in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Dr. Ambalavanan:

Thank you for submitting your manuscript to Pediatrics. We are sorry that we are not accepting it for publication. Because of the large number of submissions, the editors must reject many worthy manuscripts. Rejection reflects the priorities of the journal; it does not necessarily indicate that your manuscript is unsuitable for publication elsewhere.

Comments from our reviewers are included below. Reviewer input is one of several factors involved in making decisions on papers. Because of space limitations, even papers receiving positive comments from the reviewers are often rejected.

We look forward to receiving other articles from you in the future.

Sincerely,

Lewis R. First, MD
Editor-in-Chief, Pediatrics
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics,
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Reviewer: 1

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

(b)(4),(b)(6)

Namasivayam Ambalavanan MD
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From: Namasivayam Ambalavanan
Sent: Sunday, January 05, 2014 12:58 PM
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Higgins, Rosemary (NIH/NICHD)
Subject: RE: PaCO2 manuscript : Final uploaded draft and Submission pdf - plan submission on Jan 8, 2014

Dear All,
Attached is the final draft of the manuscript that has been uploaded to the Pediatrics journal website, and the pdf of the submission for your records. I will look over it and then click "submit" in a couple of days (Wednesday Jan 8, 2014 am), if no one has any major comments.
Thanks,
Ambal

From: Namasivayam Ambalavanan
Sent: Sunday, December 29, 2013 2:23 PM
Subject: RE: PaCO2 manuscript : Final draft (Dec 29, 2013) before submission on Jan 8, 2014

Dear All,
Attached is the most recent draft of our manuscript on PaCO2 in relation to outcome in SUPPORT. I have made some changes following NICHD clearance, Publication Subcommittee reviews, and comments by co-authors on the previous draft. One change is to emphasize that PaCO2 is a marker of illness severity and that there is for the most part no interaction between SUPPORT treatment group allocation and PaCO2. I will submit on Jan 8th (Wednesday; about 10 days from now) to Pediatrics if there are no further comments/suggestions.
Thank you,
Ambal

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: Re: Next Steps and Impact of Controversy on SoC Research
Date: Wednesday, February 19, 2014 9:02:16 PM

Thanks!

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

On Feb 19, 2014, at 8:33 PM, "Spong, Catherine (NIH/NICHD) [E]" <spongc@dir49.nichd.nih.gov> wrote:

> Alan,
> Six interventional trials were ongoing in the Neonatal Research Network NRN at the time the controversy over comparative effectiveness studies arose. All of the 6 studies were put on hold by one or more of the 18 NRN centers for varying periods of time while the investigators and the IBRs reviewed the studies. The **TOP trial** which compares a high versus low transfusion threshold for babies < 1000 grams at birth was suspended at 8 centers for a loss of 516 days for recruitment and one site which remains inactive. The inactive site has declined participation in the TOP trial pending HHS provision of clarity on what their standards will be for this type of research design due to the continuing attacks by Public Citizen regarding TOP and SUPPORT and OHRP's previous response regarding SUPPORT. The other five interventional trials were suspended at three centers each. The controversy has significantly affected recruitment into much needed neonatal clinical trials to provide evidence for which clinical practice can be improved. Extensive details can be found in the attached document.
> Cathy for Rose and Tonse
>
> On Feb 19, 2014, at 1:07 PM, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov> wrote:
>
> > What is the latest on this – one coordinated answer among you to me, please.
> >
> > Thanks
> >
> > Alan
> >
> > **From:** Patterson, Amy (NIH/OD) [E]
> > **Sent:** Wednesday, February 19, 2014 1:04 PM
> > **To:** Guttmacher, Alan (NIH/NICHD) [E]; Shurin, Susan (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Bernard, Marie A. (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]

Cc: Carr, Sarah (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]
Subject: Next Steps and Impact of Controversy on SoC Research

All:

At his next one on one with the Deputy Secretary, Francis will bring up

(b)(5)

Francis would also like t(b)(5)

(b)(5)

Could you get back to me before noon tomorrow?

Thanks,

Amy

<Six interventional trials were ongoing in the Neonatal Research Network ....docx>

From:	Laptook, Abbot
To:	Shankaran, Seetha; Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc:	Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
Subject:	RE: PaCO2 manuscript : Rejection from Pediatrics
Date:	Wednesday, February 19, 2014 8:55:51 AM

J Peds sounds fine to me. AL

-----Original Message-----
From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Wednesday, February 19, 2014 8:54 AM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Laptook, Abbot; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
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Comments from our reviewers are included below. Reviewer input is one of several factors involved in making decisions on papers. Because of space limitations, even papers receiving positive comments from the reviewers are often rejected.

We look forward to receiving other articles from you in the future.

Sincerely,

Lewis R. First, MD
Editor-in-Chief, Pediatrics
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics,
Vermont Children's Hospital at Fletcher Allen Health Care
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Reviewer: 1

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

(b)(4),(b)(6)

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Subject: RE: PaCO2 manuscript : Final draft (Dec 29, 2013) before submission on Jan 8, 2014

Dear All,
Attached is the most recent draft of our manuscript on PaCO2 in relation to outcome in SUPPORT. I have made some changes following NICHD clearance, Publication Subcommittee reviews, and comments by co-authors on the previous draft. One change is to emphasize that PaCO2 is a marker of illness severity and that there is for the most part no interaction between SUPPORT treatment group allocation and PaCO2. I will submit on Jan 8th (Wednesday; about 10 days from now) to Pediatrics if there are no further comments/suggestions.
Thank you,
Ambal

---

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From: [redacted]
To: "Jones, Travis"
Subject: RE: A Review Approval for Manuscript Manuscript#
Date: Tuesday, February 18, 2014 2:30 PM
Attachments: [redacted]

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B05
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7509
301-496-5574
301-496-1788 (FAX)
higginsr@mail.nih.gov

From: Timothy Jessica Timothy_Stevens@URMC.Rochester.edu]
Sent: Tuesday, February 18, 2014 11:29 AM
To: [redacted]
Cc: Nahmod, Lorie; Freemantle, Lisa; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Authorship Agreement form needed for MS#[redacted]

From: Stevens, Timothy
Sent: Friday, February 14, 2014 2:43 PM
To: [redacted]
Cc: Author, Stephanie [NUMC-PO] [E]; Nahmod, Lorie
Subject: Re: Authorship Agreement form needed for MS#[redacted]

Hi Evelyn,

I Pediatric Research for an authorship agreement for our [redacted] Outcomes manuscript. The link to the agreement form is below. [redacted] I copied their instructions here

Be sure to add the manuscript number and title in the space provided. Please "forward" this e-mail to [redacted] (nothing will be attached) the signed and scanned form[s]. Alternatively, you are welcome to fax the signed form[s] to (US) 513-636-7141. Please note, receiving the authorship agreement form in this place means the Editors believe the paper has potential for acceptance, although an official decision cannot be made until the form signed by all authors is received

Thanks in advance,

Tim

Our Authorship Agreement form, which must be signed by all authors, is available for downloading at

Each author must read and sign the document. If needed, you can forward the document to co-authors for their signatures, but authors can e-mail or fax their forms separately. We cannot accept agreements that are not on the Journal's formal agreements that are signed on behalf of someone else.)

---Original Message---
From: [redacted] On Behalf Of Journal Office
Sent: Friday, February 14, 2014 12:35 PM
To: Stevens, Timothy
Subject: Authorship Agreement form needed for MS#[redacted]

Manuscript Number: [redacted]
Article title: Neurodevelopmental Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT)
Corresponding author: Dr. Timothy Richard Stevens

Journal name: The Journal of Pediatrics

Dear Dr. Stevens:

Our Authorship Agreement form, which must be signed by all authors, is available for downloading at

Each author must read and sign the document. If needed, you can forward the document to co-authors for their signatures, but authors can e-mail or fax their forms separately. We cannot accept agreements that are not on the Journal's formal agreements that are signed on behalf of someone else.)

Be sure to add the manuscript number and title in the space provided. Please "forward" this e-mail to [redacted] (nothing will be attached) the signed and scanned form[s]. Alternatively, you are welcome to fax the signed form[s] to (US) 513-636-7141. Please note, receiving the authorship agreement form in this place means the Editors believe the paper has potential for acceptance, although an official decision cannot be made until the form signed by all author[s] is received

Please send the form[s] by February 18. When we receive the form signed by all authors, we can continue processing your submission. Thank you for your prompt attention to this matter.

Sincerely,

Barbara Nahmod
Editorial Assistant

The Journal of Pediatrics
Children's Hospital Medical Center
3333 Burnet Avenue, MLC 3031
Cincinnati, OH 45229-3039

The JOURNAL of PEDIATRICS

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AUTHORSHIP AGREEMENT
Must be signed by ALL authors

By signing this Authorship Agreement form, I confirm that:

I made substantial contributions to: (1) concept or design of the work; or the acquisition, analysis, or interpretation; AND (2) drafting the work or revising it critically for important intellectual content of data for the work; AND (3) final approval of the version to be published; AND (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved." Authors must meet all four conditions (as outlined by the International Committee of Medical Journal Editors [www.icjme.org]); and

I have reported all of my conflicts of interest, real and perceived, and funding sources in the latest version of the manuscript.

**** If I have any questions about authorship or conflicts of interest, I will e-mail The Journal Office as soon as possible.**

Manuscript # 20131439RL

Title: Respiratory Outcomes of the SUPPORT Trial

(Author names must be typed/printed next to signatures. All authors do not need to sign on the same form.)

Signature	Typed/printed name	Date
RHiggins	Rosemary D Higgins	2/18/2014

Note: This is not a transfer of copyright. The publisher will provide a copyright form.

From: Finer, Neil
To: Susan Hintz
Cc: Pat Barnes; DBULAS@childrensnational.org Bulas; Tom Slovis; wrage@rti.org Wrage; Abhik Das; Jon Tyson; David Stevenson; Wally Carlo, M.D.; Michele.Walsh@UHhospitals.org Walsh; Abbott Laptook; Bradley.yoder@hsc.utah.edu (Bradley.yoder@hsc.utah.edu); Krisa Van Meurs; Roger.Faix@hsc.utah.edu (Roger.Faix@hsc.utah.edu); Rich. Wade; nxs5@case.edu newman; hcheng@rti.org Cheng; Roy.Heyne@utsouthwestern.edu Heyne; Betty Vohr; Michael.Acarregui@providence.org Acarregui; Vaucher, Yvonne; Dr. Athina Pappas; mperalta@peds.uab.edu Peralta M.D.; Dee Wilson; pwildermd@gmail.com Evans; ricki.goldstein@duke.edu Goldstein M.D.; gary_myers@urmc.rochester.edu Meyers; bpoindex@iupui.edu Poindexter; emcgowan@tuftsmedicalcenter.org McGowan; Ira Adams-Chapman; JaFuller@salud.unm.edu.edu (JaFuller@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]; pandrhiggins@aol.com; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: JAMA14-0031 Decision Letter
Date: Wednesday, February 12, 2014 7:31:32 PM

I think Pediatrics is fine if JAMA PEDS is a no go
This will get published!
Neil

On Feb 12, 2014, at 9:26 AM, "Susan Hintz" <srhintz@stanford.edu<mailto:srhintz@stanford.edu>> wrote:

Dear co-authors,

Unfortunately, after another 6+ weeks under review, the SUPPORT NEURO 18-22 month outcomes manuscript was not accepted by JAMA. They have automatically forwarded to JAMA Pediatrics. As you can see below, the reviews are concerning in that there are many issues raised that either 1) suggest that the reviewers did not understand the study itself, the analysis approach, or the results, or 2) indicate that they do not like the study design and there is very little we can do about it. There are a few issues raised that we can look at further with RTI that could enhance the manuscript. However, from my perspective, these are pretty negative reviews - particularly in contrast to the generally benign comments and rather positive reviews we received from NEJM.

I reached out to the editorial contact at JAMA Pediatrics to get an idea of timeline for the "expedited" review at JAMA Pediatrics. He said only that I would receive initial information in 2-3 days. My feeling about this is that we can wait for that initial input/ response from JAMA Pediatrics, but that unless that response is stunningly positive (which I doubt given these reviews which will form the basis for the next steps at JAMA Pediatrics), we should probably redirect and next submit to Pediatrics.

I look forward to your input. Thanks again for your efforts and work on this project.

Susan

Susan R. Hintz, M.D., M.S. Epi
Professor of Pediatrics and, by courtesy, Obstetrics & Gynecology
Associate Chief for Prenatal Services
Division of Neonatal and Developmental Medicine
Stanford University School of Medicine
Medical Director, The Center for Fetal and Maternal Health
Lucile Packard Children's Hospital
750 Welch Road, Suite 315
Palo Alto, CA 94304
phone: 650-723-5711
email: srhintz@stanford.edu<mailto:srhintz@stanford.edu>

Begin forwarded message:

From: Jody.Zylke@jamanetwork.org<mailto:Jody.Zylke@jamanetwork.org>
Subject: JAMA14-0031 Decision Letter

Date: February 12, 2014 3:23:23 AM PST
To: srhintz@stanford.edu<mailto:srhintz@stanford.edu>
Cc: Gwenn.Gregg@jamanetwork.org<mailto:Gwenn.Gregg@jamanetwork.org>
Reply-To: Jody.Zylke@jamanetwork.org<mailto:Jody.Zylke@jamanetwork.org>

February 11, 2014

Dr. Susan R. Hintz
Stanford University
Division of Neonatal and Developmental Medicine
750 Welch Rd.
Suite # 315
Palo Alto, California 94304

RE: Neonatal neuroimaging and neurodevelopmental outcomes at 18-22 months corrected age in extremely preterm infants: The NEURO Study

Dear Dr. R. Hintz:

Thank you for submitting your manuscript to JAMA. Based on our editorial evaluation and the comments of our peer reviewers, I regret to inform you that we will not accept your manuscript for publication. However, as you are aware, the JAMA Network allows submitted manuscripts to have more than one opportunity for evaluation for publication. This network includes JAMA Pediatrics, for which you previously gave us permission to forward your manuscript, and we have transferred your manuscript as requested.

Since we have already obtained reviews (copies enclosed for your information), which have been forwarded with the manuscript, further evaluation of your paper will be expedited by the editor of JAMA Pediatrics. In the interest of time, however, please do not revise your manuscript to respond to reviewer comments, and you should refrain from submitting it elsewhere until you receive an editorial decision.

You will receive an acknowledgment from JAMA Pediatrics, to which you should direct all future communications about your manuscript.

Thank you for the opportunity to review your manuscript.

Sincerely yours,

Jody W Zylke, MD
Senior Editor, JAMA
E-mail: Jody.Zylke@jamanetwork.org<mailto:Jody.Zylke@jamanetwork.org>

Reviewer #1 (Remarks to the Author):

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer #2 (Remarks to the Author):

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer #3 (Remarks to the Author):

(b)(4),(b)(6)

From: Juliann DiFiore
To: Higgins, Rosemary (NIH/NICHD) [E]; "Walsh, Michele"
Cc: Martin, Richard
Subject: Re: ?Late breaker?
Date: Wednesday, February 12, 2014 11:49:02 AM

Hi Rose,

Well, the good news is I think we have some interesting preliminary findings here. The bad news is it seems to be a complicated story that will require some thought and a lot more work to make sure we get it right. So, after discussion with Richard and Michele, we are going to pass on the PAS deadline. As usual, thanks for your support. (no pun intended)

Regards,

Julie

On 2/11/2014 3:26 PM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Since this is from the SUPPORT data, NICHD may request a little more time – can you send a draft by Friday??
>
> Rosemary D. Higgins, MD
> Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
> NIH
> 6100 Executive Blvd., Room 4B03
> MSC 7510
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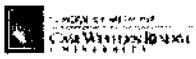
> For overnight delivery use Rockville, MD 20852
> 301-435-7909
> 301-496-5575
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov
>
> ---
>
> **From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
> **Sent:** Tuesday, February 11, 2014 3:09 PM
> **To:** Higgins, Rosemary (NIH/NICHD) [E]
> **Cc:** Martin, Richard; Juliann DiFiore
> **Subject:** RE: ?Late breaker?
>
> We will get on it- perhaps Monday next week.
>
> ***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



From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 11, 2014 12:46 PM
To: Walsh, Michele
Subject: RE: ?Late breaker?

Deadline is next Friday – can you get it to me by the end of this week? Entirely possible!!!
Thanks
Rose

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, February 11, 2014 12:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ?Late breaker?
Importance: High

HI: If we are able to put together a data analysis of the desat data is it even Possible to submit a Late Breaker- and have time for the NIH clearances?
tx

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
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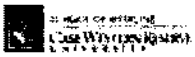

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--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
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Division of Neonatology, Room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 368-1245

3701.243 prohibit
disclosure of this information without the specific written consent of the person to whome it pertains, or as otherwise permitted.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: RE: Question about SUPPORT and TOP
Date: Tuesday, February 11, 2014 5:04:29 PM

Fine- I have meetings from 3-5

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

From: Mondoro, Traci (NIH/NHLBI) [E]
Sent: Tuesday, February 11, 2014 5:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Question about SUPPORT and TOP

Will call you tomorrow when I am done at Council—we are ending at 1:00 so will be before your 3:00.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 10, 2014 6:34 AM
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: RE: Question about SUPPORT and TOP

I have calls from 2-5 PM tomorrow afternoon – I am opan all day Wednesday until 3 PM.

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: Mondoro, Traci (NIH/NHLBI) [E]
Sent: Monday, February 10, 2014 6:29 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Question about SUPPORT and TOP

Can we talk tomorrow afternoon? I have a 1 and 1/2 think tank to run.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 10, 2014 06:24 AM Eastern Standard Time
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: RE: Question about SUPPORT and TOP

Do you have time today to discuss? I am teleworking. Let me know

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

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MSC 7510

Bethesda, MD 20892

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Mondoro, Traci (NIH/NHLBI) [E]
Sent: Sunday, February 09, 2014 9:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Question about SUPPORT and TOP

Please see below. Have you received anything from Tabak?

I will call you to catch up sometime this week.

Hope you are well, Traci

From: Pearson, Gail (NIH/NHLBI) [E]
Sent: Sunday, February 09, 2014 5:16 PM
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: Question about SUPPORT and TOP

HI, Traci,

I was having a conversation with Nakela last week about the ongoing fallout from the SUPPORT trial, and she mentioned that she thought that she had sent you some recommendations/summary of concerns about SUPPORT that resulted from a review that Larry Tabak and others in NIH OD did recently. The context was the TOP trial (not sure I have the acronym correct), if that helps. Anyway, if you have the report on SUPPORT from Larry Tabak et al, I would love to see it.

Thanks so much,

Gail

Gail D. Pearson, MD, ScD, FACC, FAHA, FAAP

Director, Adult and Pediatric Cardiac Research Program

Division of Cardiovascular Sciences

Director, Office of Clinical Research

NHLBI/NIH

6701 Rockledge Drive, Room 8132

Bethesda, MD 20892

Tel: 301-435-0477

pearsong@mail.nih.gov

<< OLE Object: Picture (Device Independent Bitmap) >>

From:	Juliann DiFiore
To:	Pickett, James; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Zaterka-Baxter, Kristin; Walsh, Michele; rxm6@case.edu
Subject:	Data Request for IH and mortality ancillary study
Date:	Friday, February 07, 2014 11:57:11 AM

RE: IH and mortality ancillary study

After discussions with Michele and Richard regarding the IH and mortality study we feel we need to include additional covariates that may influence IH. Therefore, I am asking for one more amendment to the DUA (and hopefully the last). Would you please add the following:

Early Sepsis (< 72 hrs) and Late Sepsis (>= 72 hrs)

IVH: Any and Severe

NEC- any and medical vs surgical.

Cause of Death.

Thank you,

Julie

--
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

From: Kaeser, Lisa (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: WF 327774 - FYI - SUPPORT Study
Date: Thursday, February 06, 2014 8:40:01 AM

Hi Rose! Thanks for being so conscientious!

I am not sure we need to talk – I can send you the Public Citizen letter when you return. As Cathy said, we are not being asked to reply at this time. Even if they ask us at some point, it will be after you get back.

On the GAO, Belinda found only one relevant grant. Building 1 couldn't find any times next week, so they're looking at the week after. I told them you were more important than me, but I will make it if I can, too.

If you'd still like to talk, around 4:30 EST today would be best, but if you're on leave, please don't worry about it!

Thanks again,

Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, February 06, 2014 8:05 AM
To: Spong, Catherine (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: WF 327774 - FYI - SUPPORT Study

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

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, February 06, 2014 8:04 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: WF 327774 - FYI - SUPPORT Study

We are not being asked to respond at this time

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, February 06, 2014 8:02 AM
To: Kaeser, Lisa (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: WF 327774 - FYI - SUPPORT Study

Hi
I cannot access the TASK bar below – do we need to respond and if so, can someone send me the instructions? I am on travel through Saturday but will have time to get to this.
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

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Monday, February 03, 2014 8:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: WF 327774 - FYI - SUPPORT Study

Hi – you may have seen this already, but just in case. We are not being asked to respond at this time.

Thanks,
Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Ott, Sandra (NIH/NICHD) [E]
Sent: Saturday, February 01, 2014 12:01 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 327774 - FYI - SUPPORT Study

Hi there!

This has been assigned to NICHD and OSP as an FYI. FYI's were also sent to DIR, DEPD, and DDSOP.

This is a follow-up letter from the Public Citizen's Health Research group regarding the SUPPORT study.

Sandy
Sandra Ott
Staff Assistant to the 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: 301-496-1849
Fax: 301-402-1104
E-mail: otts@mail.nih.gov

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
To: Brown, Crystal (NIH/NICHD) [C]; EDRMS_NO_REPLY (NIH/OD); EDRMS_NO_REPLY (NIH/OD); Ott, Sandra (NIH/NICHD) [E]; EDRMS_NO_REPLY (NIH/OD); Wood, Vandora (NIH/CIT) [C]
Subject: WF 327774 - Review FYI (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

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the task:

Task

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Work Folder Information
Work Folder: WF 327774
Process: IC FYI - WF 327774
Program Analyst: Dozier, Monica (NIH/OD) [E]
WF Subject: "Follow-up letter from the Public Citizen's Health Research group regarding the NIH-funded SUPPORT study involving extremely premature infants."
IC: NICHD
From: Wolfe, Sidney;Carome, Michael;
To: Sebelius, Kathleen;
Remarks: Assigned to NICHD and OSP as an FYI. FYI's will also be sent to DIR, DEPD, and DDSOP. Thank you:)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Carrie Rau
Cc: srhintz@stanford.edu; Bradley Yoder; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: citation of CCTS grant for SUPPORT FU visit.
Date: Wednesday, February 05, 2014 5:32:56 PM

Stephanie archer can provide the needed language

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 5, 2014, at 10:09 AM, "Carrie Rau" <Carrie.Rau@hsc.utah.edu> wrote:

Hi Susan,
I sent this question out to Rosemary and she is (b)(6) until next week. I really want to get this application in as we are doing this concurrently with finding a psychologist. Are you able to answer the below question? I have also put in a call to the number that Rosemary left in her email and am waiting a return phone call.
Thanks so much,
Carrie Rau, RN, CCRC

Research Nurse, Division of Neonatology
801-213-3360 (office)
801-581-5658 (secondary office)
(b)(6) (cell)

From: Carrie Rau
Sent: Wednesday, February 05, 2014 10:56 AM
To: higginsr@mail.nih.gov
Cc: Bradley Yoder; Debbie Carter; Manndi Loertscher; Shawna Baker
Subject: citation of CCTS grant for SUPPORT FU visit.
Importance: High

Hi Rosemary,
We are applying to use our CCTS (Center for Clinical & Translational Science) for the SUPPORT FU study (since we won't be using the UDOH), and part of the usage agreement is that the CCTS grant will be cited in any publications. The language used depends on the type of grant that is for the SUPPORT Study. I'm copying all of the possible verbatim paragraphs. Can you let me know if this is possible to do and whether or not I can agree to this?

For UL1 supported studies: "Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number 1ULTR001067. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH."
For KL2 Mentored Career Development support: "Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number 1KL2TR001065. The content is solely the responsibility of the authors and does not

necessarily represent the official views of the NIH."

For TL1 Research Training support: "Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number 1TL1TR001066. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH."

Thanks so much!

Carrie Rau, RN, CCRC
Research Nurse, Division of Neonatology
801-213-3360 (office)
801-581-5658 (secondary office)
(b)(6) (cell)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: PLEASE READ: FW: citation of CCTS grant for SUPPORT FU visit.
Date: Wednesday, February 05, 2014 5:31:00 PM

Stephanie ca. Provide the needed language

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 5, 2014, at 11:46 AM, "Das, Abhik" <adas@rti.org> wrote:

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, February 05, 2014 2:44 PM
To: Carrie Rau
Cc: Rosemary Higgins; Bradley Yoder; Das, Abhik; Zaterka-Baxter, Kristin; Stephanie Archer
Subject: Re: citation of CCTS grant for SUPPORT FU visit.
Importance: High

Hi Carrie,

I am not sure I can answer this properly - but I am cc'ing Abhik, Kris Zaterka, and Stephanie Archer, who I think will be able to either answer or to find the right person to answer for you -

Thanks,

Susan

On Feb 5, 2014, at 10:08 AM, Carrie Rau <Carrie.Rau@hsc.utah.edu> wrote:

Hi Susan,
I sent this question out to Rosemary and she is (b)(6) until next week. I really want to get this application in as we are doing this concurrently with finding a psychologist. Are you able to answer the below question? I have also put in a call to the number that Rosemary left in her email and am waiting a return phone call.
Thanks so much,
Carrie Rau, RN, CCRC

Research Nurse, Division of Neonatology
801-213-3360 (office)
801-581-5658 (secondary office)
(b)(5) (cell)

From: Carrie Rau
Sent: Wednesday, February 05, 2014 10:56 AM
To: higginsr@mail.nih.gov
Cc: Bradley Yoder; Debbie Carter; Manndi Loertscher; Shawna Baker
Subject: citation of CCTS grant for SUPPORT FU visit.
Importance: High

Hi Rosemary,

We are applying to use our CCTS (Center for Clinical & Translational Science) for the SUPPORT FU study (since we won't be using the UDOH), and part of the usage agreement is that the CCTS grant will be cited in any publications. The language used depends on the type of grant that is for the SUPPORT Study. I'm copying all of the possible verbatim paragraphs. Can you let me know if this is possible to do and whether or not I can agree to this?

For UL1 supported studies: "Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number 1ULTR001067. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH."

For KL2 Mentored Career Development support: "Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number 1KL2TR001065. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH."

For TL1 Research Training support: "Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number 1TL1TR001066. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH."

Thanks so much!

Carrie Rau, RN, CCRC
Research Nurse, Division of Neonatology
801-213-3360 (office)
801-581-5658 (secondary office)
(b)(6) cell)

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Date: Monday, February 03, 2014 6:44:35 PM

I think that it (b)(5)

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: Monday, February 03, 2014 4:31 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research

Not on the current regs- this is really the (b)(5)
(b)(5)

Rosemary D Higgins, MD

Sent from my iPhone

On Feb 1, 2014, at 7:16 AM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

What do you think of Steve's comments re (b)(5)
(b)(5)

Begin forwarded message:

> **From:** "Hirschfeld, Steven (NIH/NICHD) [E]" <hirschfs@mail.nih.gov>
> **Date:** January 31, 2014, 6:57:34 PM EST
> **To:** "Carr, Sarah (NIH/OD) [E]" <CarrS@OD.NIH.GOV>, TNBC

<TNBC@OD.NIH.GOV>
Cc: "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>, "Maddox, Yvonne (NIH/NICHD) [E]" <maddoxy@exchange.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Spong, Catherine (NIH/NICHD) [E]" <spongc@dir49.nichd.nih.gov>, "Zajicek, Anne (NIH/NICHD) [E]" <zajiceka@mail.nih.gov>, "Slutsman, Julia (NIH/NICHD) [E]" <slutsmaj@mail.nih.gov>
Subject: RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research

Sarah:

Attached are comments, as requested, submitted as a member of the TNBC. Thank you for coordinating this effort and for the opportunity to respond.

Kind regards,

Steven H.

Steven Hirschfeld, MD PhD
Captain, U.S. Public Health Service
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
U.S. Public Health Service Rapid Deployment Force PHS-1

31 Center Drive, MSC-2425
Bethesda, MD 20914 (for express packages use 20892)

From: Carr, Sarah (NIH/OD) [E]
Sent: Thursday, January 30, 2014 8:28 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]
Subject: RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Importance: High

All:

HHS has extended the deadline for receipt of agency comments, so we can now give you a bit more time for review and comment – until **COB Tuesday, February 4**.

Sarah

From: Carr, Sarah (NIH/OD) [E]
Sent: Wednesday, January 29, 2014 3:52 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]; Carr, Sarah

(NIH/OD) [E]
Subject: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research

Dear T-NBC:

Please find attached for your review and comment OHRP's draft guidance on research involving standard of care interventions (the term used in the draft guidance is "accepted therapies"). This CONFIDENTIAL draft guidance is, as you know, an outgrowth of the confusion and debate last year about what risks need to be considered and disclosed in standard of care studies. Further background is provided in the attached memorandum from the Assistant Secretary for Health. After OHRP considers HHS comments and makes any necessary revisions, the revised draft guidance will be reviewed by the other Common Rule agencies before being published for public comment.

We have been given less than a week to submit comments. Consequently, we will need to receive any comments you have on the document by **COB, Friday, January 31, 2014**. Your comments should be in a narrative form, citing the document page number, the number of the question, and the line number; please do not embed comments in the draft guidance document itself.

If you have any questions, please let us know.

Sarah

Sarah Carr
Office of Clinical Research and Bioethics Policy
NIH Office of Science Policy
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
301-435-6753 (direct)
301-496-9838 (main)
301-496-9839 (fax)
carrs@od.nih.gov

<Responses to OHRP Draft Guidance-SH.docx>

From: Rowe, Mona (NIH/NICHD) [E]
To: Kaeser, Lisa (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Underwood, Brenda (NIH/NICHD) [E]
Subject: RE: ACTION: Please provide your availability for a follow-up meeting with GAO - "Newborns With Drug Withdrawal" (291168) (due 2/4/14)
Date: Monday, February 03, 2014 2:55:32 PM

Thanks for asking -- Sure let us know the question and we can also work with Rose – copying Brenda

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: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Monday, February 03, 2014 2:15 PM
To: Rowe, Mona (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: ACTION: Please provide your availability for a follow-up meeting with GAO - "Newborns With Drug Withdrawal" (291168) (due 2/4/14)

Hi – We have had one very introductory phone call with GAO on this inquiry. (It's a request from the Hill but they won't tell us who.) Rose is our lead, but we didn't really provide any information on the first call (NIDA did most of the talking).

GAO is now asking about "databases" with info on our grants. Seems like we just need a run on our grants related to neonatal abstinence syndrome/drug withdrawal. Would someone in Brenda's branch be able to do that? I will provide the question set as soon as we receive it.

Thanks,
Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy

Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Brown, Tiffany (NIH/OD) [E]
Sent: Monday, February 03, 2014 2:04 PM
To: Stein, Jack (NIH/NIDA) [E]; Weiss, Susan (NIH/NIDA) [E]; Boyce, Cheryl (NIH/NIDA) [E]; Perl, Harold (NIH/NIDA) [E]; Montoya, Ivan (NIH/NIDA) [E]; Kaeser, Lisa (NIH/NICHD) [E]; Dammann, Fl (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Gottesman, Michael (NIH/OD) [E]; Wyatt, Richard G (NIH/OD) [E]
Cc: Rais, Sahar (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Stein, Meredith (NIH/OD) [E]; Mazzarino, Mary Anne (NIH/OD) [E]; McBurney, Margaret (NIH/OD) [E]; Kleinman, Joe (NIH/OD) [E]
Subject: ACTION: Please provide your availability for a follow-up meeting with GAO - "Newborns With Drug Withdrawal" (291168) (due 2/4/14)

ACTION: Please provide your availability to meet with GAO
DUE DATE: COB, February 4, 2014
CONTACT: Tiffany Brown, OMA, 301-496-2464

GAO would like to conduct a follow-up meeting to discuss a potential data request in reference to the review entitled, "Newborns With Drug Withdrawal" (291168). GAO would like to discuss the best way for them to request comprehensive information on NIDA- and NICHD-funded research that seeks to understand, prevent, or treat drug use disorders in pregnant women and neonatal abstinence syndrome (NAS). In particular, they are interested in learning more about the NIDA and NICD databases that contain this information, the variables available, and an estimated timeframe for providing them with the data.

They will provide a question-set prior to the meeting.

Please review the proposed times below and let me know what works for you. The meeting will be a 1-hr teleconference.

February 10: 1:30pm – 4:30pm
February 11: 1:30pm – 4:30pm
February 12: 3:30pm – 3:30pm
February 13: 1:30pm – 3:30pm

Please let me know your availability by **COB on February 4th**.

Thanks!

TIFFANY BROWN
NIH/OD/OMA
(301) 496-2464 - DIRECT
(301) 402-0169 - FAX

From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: WF 327774 - FYI - SUPPORT Study
Date: Monday, February 03, 2014 9:46:42 AM
Attachments: 327774 - Incoming - 1a 140124 Letter to HHS Secretary Sebelius re Monitoring of SUPPORT Study Trial- Final.pdf
327774 - Incoming - 1 Follow-up letter regarding the SUPPORT Study Message.pdf

---

Have you seen this?

From: Ott, Sandra (NIH/NICHD) [E]
Sent: Saturday, February 01, 2014 12:01 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 327774 - FYI - SUPPORT Study

Hi there!

This has been assigned to NICHD and OSP as an FYI. FYI's were also sent to DIR, DEPD, and DDSOP.

This is a follow-up letter from the Public Citizen's Health Research group regarding the SUPPORT study.

Sandy
Sandra Ott
Staff Assistant to the 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: 301-496-1849
Fax: 301-402-1104
E-mail: otts@mail.nih.gov

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
To: Brown, Crystal (NIH/NICHD) [C]; EDRMS_NO_REPLY (NIH/OD); EDRMS_NO_REPLY (NIH/OD); Ott, Sandra (NIH/NICHD) [E]; EDRMS_NO_REPLY (NIH/OD); Wood, Vandora (NIH/CIT) [C]
Subject: WF 327774 - Review FYI (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

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Task

Please do not reply to this email, this is an automated message.

If you have concerns please contact the NIH Help Desk at (301) 496-4357.

Work Folder Information
Work Folder: WF 327774
Process: IC FYI - WF 327774
Program Analyst: Dozier, Monica (NIH/OD) [E]
WF Subject: "Follow-up letter from the Public Citizen's Health Research group regarding the NIH-funded SUPPORT study involving extremely premature infants."
IC: NICHD
From: Wolfe, Sidney;Carome, Michael;
To: Sebelius, Kathleen;
Remarks: Assigned to NICHD and OSP as an FYI. FYI's will also be sent to DIR, DEPD, and DDSOP. Thank you:)

From: Michael Carome
Sent:27 Jan 2014 06:48:35 -0500
To: Sebelius, Kathleen (HHS/OS)
Cc: Corr, Bill (HHS/IOS);Koh, Howard (HHS/OASH);Menikoff, Jerry (HHS/OASH);Borror, Kristina C (HHS/OASH);Collins, Francis (NIH/OD) [E];Guttmacher, Alan (NIH/NICHD) [E]
Subject: Follow-up letter regarding the SUPPORT study
Attachments:140127_Letter to HHS Secretary re Monitoring of SUPPORT Trial_FINAL.pdf

Dear Secretary Sebelius:

Attached please find a follow-up letter from Public Citizen□s Health Research Group regarding the NIH-funded SUPPORT study involving extremely premature infants. 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.

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

PUBLICCITIZEN

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

January 27, 2014

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

RE: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial – Inadequate Safety Monitoring

Dear Secretary Sebelius:

We are writing in follow-up to Public Citizen's April 10, 2013, letter and May 8, 2013, report regarding the SUPPORT study funded by the National Institutes of Health (NIH) and conducted by approximately two dozen academic medical institutions of the Neonatal Research Network.[1,2] That letter and report highlighted important and material factual omissions regarding the purpose, nature, and risks of the research in the consent forms approved by the institutional review boards (IRBs) and signed by parents of infants enrolled in the SUPPORT study, and also brought to light deficiencies in the study design that resulted in a failure to ensure that risks to subjects were minimized.

To date, the Department of Health and Human Services' (HHS's) response to the serious ethical lapses in the conduct of the SUPPORT study has been unsatisfactory. Rather than taking substantive steps to remedy these ethical lapses, HHS bowed to pressure from NIH and an academic research establishment dependent on NIH for support and stifled appropriate compliance oversight enforcement action by the Office for Human Research Protections (OHRP).

We write to you now to highlight the following additional important issues related to the SUPPORT study that have come to our attention and also have not been adequately addressed by HHS:

(1) The SUPPORT study protocol appears to have lacked a safety monitoring plan for *separately* monitoring for differences in severe retinopathy of prematurity (ROP) between the two experimental oxygen study groups. If such a plan had been

[1] Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. April 10, 2013. http://www.citizen.org/documents/2111.pdf. Accessed January 20, 2014.
[2] Carome M, Wolfe S, Macklin R. Analysis of the complete protocol and consent form for the SUPPORT study: Lack of informed consent and a failure to ensure that risks were minimized. May 8, 2013. http://www.citizen.org/documents/2124.pdf. Accessed January 20, 2014.

implemented, the study likely would have been terminated early, sparing some extremely premature infants enrolled in the study from suffering severe ROP or death.

(2) In spite of evidence we presented previously,[3] the SUPPORT study investigators — in an attempt to defend the adequacy of their study consent forms — have continued to repeatedly assert that they all had no expectation that the low-oxygen group subjects would have a higher mortality rate than the high-oxygen group subjects and indeed were surprised when the final study results revealed such an outcome. We provide below additional clear evidence that before the study began, there was an awareness among at least some of the investigators — including among the lead investigators who developed the study protocol — that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study. Moreover, as neonatology experts, the SUPPORT study investigators had an ethical obligation to thoroughly research the literature, to understand areas of ongoing uncertainty regarding oxygen management, and to be aware of all plausible study risks. To not have known that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study would have constituted reckless ignorance.

(3) The SUPPORT study was one of five concurrently planned, coordinated, and conducted studies around the world using nearly identical study designs for testing low- versus high-oxygen interventions in extremely premature infants. To minimize risks to subjects across all five studies, the protocols should have specified a mechanism for joint safety monitoring. Ideally, there should have been a formal data and safety monitoring plan involving interim analyses of pooled data from all five studies combined. At a minimum, there should have been a plan for informally sharing any troubling safety signal arising in one study with the investigators and data monitoring committees for the other studies. No such formal or informal plan was described in the SUPPORT protocol. Of note, the members of the data monitoring committee for at least one of the five studies recognized early on the need to see interim data from the other four parallel studies to ensure the safety of subjects across all trials, but their attempts to obtain data from the other studies were either ignored or rebuffed.

We describe below each of these issues in detail and conclude by asking key questions for which the parents of SUPPORT study subjects and the public deserve clear answers from HHS.

A. Background

As you are aware, the SUPPORT study involved two simultaneous complex experiments. In one experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing (ventilation of the lungs) following delivery.[4]

For the other experiment (the oxygen experiment), babies assigned to each of the two ventilation groups were further randomly divided between a low-oxygen group and a high-oxygen group.[5]

---

[3] *Ibid.*

[4] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely premature infants. *N Engl J Med.* 2010;362(21):1970-1979.

For the low-oxygen group, the SUPPORT study investigators tried to maintain the babies' blood oxygen levels in a low target range (oxygen saturation level of 85 to 89 percent), and for the high-oxygen group in a high target range (oxygen saturation level of 91 to 95 percent), regardless of the infants' clinical status.

The primary efficacy outcome measure for the oxygen experiment was a combination of severe retinopathy of prematurity (ROP, which can lead to visual impairment and blindness and often requires surgery to preserve vision), death before discharge from the hospital, or both.

For both experimental oxygen groups, oxygen monitors relied upon by the medical teams caring for the infants in the study displayed either intentionally falsely high (low-oxygen group) or intentionally falsely low (high-oxygen group) values when the infants' actual oxygen saturation levels were between 85 and 95 percent.

Premature infants enrolled in the SUPPORT study were not given the same care with respect to oxygen management that otherwise similar infants would have received at the same participating hospitals. In particular, oxygen management of enrolled infants lacked the following features of usual care:

(1) fully functional, properly operating pulse oximeters that displayed accurate oxygen saturations for use by health care providers to guide care;

(2) access to the entire range of target oxygen saturations endorsed in guidelines (85 to 95 percent) for management of premature infants, including the possibility of employing the center of this range (88 to 92 percent); and

(3) adjustment of supplemental oxygen and oxygen saturation targets based on an assessment of risks and benefits for each infant's particular characteristics. Some of the clinical factors that are often considered in individualizing oxygen management include level of prematurity; capillary refill time (a simple physical exam test to assess the adequacy of tissue perfusion); cardiopulmonary, hepatic, and renal function; hematocrit; intravascular volume; acid-base status; oxygen requirements in the toxic range; and clinical signs suggestive of impending necrotizing enterocolitis.

For the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. The low-oxygen intervention presented the foreseeable risks of neurologic injury and death.

In contrast, for the high-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 91 to 95 percent using oxygen monitors that displayed falsely *low* readings predictably caused, on average, higher levels of oxygen exposure than

[5] 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.

would have occurred under usual care using accurately reading oxygen monitors. The high-oxygen intervention presented the foreseeable risk of severe ROP.

B. Inadequate safety monitoring plan: Apparent failure to monitor for severe ROP as a separate adverse event and to terminate the study early because of harm to subjects in the high-oxygen group

Minimization of risks to research subjects requires adequate safety monitoring. Both death and severe ROP comprised the primary risks of the SUPPORT study's oxygen experiment, and each should have been monitored *separately as adverse events* during the conduct of the trial in order to minimize risks to subjects. If separate monitoring of both had been implemented, the study likely would have been terminated early, sparing some extremely premature infants enrolled in the study from suffering severe ROP or death.

However, as reflected in the following excerpts from the data and safety monitoring plan in the SUPPORT study protocol, it appears that unlike death, severe ROP was not monitored *separately as an adverse event* during the course of the trial. Instead, severe ROP apparently was monitored only in combination with death as a component of the composite primary efficacy endpoint, and the study was not terminated early. The protocol stated:[6]

> **4.4 Adverse Events**
>
> Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:
>
> 1. Air leak on admission to the NICU, or during the initial 14 days of life
> 2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
> 3. The occurrence of severe IVH (Grades 3-4, Papile)
> 4. Death
>
> These outcomes will be evaluated on a monthly basis by RTI [Research Triangle Institute], and if the incidence of any of these outcomes is determined to be 5% -10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.
>
> **4.5 Data Safety Monitoring Committee**
>
> The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome

[6] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

Monitoring of the *composite* primary efficacy endpoint of severe ROP or death before discharge during the conduct of the SUPPORT study as designed was not sufficient for monitoring safety related to the occurrence of severe ROP because of the following factors:

(1) The SUPPORT study's oxygen experiment involved only two experimental groups (the low-oxygen group and the high-oxygen group) and no usual care (or current-practice) control group; and

(2) The two components of the composite primary efficacy endpoint — death and severe ROP — were countervailing, but asymmetric, potential harms:

(a) For the high-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 91 to 95 percent using oxygen monitors that displayed falsely low readings predictably caused, on average, higher levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. As a result, the research procedures for these subjects presented a reasonably foreseeable increased risk of suffering severe ROP (a risk that was not described in 20 of 22 IRB-approved SUPPORT study consent forms as required by HHS human subjects protection regulations at 45 CFR 46.116(a)(2)).[7]

(b) For the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors. As a result, the research procedures for these subjects presented a reasonably foreseeable risk of death (a risk that was not disclosed in any of 22 IRB-approved SUPPORT study consent forms).

Adequate safety monitoring of the study as designed would have required periodic checking for differences between the low-oxygen and high-oxygen groups for *both* death and retinopathy *separately*. The importance of such separate comparisons was reflected in the way the results were presented in the published paper describing the primary results of the study (see Table 1 below).[8]

[7] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed January 20, 2014.

[8] 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.

Table 1: Key Major Outcomes from SUPPORT Study

Outcome	Low-Oxygen Group *no./total no.(%)*	High-Oxygen Group *no./total no.(%)*	Adjusted Relative Risk (95% Confidence Interval)	P-value
Primary efficacy outcome: severe ROP or death before discharge	171/605 (28.3%)	198/616 (32.1%)	0.90 (0.76-1.06)	0.20
Severe ROP	41/475 (8.6%)	91/509 (17.9%)	0.52 (0.37-0.73)	<0.001
Death before discharge	130/654 (19.9%)	107/662 (16.2%)	1.27 (1.01-1.60)	0.04

Because severe ROP often requires surgery and can lead to blindness, it represented a clear potential harm to the high-oxygen group infants of significant-enough degree to require separate safety monitoring, as was done for death. Yet the protocol's data and safety monitoring plan did not indicate that it was separately monitored. Indeed, the problem of ROP in premature infants was considered such a serious health problem in premature infants that NIH spent more than $20 million on the SUPPORT study to find out whether using the low-oxygen intervention would reduce the incidence of this important adverse outcome in comparison to the high-oxygen intervention without causing an increase in mortality or brain injury.

In what obviously came as no surprise to the SUPPORT study investigators and was not an unexpected finding, the study results, after SUPPORT was concluded, demonstrated that the high-oxygen group babies had a highly significant increase in retinopathy in comparison to the low-oxygen group babies (17.9 percent versus 8.6 percent, respectively; $p<0.001$).[9]

If the incidence of severe ROP had been monitored separately as an important adverse event in the high-oxygen group at increased risk for this adverse outcome and compared to the incidence in the low-oxygen group, the trial conceivably could have been stopped early, thus preventing the occurrence of retinopathy and avoiding retinal surgery in many high-oxygen group infants.

To estimate the approximate point at which one of the planned interim analyses of study data would have demonstrated a statistically significant difference in the rate of severe ROP between the high- and low-oxygen groups, we performed a series of hypothetical interim analyses using the chi-square test based on enrollments of 25, 50, and 75 percent of the actual final enrollment (i.e., 1,316 infants). Because interim data were not available to us for these analyses, we assumed that the following factors remained constant throughout the study: the incidence of severe ROP, the proportion of high- and low-oxygen group subjects, and the proportion of subjects in each group who survived to the time of discharge and had a determination made regarding whether severe ROP had developed.

[9] *Ibid.*

The contingency tables below (Tables 2-4) summarize our analysis. Following each table is the chi-square statistic without Yates correction and two-tailed P-value (uncorrected for multiple looks):

Table 2: 25 Percent of Final Enrollment*Group	No Severe ROP	Severe ROP	Total
High-Oxygen	104	23	127
Low-Oxygen	109	10	119
Total	213	33	246

*Assumes 329 subjects enrolled and 246 survived to discharge and had retinopathy status determined
χ^2=4.984; P=0.0256

Table 3: 50 Percent of Final Enrollment*

Group	No Severe ROP	Severe ROP	Total
High-Oxygen	209	45	254
Low-Oxygen	217	21	238
Total	426	66	492

*Assumes 658 subjects enrolled and 492 survived to discharge and had retinopathy status determined
χ^2=8.366; P=0.0038

Table 4: 75 Percent of Final Enrollment*

Group	No Severe ROP	Severe ROP	Total
High-Oxygen	314	68	382
Low-Oxygen	325	31	356
Total	639	99	738

*Assumes 987 subjects enrolled and 738 survived to discharge and had retinopathy status determined
χ^2=13.118; P=0.0003

Based on the above analyses, with respect to the harmful outcome of severe ROP, a statistically significant greater incidence of harm in the high-oxygen group might have been detected after reaching just 25 percent of target subject enrollment, and almost certainly would have been detected after reaching 50 percent of target enrollment. Early termination of the study following enrollment of either one-quarter or one-half of the projected final target enrollment likely would have spared some of the subsequently enrolled infants randomized to the high-oxygen group from developing severe ROP that resulted from receiving a higher level of oxygen exposure than they would have otherwise received if they had not been enrolled in the study. We are not able to reliably estimate the number of children who would have been spared severe ROP had the study been terminated early because the study lacked a current-practice control group.

It is important to recognize that the inclusion of a plan to separately monitor for severe ROP as an important adverse outcome during the conduct of the study would not have been sufficient to

address the other fundamental flaw in the SUPPORT study design — the lack of a usual-care control group. By experimentally increasing oxygen exposure in one study group relative to current practice and lowering it in the other, the harms resulting from each experimental intervention *relative to current practice* could not be monitored for or determined, and therefore, risks to subjects were not minimized.

The SUPPORT study investigators may argue that separately monitoring for severe ROP as an adverse event could have led to premature termination of the study and prevented the detection of the higher mortality rate that was seen in the low-oxygen group, which in turn could have led to a dangerous recommendation to routinely target oxygen saturation levels at 85 to 89 percent in all extremely premature infants. (Indeed, as discussed in the next section of our letter, this thought process may explain why separate monitoring for severe ROP did not occur.) However, if the study had been stopped early based on an interim analysis showing a statistically significant higher incidence of severe ROP in the high-oxygen group, without a usual-care control group there would have been no sound basis for concluding that the lower-oxygen intervention was better than usual care. The higher incidence of severe ROP in the low-oxygen group may have been due to oxygen exposure being experimentally raised in the high-oxygen group (relative to usual care), experimentally lowered in the low oxygen group (relative to usual care), or both. The study results were ultimately uninformative in this regard given the lack of a usual-care control group. In addition, interim analyses may have revealed a non-statistically significant higher death rate in the low-oxygen group compared to the high-oxygen group, which should have precluded anyone from making recommendations to modify current practice to routinely using the lower oxygen saturation target in the clinical care of extremely premature infants.

All of these problems could have been avoided with an alternative study design that employed a usual-care control group and low-oxygen experimental group. Such a design could have informed the medical community whether oxygen could be safely lowered to prevent severe ROP without increasing the mortality rate. Moreover, because experimentally lowering oxygen was unlikely to increase the incidence of severe ROP and blindness relative to current practice, it would not have been necessary to monitor this outcome as a separate adverse event.

C. The higher mortality rate in low-oxygen group infants: *Not* a surprising finding

As noted above, for the low-oxygen group infants, the experimental strategy for attempting to maintain oxygen saturation levels at 85 to 89 percent using oxygen monitors that displayed falsely high readings predictably caused, on average, lower levels of oxygen exposure than would have occurred under usual care using accurately reading oxygen monitors.

Over the past several months, in an awkward attempt to explain why death was not identified as a risk of the research in the SUPPORT study consent forms, the study investigators have repeatedly asserted that they all had no expectation that the low-oxygen group subjects would have a higher mortality rate than the high-oxygen group subjects, and indeed some investigators

have indicated that they were surprised when the final study results revealed such an outcome.[10,11,12,13]

In contrast, the investigators in recent months have not asserted that they were surprised to find a higher rate of severe ROP in the high-oxygen group than in the low-oxygen group, and as previously noted, such a finding undoubtedly was not a surprise.

All physicians understand the well-established pathophysiologic relationship in which increasing degrees of hypoxemia result in progressively higher mortality rates. At the time of the SUPPORT study, all neonatologists knew that increasing the degree of hypoxemia in premature infants *at some point* would increase the infants' mortality rate. The exact shape of the curve for the relationship between the degree of hypoxemia and mortality and the exact threshold of oxygen exposure below which mortality will start to increase in premature infants were not known at the time the SUPPORT study was conducted and remain unknown today.

The SUPPORT study investigators may have believed that targeting oxygen saturations at 85 to 89 percent in extremely premature infants was unlikely to cross below the oxygen exposure threshold that would increase the mortality rate. However, they did not know for certain that this was the case, and the available data from the medical literature cited by the investigators in their protocol were clearly insufficient to prove that maintaining oxygen saturations at 85 to 89 percent would *not* have an adverse impact on the mortality rate of extremely premature infants. Indeed, assessing whether the lower oxygen saturation target could decrease the incidence of severe ROP in severely premature infants without increasing mortality was one of the major reasons for conducting the study.

As neonatology experts, the SUPPORT study investigators had an ethical obligation to thoroughly research the literature, to understand areas of ongoing uncertainty regarding oxygen management, and to be aware of all plausible study risks. To not have known that an increased mortality rate in the low-oxygen group was one foreseeable, plausible outcome of their study would have constituted reckless ignorance.

Investigators in New Zealand undertaking a similarly designed study (discussed below) understood that regardless of their expectations about the study outcome, it was appropriate to

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[10] Transcript for the Diane Rehm Show from WAMU and National Public Radio: Clinical trials and premature babies. April 17, 2013. http://thedianerehmshow.org/shows/2013-04-17/clinical-trials-and-premature-babies/transcript. Accessed January 20, 2014. (SUPPORT study investigator Dr. Edward Bell stated, "As a matter of fact, there was no reason for us to suspect that there would be a difference in mortality, and that was a surprising finding.")

[11] Finer NN, Bell EF, Van Meurs K. Consent forms in a clinical trial of premature babies (letter to the editor). *The New York Times*. April 18, 2013. http://www.nytimes.com/2013/04/19/opinion/consent-forms-in-a-clinical-trial-of-premature-babies.html. Accessed January 20, 2014. ("When the study was planned, the best evidence showed that lower oxygen targets — even lower than used in the study — resulted in less eye disease without a higher death rate. The finding of a higher death rate in one study group was not anticipated.")

[12] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med.* 2013;368(20):1949-1950. ("Death was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected.")

[13] D'Angio C, Finer N, Newman N, et al. Misconceptions about the SUPPORT trial. Posted September 10, 2013. http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2013-0004-0067. Accessed January 20, 2014.

explain to subjects' parents in the consent forms the well-known and previously established separate risks of death from lowering oxygen exposure, as well as ROP from raising oxygen exposure, for premature infants enrolled in the study. It is unclear why the SUPPORT study investigators in the U.S. would have lacked such an understanding.

Although the SUPPORT study investigators undoubtedly were *hopeful* at the onset of the study that the low-oxygen intervention would result in a decreased incidence in severe ROP without a concomitant increase in mortality, there is clear evidence that before initiating the study at least some of them were aware that a higher mortality rate in the low-oxygen group relative to the high-oxygen group could have been one plausible finding of their study. In particular, the SUPPORT study investigators cited in their protocol a 2003 paper by Cole et al, published in the journal *Pediatrics,* discussing the planning and design of studies comparing the low- and high-oxygen interventions that were to be used in their study[14] (see reference 55 in the SUPPORT study protocol[15]). The authors of this paper were members of the Pulse Oximetry Saturation Trial for Prevention of Retinopathy of Prematurity (POST ROP) Planning Study Group.

The POST ROP study was to be a multicenter, multinational prospective trial to evaluate different levels of oxygen in premature babies. It is our understanding that the POST ROP study comprised the Benefits of Oxygen Saturation Targeting (BOOST) II studies in the United Kingdom (UK), Australia, and New Zealand, and the Canadian-funded Canadian Oxygen Trial (COT). The SUPPORT study protocol made reference to this study as follows: "The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial…"

Of note, Dr. Waldemar Carlo at the University of Alabama at Birmingham — who was one of the lead investigators for the SUPPORT study and was on the Neonatal Research Network working group that developed and wrote the SUPPORT study protocol — was a member of the POST ROP Planning Study Group. The acknowledgements section at the end of the Cole et al paper states that Dr. Carlo was among the POST ROP Planning Study Group members who reviewed and critiqued the paper.[16]

The 2003 Cole et al paper makes clear that when the SUPPORT study and the parallel POST ROP studies were being designed, there were real concerns among neonatologists that the low-oxygen intervention could expose extremely premature infants to an increased risk of death or neurologic injury. In particular, the paper emphasized that large numbers of patients would have to be studied to address concerns about mortality risk with the low oxygen dose, noting the following:[17]

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[14] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[15] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

[16] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[17] *Ibid.*

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

Emphasizing the need for a data and safety monitoring committee and plan for the POST ROP studies, the 2003 *Pediatrics* paper stated the following:[18]

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

Further indication of the serious concern among some neonatologists that the low-oxygen intervention could expose extremely premature infants to an increased risk of death or neurologic injury was provided in the 2005 version of the consent form used in the New Zealand BOOST II study discussed above, which included the following:[19]

> Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . The aim of this study is to determine, within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%), **whether targeting the lower end of this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision**

[18] *Ibid.*

[19] Lantos JD. OHRP and Public Citizen are wrong about neonatal research on oxygen therapy research. The Hastings Center Bioethics Forum. Posted April 18, 2013. http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blog+140. Accessed January 20, 2014. Cited as "BOOST-NZ consent form, July 2005, personal communication from Brian Darlow, principal investigator of BOOST-NZ."

> **(ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability**. [Emphasis added]

Finally, members of the data monitoring committee for the BOOST II UK study noted the following in a recent commentary article discussing the four POST-ROP studies and the SUPPORT study: [20]

> Evidence from controlled trials had shown that if the oxygen levels are relatively high there is an increased risk of the infant developing the blinding condition retinopathy of prematurity. On the other hand, observational data had suggested that keeping levels of arterial oxygen relatively low might result in increased mortality, and neurological handicap among long term survivors.
>
> During the past decade, five similar trials - in the USA, New Zealand, Canada, Australia and the UK - **were organized more or less concurrently to investigate this therapeutic dilemma**. Although they were separately organized and funded, all of them compared different oxygen tension targeting strategies intended to minimize both mortality and serious morbidity. **It was recognized at the outset that none of the five trials, individually, would have the statistical power to provide a reliable estimate of survival without serious morbidity 18 to 24 months after birth.** Indeed, two of these trials were only funded on the understanding that the data from several similar trials would be combined. [Emphasis added]

All of the above statements could not be clearer. At least some of the expert neonatologists involved in the design of the SUPPORT study and parallel studies to be conducted in other countries were well aware when designing these studies that there were real concerns within the neonatology community that the low-oxygen intervention to be used in these studies might increase the risk of death.

In view of the commentary paper authored by members of the POST ROP Planning Study Group and cited by the SUPPORT study investigators in their own protocol, it is remarkably disingenuous of the SUPPORT study investigators to now assert that because some of them were surprised to find a higher mortality rate in the low-oxygen group subjects in their study, it was not necessary to inform parents about the reasonably foreseeable risk of death for subjects assigned to the low-oxygen group. Such a finding was one reasonably foreseeable and highly plausible outcome. This undoubtedly is one of the reasons why, as noted above, death was to be monitored according to the SUPPORT study protocol and was a component of the primary outcome being studied.

The investigators certainly had hoped for a different result and perhaps had reason to be disappointed when they found the significantly higher mortality rate in the low-oxygen group, but they could not genuinely have been shocked by the fact that when they lowered oxygen exposure, the mortality rate increased in premature infants in the study. Indeed, none of the

[20] Chalmers I, Altman DG, McHaffie H, et al. Data sharing among data monitoring committees and responsibilities to patients and science. *Trials.* 2013;14:102. http://www.trialsjournal.com/content/14/1/102. Accessed January 20, 2014.

investigators at any point in discussing the results of the SUPPORT study have proposed an alternative hypothesis to explain the higher mortality rate in the low-oxygen group compared to the high-oxygen group. They implicitly recognize that the well-established pathophysiologic relationship in which decreasing oxygen exposure results in increasing hypoxemia and mortality is undoubtedly the explanation for their study findings, whether unexpected by some of the investigators or not.

Finally, we strongly suspect that the apparent failure to monitor separately for severe ROP and to have stopping criteria based on finding a difference in the incidence of severe ROP between the high- and low-oxygen groups at the time of any planned interim analyses was due to concern among the investigators that stopping the oxygen experiment early based on a statistically significant difference in ROP between groups could have resulted in a failure to detect a difference in the mortality rate between the two study groups.

D. Failure to minimize risks to subjects by not having a data and safety monitoring plan involving interim analyses of pooled data from the SUPPORT study and the four concurrent POST ROP studies

As noted above, the SUPPORT study and the four POST ROP studies were five parallel studies concurrently planned and conducted around the world using nearly identical study designs comparing high- and low-oxygen interventions in extremely premature infants. The planning and designing of these studies were coordinated,[21,22] and the investigators for each study obviously were aware of the other studies.

To minimize risks to subjects across all five studies, the protocols should have specified a mechanism for joint safety monitoring. Ideally, there should have been a formal data and safety monitoring plan involving interim analyses of pooled data from all five studies combined. At a minimum, there should have been a plan for informally sharing any troubling safety signal arising in one study with the investigators and data monitoring committees for the other studies. No such formal or informal plan was described in the SUPPORT protocol. Instead, monitoring of data and safety was conducted independently and separately across these studies. Not having pooled monitoring across all five studies, even in some informal manner, represents a troubling failure to ensure the protection of human subjects.

Disturbingly, members of the data monitoring committee for the BOOST II UK study recognized the importance of seeing interim data from the other four parallel studies, but their attempts to obtain data from the other studies, which began as early as 2006, apparently were ignored or rebuffed by the data monitoring committees for the other four parallel studies.[23] For example,

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[21] Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics.* 2003;112:1415-1419.

[22] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed January 20, 2014.

[23] Chalmers I, Altman DG, McHaffie H, et al. Data sharing among data monitoring committees and responsibilities to patients and science. *Trials.* 2013;14:102. http://www.trialsjournal.com/content/14/1/102. Accessed January 20, 2014.

they noted the following in a recent commentary article discussing the four POST-ROP studies and the SUPPORT study:

> Accordingly, because data from the other four trials were of obvious relevance to our responsibility, the chair of our DMC wrote to the DMC chairs of the other trials in 2006, expressing the **'hope that we can help each other fulfil our respective commitments to the babies being treated in these trials'** (Emails sent 11 and 15 July 2006).
>
> **No response was received from the other DMC chairs for several years**; but consideration of the proposal became urgent when, more than three years later, in 2009, the management group of the US trial sent results, in advance of publication, to those associated with the trials that were still recruiting.

E. Conclusions and requested actions

For each of the three critical issues described above, parents of subjects enrolled in the SUPPORT study, as well as the public, deserve clear answers to the following questions:

(1) With respect to monitoring separately for difference in the incidence of severe ROP between groups:

(a) Was ROP monitored separately during the course of the trial as an important adverse event? If not, why not?

(b) If ROP was monitored separately during the course of the trial, at the time of any of the planned interim analyses, did the difference in the incidence of severe ROP between the low- and high-oxygen groups reach statistical significance? If so, when did this occur, and why wasn't the study terminated at that point?

(c) Did OHRP consider the lack of appropriate safety monitoring during the SUPPORT study and the lack of a usual-care control group when it evaluated adequacy of the SUPPORT study design?

(d) Since the SUPPORT study investigators must have recognized that the incidence of severe ROP was likely to be higher in the high-oxygen group and have voiced no surprise in finding this result, does HHS agree or disagree with OHRP's finding that the IRB-approved consent forms failed to comply with HHS regulations under 45 C.F.R. 46.116(a)(2) by not disclosing severe ROP as a risk of the research?

(2) With respect to the investigators' statements about being surprised to find a higher mortality rate in the low-oxygen group: Since the SUPPORT study investigators either knew or should have known prior to initiating the study that an increased death rate in the low-oxygen group was a foreseeably plausible outcome of the SUPPORT study, does HHS agree or disagree with OHRP's finding that the IRB-approved consent forms failed to comply with HHS regulations under 45 C.F.R. 46.116(a)(2) by not disclosing death as a risk of the research?

(3) With respect to the failure to establish a plan to monitor data pooled across the SUPPORT study and the four POST ROP studies:

(a) Why didn't the SUPPORT study protocol include a plan for joint safety monitoring with the POST ROP studies, either formally, via pooled interim analyses across all five studies, or informally, by sharing any troubling safety signals arising in one study with the investigators and data monitoring committees for the other studies?

(b) Were the SUPPORT study investigators or NIH officials aware of the BOOST II UK data monitoring committee's requests for SUPPORT study data for the purposes of pooled interim analysis? If so, what was their response to those requests? Why were the requests not granted?

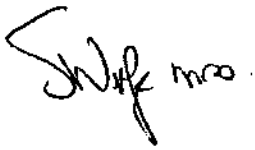
We urge HHS to provide prompt answers to these important questions. We also request an opportunity to meet with you or your representative to discuss these important issues, which have critically important implications for the safety and welfare of premature infants participating in ongoing clinical trials funded by HHS.

In closing, we renew our April 10, 2013, request that you issue a formal apology 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. Such an apology is the most critical step for redressing the ethical lapses that occurred during the conduct of this study.

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

Sincerely,

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



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

cc: The Honorable Bill Corr, Deputy Secretary, HHS
The Honorable Howard K. Koh, Assistant Secretary for Health, HHS
Dr. Francis Collins, Director, NIH

Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borror, Director, Division of Compliance Oversight, OHRP

From: Kaeser, Lisa (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 327774 - FYI - SUPPORT Study
Date: Monday, February 03, 2014 8:48:25 AM

May all your wishes be granted!

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
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From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, February 03, 2014 8:46 AM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: WF 327774 - FYI - SUPPORT Study

My bad!!!!!

I was cc:ed and forwarded it to Cathy and Rose but somehow neglected you. Maybe it was my wishful thinking that we would not need to respond...

Alan

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Monday, February 03, 2014 8:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: WF 327774 - FYI - SUPPORT Study

Hi – you may have seen this already, but just in case. We are not being asked to respond at this time.

Thanks,
Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH

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kaeserl@mail.nih.gov

From: Ott, Sandra (NIH/NICHD) [E]
Sent: Saturday, February 01, 2014 12:01 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 327774 - FYI - SUPPORT Study

Hi there!

This has been assigned to NICHD and OSP as an FYI. FYI's were also sent to DIR, DEPD, and DDSOP.

This is a follow-up letter from the Public Citizen's Health Research group regarding the SUPPORT study.

Sandy
Sandra Ott
Staff Assistant to the 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: 301-496-1849
Fax: 301-402-1104
E-mail: otts@mail.nih.gov

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
To: Brown, Crystal (NIH/NICHD) [C]; EDRMS_NO_REPLY (NIH/OD); EDRMS_NO_REPLY (NIH/OD); Ott, Sandra (NIH/NICHD) [E]; EDRMS_NO_REPLY (NIH/OD); Wood, Vandora (NIH/CIT) [C]
Subject: WF 327774 - Review FYI (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

You have received a task notification requiring your attention.

Additional instructions are included on the task form, please click the following link to open the task:

Task

Please do not reply to this email, this is an automated message.

If you have concerns please contact the NIH Help Desk at (301) 496-4357.

Work Folder Information
Work Folder: WF 327774
Process: IC FYI - WF 327774
Program Analyst: Dozier, Monica (NIH/OD) [E]
WF Subject: "Follow-up letter from the Public Citizen's Health Research group regarding the NIH-funded SUPPORT study involving extremely premature infants."
IC:NICHD
From: Wolfe, Sidney;Carome, Michael;
To: Sebelius, Kathleen;
Remarks: Assigned to NICHD and OSP as an FYI. FYI's will also be sent to DIR, DEPD, and DDSOP. Thank you:)

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Date: Saturday, February 01, 2014 12:16:01 PM
Attachments: Responses to OHRP Draft Guidance-SH.docx
ATT00001.htm

What do you think of Steve's comments (b)(5)
(b)(5)

Begin forwarded message:

From: "Hirschfeld, Steven (NIH/NICHD) [E]" <hirschfs@mail.nih.gov>
Date: January 31, 2014, 6:57:34 PM EST
To: "Carr, Sarah (NIH/OD) [E]" <CarrS@OD.NIH.GOV>, TNBC <TNBC@OD.NIH.GOV>
Cc: "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>, "Maddox, Yvonne (NIH/NICHD) [E]" <maddoxy@exchange.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Spong, Catherine (NIH/NICHD) [E]" <spongc@dir49.nichd.nih.gov>, "Zajicek, Anne (NIH/NICHD) [E]" <zajiceka@mail.nih.gov>, "Slutsman, Julia (NIH/NICHD) [E]" <slutsmaj@mail.nih.gov>
Subject: RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research

Sarah:

Attached are comments, as requested, submitted as a member of the TNBC. Thank you for coordinating this effort and for the opportunity to respond.

Kind regards,

Steven H.

Steven Hirschfeld, MD PhD
Captain, U.S. Public Health Service
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
U.S. Public Health Service Rapid Deployment Force PHS-1

31 Center Drive, MSC-2425
Bethesda, MD 20914 (for express packages use 20892)

From: Carr, Sarah (NIH/OD) [E]
Sent: Thursday, January 30, 2014 8:28 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]
Subject: RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Importance: High

All:

HHS has extended the deadline for receipt of agency comments, so we can now give you a bit more time for review and comment – until **COB Tuesday, February 4.**

Sarah

From: Carr, Sarah (NIH/OD) [E]
Sent: Wednesday, January 29, 2014 3:52 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research

Dear T-NBC:

Please find attached for your review and comment OHRP's draft guidance on research involving standard of care interventions (the term used in the draft guidance is "accepted therapies"). This CONFIDENTIAL draft guidance is, as you know, an outgrowth of the confusion and debate last year about what risks need to be considered and disclosed in standard of care studies. Further background is provided in the attached memorandum from the Assistant Secretary for Health. After OHRP considers HHS comments and makes any necessary revisions, the revised draft guidance will be reviewed by the other Common Rule agencies before being published for public comment.

We have been given less than a week to submit comments. Consequently, we will need to receive any comments you have on the document by **COB, Friday, January 31, 2014**. Your comments should be in a narrative form, citing the document page number, the number of the question, and the line number; please do not embed comments in the draft guidance document itself.

If you have any questions, please let us know.

Sarah

Sarah Carr
Office of Clinical Research and Bioethics Policy
NIH Office of Science Policy
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
301-435-6753 (direct)
301-496-9838 (main)
301-496-9839 (fax)

carrs@od.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Carr, Sarah (NIH/OD) [E]
Cc: Hirschfeld, Steven (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: Re: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Date: Friday, January 31, 2014 7:03:57 PM

Yes, they are.

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

On Jan 31, 2014, at 7:02 PM, "Carr, Sarah (NIH/OD) [E]" <CarrS@OD.NIH.GOV> wrote:

> Steve, just to clarify, these are additional NICHD comments, augmenting the ones Alan sent to Amy this afternoon?
>
> Sarah
>
> Sarah Carr
> Office of Clinical Research and Bioethics Policy
> NIH Office of Science Policy
> 6705 Rockledge Drive, Suite 750
> Bethesda, MD 20892
> 301-435-6753 (direct)
> 301-496-9838 (main)
> 301-496-9839 (fax)
> carrs@od.nih.gov
>
> ---
>
> **From:** Hirschfeld, Steven (NIH/NICHD) [E]
> **Sent:** Friday, January 31, 2014 6:58 PM
> **To:** Carr, Sarah (NIH/OD) [E]; TNBC
> **Cc:** Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Zajicek, Anne (NIH/NICHD) [E]; Slutsman, Julia (NIH/NICHD) [E]
> **Subject:** RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
>
> Sarah:
>
> Attached are comments, as requested, submitted as a member of the TNBC. Thank you for coordinating this effort and for the opportunity to respond.
>
> Kind regards,
>
> Steven H.
>
> Steven Hirschfeld, MD PhD
> Captain, U.S. Public Health Service
> Associate Director for Clinical Research
> Eunice Kennedy Shriver National Institute of Child Health and Human Development

Director
National Children's Study
Chief Medical Officer
U.S. Public Health Service Rapid Deployment Force PHS-1

31 Center Drive, MSC-2425
Bethesda, MD 20914 (for express packages use 20892)

From: Carr, Sarah (NIH/OD) [E]
Sent: Thursday, January 30, 2014 8:28 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]
Subject: RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Importance: High

All:

HHS has extended the deadline for receipt of agency comments, so we can now give you a bit more time for review and comment – until **COB Tuesday, February 4.**

Sarah

From: Carr, Sarah (NIH/OD) [E]
Sent: Wednesday, January 29, 2014 3:52 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research

Dear T-NBC:

Please find attached for your review and comment OHRP's draft guidance on research involving standard of care interventions (the term used in the draft guidance is "accepted therapies"). This CONFIDENTIAL draft guidance is, as you know, an outgrowth of the confusion and debate last year about what risks need to be considered and disclosed in standard of care studies. Further background is provided in the attached memorandum from the Assistant Secretary for Health. After OHRP considers HHS comments and makes any necessary revisions, the revised draft guidance will be reviewed by the other Common Rule agencies before being published for public comment.

We have been given less than a week to submit comments. Consequently, we will need to receive any comments you have on the document by **COB, Friday, January 31, 2014**. Your comments should be in a narrative form, citing the document page number, the number of the question, and the line number; please do not embed comments in the draft guidance document itself.

If you have any questions, please let us know.

Sarah

Sarah Carr
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NIH Office of Science Policy
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301-496-9838 (main)
301-496-9839 (fax)
carrs@od.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Patterson, Amy (NIH/OD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Date: Friday, January 31, 2014 3:00:57 PM
Attachments: NICHD Comments.docx

Dear Counselor (aka Amy) –

(b)(5)

Thanks and good luck! We will be interested in your distillation of NIH comments...

See you in court, Alan

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

From: Patterson, Amy (NIH/OD) [E]
Sent: Wednesday, January 29, 2014 3:40 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Shurin, Susan (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Bernard, Marie A. (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]
Subject: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Importance: High

Dear Colleagues:

Per discussion at our planning meeting for the standard of care research workshop, please find attached for your review and comment OHRP's CONFIDENTIAL draft guidance on research involving standard of care interventions (the term used in the guidance is "accepted therapies"). This draft guidance is, as you know, an outgrowth of the confusion and debate that arose last year about what risks need to be considered and disclosed in standard of care studies. Further background is provided in the attached memorandum from the Assistant Secretary for Health. After OHRP considers HHS comments and makes any necessary revisions, the revised draft guidance will be reviewed by the other Common Rule agencies before being published for public comment.

We have been given less than a week to submit comments. Consequently, we will need to receive any comments you have on the document by **COB, Friday, January 31, 2014**. Your

comments should be in a narrative form, citing the document page number, the number of the question, and the line number; please do not embed comments in the draft guidance document itself.

We will also be circulating the draft to the ICs through T-NBC. We will notify your T-NBC representative that we also have sought your input and ask them to coordinate with you.

If you have any questions, please let me know.

Amy

Amy P. Patterson, M.D.
Associate Director for Science Policy, NIH

Page 0998 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0999 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Bock, Robert (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Embargoed JAMA News Releases
Date: Friday, January 31, 2014 8:38:34 AM

Is this study in your portfolio?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, January 30, 2014 5:54 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Re: Embargoed JAMA News Releases

Yes she is and is PI of Penn/CHOp site

Rosemary D Higgins, MD

Sent from my iPhone

On Jan 30, 2014, at 5:29 PM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

FYI, see the item on ROP. Barbara Schmidt is in the NRN, isn't she?

From: The JAMA Network [mailto:reply-119756@hq.ama-assn.org]
Sent: Thursday, January 30, 2014 5:06 PM
To: Bock, Robert (NIH/NICHD) [E]
Subject: Embargoed JAMA News Releases

News Releases From *JAMA*

Embargoed for Release: 3:00 p.m. CT Tuesday, February 4, 2014

Pattern of Higher Blood Pressure in Early Adulthood Helps Predict Risk of Atherosclerosis in Middle-Age

Non-Invasive Measure of Heart Tissue Scarring May Be Useful For Determining Patients Most Suitable For Procedure for Irregular Heart Beat

Pre-Term Infants with Severe Retinopathy More Likely to Have Non-Visual Disabilities at Age 5

Viewpoint in This Issue of *JAMA*

Patient-Centered and Practical Application of New High Cholesterol Guidelines to Prevent Cardiovascular Disease

TV Note – This week's ***JAMA* Report video** is on how high blood pressure in early adulthood can help predict risk of atherosclerosis in middle-age. The report will be fed Tuesday, February 4, from 9:00 - 9:15 a.m. ET and 2:00 - 2:15 p.m. ET, on Galaxy 19, Transponder 12 (C band), lower 18 mhz HD; downlink frequency: 3931; horizontal symbol rate 12.8 FEC ¾ QPSK. For more information, call 312/464-JAMA.

There will also be a **digital news release** available for this study, including the *JAMA* Report video, embedded and downloadable video, audio files, text, documents, and related links. This content will be available at 3 p.m. CT Tuesday, February 4 at this link.

The *JAMA* Report video is also available on **Pathfire** every Tuesday, in VNF Provider A. Please look for the *JAMA* Report tab.

EMBARGOED FOR RELEASE: 3 P.M. (CT) TUESDAY, FEBRUARY 4, 2014

Media Advisory: To contact Norrina B. Allen, Ph.D., M.P.H., call Marla Paul at 312-503-8928 or email marla-paul@northwestern.edu. To contact editorial co-author George L. Bakris, M.D., call John Easton at 773-795-5225 or email john.easton@uchospitals.edu.

Pattern of Higher Blood Pressure in Early Adulthood Helps Predict Risk of Atherosclerosis in Middle-Age

Chicago – In an analysis of blood pressure patterns over a 25-year span from young adulthood to middle age, individuals who exhibited elevated and increasing blood pressure levels throughout this time period had greater odds of having higher measures of coronary artery calcification (a measure of coronary artery atherosclerosis), according to a study in the February 5 issue of *JAMA*.

"Blood pressure (BP) represents a major modifiable risk factor for cardiovascular disease (CVD). Current risk prediction models take into account BP level only at the time of risk prediction, usually in middle or older age, and do not consider the potential effect of BP levels earlier in life or the changes in BP levels over time," according to background information in the article.

Norrina B. Allen, Ph.D., M.P.H., of the Feinberg School of Medicine, Northwestern University, Chicago, and colleagues identified common BP trajectories (patterns) throughout early adulthood and sought to determine their association with the presence of coronary artery

calcification (CAC) during middle age among 4,681 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study. The participants were black and white men and women, 18 to 30 years of age at the beginning of the study in 1985-1986. Data were collected through 25 years of follow-up on systolic BP, diastolic BP, and mid-BP (calculated as [SBP+DBP]/2, an important marker of coronary heart disease risk among younger populations). The primary measured outcome for the study was a higher level of coronary artery calcification detected by computed tomography scan.

The researchers identified 5 distinct trajectories in mid-BP from young adulthood to middle age: 22 percent of participants maintained low BP throughout follow-up (low-stable group); 42 percent had moderate BP levels (moderate-stable group); 12 percent started with moderate BP levels which increased at an average age of 35 years (moderate-increasing group); 19 percent had relatively elevated BP levels throughout (elevated-stable group); and 5 percent started with elevated BP's which increased during follow-up (elevated-increasing group).

The prevalence of a high CAC score varied from 4 percent in the low-stable BP trajectory group to 25 percent in the elevated-increasing BP trajectory group. Participants who exhibited elevated BP levels throughout the study period and those who had increases in BP levels over this time had larger odds of having a high CAC score.

"Although BP has been a well-known risk factor for CVD for decades, these findings suggest that an individual's long-term patterns of change in BP starting in early adulthood may provide additional information about his or her risk of development of coronary calcium," the authors write. "Additional research is needed to examine the utility of specific BP trajectories in risk prediction for clinical CVD events and to explore the effect of lifestyle modification, treatment, and timing of intervention on lifetime trajectories in BP and outcomes." (doi:10.1001/jama.2013.285122; Available pre-embargo to the media at http://media.jamanetwork.com)

Editor's Note: Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, funding and support, etc.

There will also be a **digital news release** available for this study, including the *JAMA* Report video, embedded and downloadable video, audio files, text, documents, and related links. This content will be available at 3 p.m. CT Tuesday, February 4 at this link.

Editorial: Early Patterns of Blood Pressure Change and Future Coronary Atherosclerosis

Pantelis A. Sarafidis, M.D., M.Sc., Ph.D., of Aristotle University of Thessaloniki School of

Medicine, Thessaloniki, Greece, and George L. Bakris, M.D., of University of Chicago Medicine, comment on the findings of this study in an accompanying editorial.

"The study by Allen and colleagues presents a novel approach for assessing coronary heart disease and CVD risk, and the data offer an important perspective to support a preventive approach to reduce coronary heart disease risk by demonstrating the existence of widely different BP trajectories ranging from young adulthood through middle age … Further research is warranted to explore the associations of BP trajectories with development of advancing chronic kidney disease and heart failure and to provide novel tools for risk prediction to guide interventions for BP lowering in everyday practice."
(doi:10.1001/jama.2013.285123; Available pre-embargo to the media at http://media.jamanetwork.com)

Editor's Note: Please see the article for additional information, including financial disclosures, funding and support, etc.

# # #

EMBARGOED FOR RELEASE: 3 P.M. (CT) TUESDAY, FEBRUARY 4, 2014
Media Advisory: To contact Nassir F. Marrouche, M.D., call Phil Sahm at 801-581-2517 or email phil.sahm@hsc.utah.edu.

Non-Invasive Measure of Heart Tissue Scarring May Be Useful For Determining Patients Most Suitable For Procedure for Irregular Heart Beat

Chicago – Scarring of tissue in the upper chamber of the heart (atrium) was associated with recurrent rhythm disorder after treatment, according to a study in the February 5 issue of *JAMA*.

Left atrial fibrosis (formation of scar tissue in the heart) is prominent in patients with atrial fibrillation (AF), according to background information in the article. Extensive atrial tissue fibrosis identified by delayed enhancement magnetic resonance imaging (MRI) has been associated with poor outcomes of AF catheter ablation, a procedure in which electrical energy is used to treat AF.

Nassir F. Marrouche, M.D., of the University of Utah School of Medicine, Salt Lake City, and colleagues conducted a study to characterize the feasibility of measuring atrial scar tissue using delayed enhancement magnetic resonance imaging (MRI), and assessed the association between the amount of scar tissue and response to ablation. The study was conducted between August 2010 and August 2011 at 15 centers in the United States, Europe, and Australia;

delayed enhancement MRI images were obtained up to 30 days before ablation.

There were 329 patients enrolled in the study; 57 patients (17.3 percent) were excluded due to poor MRI quality. The researchers found that the incidence of recurrence increased with the amount of scarring, from 15.3 percent recurrence at day 325 with less than 10 percent scarring of the atrial wall to 51.1 percent recurrence for 30 percent or greater scarring.

The authors write that this study demonstrates the feasibility and potential clinical value of using delayed enhancement MRI in the management of patients with AF considered for ablation. "In current practice, criteria for selecting good candidates for AF ablation are limited." They add that the amount of left atrial wall fibrosis estimated by delayed enhancement MRI has the potential to offer a noninvasive and effective method for determining which patients with AF are likely to benefit from ablation while avoiding procedures in patients likely to have arrhythmia recurrence.
(doi:10.1001/jama.2014.3; Available pre-embargo to the media at http://media.jamanetwork.com)

Editor's Note: The Comprehensive Arrhythmia and Research Management Center at the University of Utah provided funding for the study. The George S. and Dolores Dore Eccles Foundation funded part of this study. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, etc.

# # #

EMBARGOED FOR RELEASE: 3 P.M. (CT) TUESDAY, FEBRUARY 4, 2014
Media Advisory: To contact Barbara Schmidt, M.D., M.Sc., call Alison Fraser at 267-426-6054 or email FraserA1@email.chop.edu.

Pre-Term Infants with Severe Retinopathy More Likely to Have Non-Visual Disabilities at Age 5

Chicago – In a group of very low-birth-weight infants, severe retinopathy of prematurity was associated with nonvisual disabilities at age 5 years, according to a study in the February 5 issue of *JAMA*.

Severe retinopathy (disease of the retina) of prematurity occurs in premature infants treated with excessive concentrations of oxygen and is a serious complication of neonatal intensive care for preterm infants. "Although the incidence of severe retinopathy has increased since the late 1980s, blindness caused by retinopathy has become rare in developed countries. Consequently, clinicians and parents may conclude that severe retinopathy is no longer

associated with childhood impairments," according to background information in the article.

Barbara Schmidt, M.D., M.Sc., of Children's Hospital of Philadelphia, and colleagues investigated whether infants with severe retinopathy retain an increased risk of nonvisual disabilities compared with those without severe retinopathy. This analysis (using data from a trial, Caffeine for Apnea of Prematurity), included infants with birth weights between 1.1 and 2.8 lbs. who were born between 1999 and 2004 and followed-up at age 5 years (2005-2011).

Of 1,815 eligible infants, 1,582 (87 percent) had complete (n = 1,523) or partial (n = 59) 5-year assessments. Of 95 with severe retinopathy, 40 percent had at least 1 nonvisual disability at 5 years compared with 16 percent of children without it. Fourteen of 94 children (15 percent) with and 36 of 1,487 children (2.4 percent) without severe retinopathy had more than 1 nonvisual disability. Motor impairment, cognitive impairment, and severe hearing loss were 3 to 4 times more common in children with severe retinopathy than those without severe retinopathy.

The authors write that these findings may help improve the ability to counsel parents and to select high-risk infants for long-term follow-up.

"Severe retinopathy of prematurity remains an adverse outcome of neonatal intensive care with poor prognosis for child development, although blindness can mostly be prevented by timely retinal therapy."

(doi:10.1001/jama.282153; Available pre-embargo to the media at http://media.jamanetwork.com)

Editor's Note: The Caffeine for Apnea of Prematurity trial was supported by a grant from the Canadian Institutes of Health Research and by the National Health and Medical Research Council of Australia. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

# # #

Viewpoint in This Issue of *JAMA*

(Available pre-embargo at http://media.jamanetwork.com/)

Patient-Centered and Practical Application of New High Cholesterol Guidelines to Prevent Cardiovascular Disease

# # #

From:	Barbara Stoll
To:	Truog, William (MD)
Cc:	Nelin, Leif; " <adas@rtl.org>, " "Kendrick@ndb-mr3.cc.emory.edu; in StatEpi; Edward (Pediatrics)"" <edward-bell@uiowa.edu>, ""; Higgins, Rosemary (NIH/NICHD) [E]; " <alaptook@wihri.org>, " Sanchez@ndb-mr3.cc.emory.edu; Pablo <Pablo.Sanchez@nationwidechildrens.org>, ; "Krisa Van Meurs"; "" <mcw3@po.cwru.edu>, " Truog@ndb-mr3.cc.emory.edu; MD
Subject:	Re: FW: Your Manuscript # 20131681R1 submitted to JPediatr
Date:	Thursday, January 30, 2014 3:43:36 PM

Agree with Wally BUT also agree with your thought about emphazing the first message in the paper-- change in use of iNO
Regards

BJS**"Truog, William (MD)" <wtruog@cmh.edu> writes:**

Disappointing news.
Sorry, my revisions did not buy us a place in the bright sun of J. Peds.

Several options have occurred to me for going forward. They include: emphasizing the first message of the paper even more and deemphasizing the second (propensity analysis).
The first message was the change in usage of INO before/after the NRN conference. We could freshen up this message by including the CY 2012 data, which I presume shows the same pattern as the 2011 data--greatly diminished use. Then, instead of trying to tease out characteristics of the INO recipients, I suggest we limit the second analysis to infants > 7 days as before, only for the 2011-2012 group if agreeable, and simply show that they were small and quite sick based on usual outcomes of death or BPD. We should forget the analysis of the infants treated in the pre-conference era, and I still think we should limit the analysis to those treated > 7 days, and the limitations imposed on the analysis by the lack of knowledge of duration, dose, baseline starting vent support etc. would then be less crucial.
I am thinking of J. Perinatology as the second choice. If all or most all agree, I will proceed.
Reminder: this was presented at PAS only 9 months ago, so it may still be timely, but time is short.
Bill T.
-----Original Message-----
From:
"eesjpeds.0a6eff3.fe9a0cec@eesmail.elsevier.com [mailto:eesjpeds.0a6eff3.fe9a0cec@eesmail.elsevier.com]On Behalf Of Journal Office
Sent: Thursday, January 30, 2014 9:40 AM
To: Truog, William (MD)
Subject: Your Manuscript # 20131681R1 submitted to JPediatr

Ref.: Ms. No. 20131681R1
Inhaled Nitric Oxide Usage in Preterm Infants in the NICHD Neonatal Research Network: Inter-site Variation and Propensity Evaluation
The Journal of Pediatrics

Dear Dr. Truog,

Thank you for revising and resubmitting your manuscript. The Editors appreciate your efforts to satisfy the concerns of the reviewers and the requirements of The Journal of Pediatrics. We are very sorry to inform you that we will not be able to publish your manuscript because the consensus of the Editors was that it did not attain high enough priority for publication in the Journal.

Some themes were consistent among the reviewers. The results are mainly descriptive, and key data to make the description more meaningful is missing (e.g. indication for starting NO, enough data to compare patients treated with iNO across epochs). Lacking these data, the conclusion as stated in the abstract (that iNO was associated with more severe outcomes) may be overstated based on the robustness of the data from which this conclusion was

drawn. Specifically, the analysis includes babies born across both epochs, and thus the findings of the propensity analysis do not reflect any post-consensus shifts in practice. More robust meta-analysis performed on data from randomized, controlled trials have not replicated this finding. Additionally, one issue consistently raised by the reviewers was confusion regarding the propensity analysis. The text says that "Step 1" (probability of receiving iNO as defined in the Methods) is reported in Table 2 (however, it is actually Table 2A).
Furthermore, Table 2A is titled "Propensity analysis of severe BPD or Death," which is described in the Methods as Step 2. It appears that no table is present for Step 1, although the text includes description of this data.

Because of space limitations, we are able to accept <20% of submitted manuscripts. When establishing a priority for each manuscript and in reaching an editorial decision, the Editors consider the quality of the manuscript, the novelty and importance of the observation, and appropriateness for our readership. Because we have many meritorious manuscripts and very strict page limitations from the publisher, we are forced to make some difficult decisions. We hope this process was helpful in improving your manuscript for submission to another journal. Further comments from Reviewer 2 are appended below.

Again, thank you for the submission and your support of The Journal of Pediatrics. Our best wishes for your success in publishing your paper elsewhere.

Sincerely,

Clyde J. Wright, MD
Associate Editor

/rlf

Reviewer 2's Comments:

I appreciate the edits that have been made to the manuscript. The objectives and results are more coherent now. I still would recommend changing the title of Table 2 to "Propensity Analysis for Use of Nitric Oxide". This would make it clear that the odds ratios provided refer to the likelihood that nitric was used, not the likelihood of BPD/death. On page 10 of the discussion, I would recommend changing the use of iNO "...failed to show improvement..." to the use of iNO "...was not associated with improvement" as the first implies more causality than allowed for by the analysis.

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair
Department of Pediatrics, Emory University School of Medicine
Director, The Pediatric Center of Emory and Children's Healthcare of Atlanta
President, Emory-Children's Center

1760 Haygood Drive
Atlanta, GA 30322
Office: 404-727-2456 Fax: 404-727-5737
bstoll@emory.edu

Confidential - Please do not forward.

From: Maddox, Yvonne (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Confidential OHRP Draft Guidance_AcceptedTherapiesFAQs_Jan22.docx
Date: Thursday, January 30, 2014 12:01:31 PM
Attachments: Confidential OHRP Draft Guidance_AcceptedTherapiesFAQs_Jan22.docx

This document is (b)(5) (b)(5) I don't think (b)(5) (b)(5) I got through it, but with difficulty. Made a couple of notes. Seems as if there needs to be more Q and A, but not sure of what they should be. Thanks for sharing.

Page 1011 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1012 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1013 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1014 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1015 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1016 of 2000

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Page 1017 of 2000

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Page 1018 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1019 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1020 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Hirschfeld, Steven (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rogers, Christine (NIH/NICHD) [E]
Subject: FW: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Date: Wednesday, January 29, 2014 3:46:43 PM
Attachments: Confidential OHRP Draft Guidance_AcceptedTherapiesFAQs_Jan22.docx
ASH Memo.pdf
Importance: High

1) Please treat as close hold confidential. Do not send further.
2) Please send me any thoughts you have by noon Friday (sorry). Please follow format requested below.

Thanks, Alan

From: Patterson, Amy (NIH/OD) [E]
Sent: Wednesday, January 29, 2014 3:40 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Shurin, Susan (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Bernard, Marie A. (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Miner, Lauren (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]
Subject: URGENT: Please Review OHRP Draft Guidance on Standard of Care Research
Importance: High

Dear Colleagues:

Per discussion at our planning meeting for the standard of care research workshop, please find attached for your review and comment OHRP's CONFIDENTIAL draft guidance on research involving standard of care interventions (the term used in the guidance is "accepted therapies"). This draft guidance is, as you know, an outgrowth of the confusion and debate that arose last year about what risks need to be considered and disclosed in standard of care studies. Further background is provided in the attached memorandum from the Assistant Secretary for Health. After OHRP considers HHS comments and makes any necessary revisions, the revised draft guidance will be reviewed by the other Common Rule agencies before being published for public comment.

We have been given less than a week to submit comments. Consequently, we will need to receive any comments you have on the document by **COB, Friday, January 31, 2014**. Your comments should be in a narrative form, citing the document page number, the number of the question, and the line number; please do not embed comments in the draft guidance document itself.

We will also be circulating the draft to the ICs through T-NBC. We will notify your T-NBC representative that we also have sought your input and ask them to coordinate with you.

If you have any questions, please let me know.

Amy

Amy P. Patterson, M.D.
Associate Director for Science Policy, NIH

From: Juliann DiFiore
To: Pickett, James
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele; Auman, Jeanette O.; Gantz, Marie; Zaterka-Baxter, Kristin
Subject: Re: IH and mortality data
Date: Tuesday, January 28, 2014 3:04:44 PM
Attachments: Missing data for 1st wks of monitoring query sent back to RTI.xlsx

---

Hi James,

I was wondering if you had looked at the list of missing infants yet?

Also, I was rather surprised to see that about 20% of the infants on the DVD have missing data during the first week of monitoring.
I have attached a spreadsheet with the individual data for the infants in question. Some of the missing data could be explained by token errors when converting the files. I have removed those from the list. Others had either the first download missing or questionable starting dates as categorized by the following:

1) the first download missing - Please verify that you do not have the missing files
2) the first file contained old data followed by empty days then a delayed start date for correct infant - Please verify 1st day of monitoring
3) No explanation. - Please, again, verify 1st day of monitoring.

Thanks!

Julie

On 1/9/2014 5:10 PM, Juliann DiFiore wrote:
> Sounds good.
>
> Regards,
>
> Julie
>
> On 1/9/2014 5:08 PM, Pickett, James wrote:
>> Hi Julie,
>> Thanks, I hope your year is off to a glowing start.
>> I will be happy to review your data and see what additional details I
>> can provide. I won't be able to review immediately as I am currently
>> on deadline to complete activities for the INS3 trial that will be
>> launching shortly. I am putting this on my schedule to review on
>> Monday (1/13) and respond asap with results.
>>
>> J
>>
>> James Pickett - Res. Programmer / Analyst - Clinical Research
>> Informatics * (919) 541-1253 * Haynes 399L *
>> japickett@rti.org
>> RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research
>> Triangle Park, NC 27709-2194
>>
>>

>> -----Original Message-----
>> From: Juliann DiFiore [mailto:jmd3@case.edu]
>> Sent: Thursday, January 09, 2014 1:51 PM
>> To: Pickett, James
>> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele;
>> Auman, Jeanette O.; Gantz, Marie; Zaterka-Baxter, Kristin
>> Subject: Re: IH and mortality data
>>
>> Hi James,
>>
>> Happy New Year!
>>
>> I am following up on the missing infant data that we discussed before
>> the holidays. I have attached a spreadsheet which shows the specific
>> infants that were not on the DVD. This list was extrapolated from the
>> zipped raw waveform files on the DVD and the Excel file
>> ihdatarequest_forJulie.xlsx. In summary, there are a total of 63
>> infants missing with the following criteria:
>> 1. 24 died.
>>   a. 18 of the infants died within 1-5 days of life. Not
>> expecting any data from those.
>>   b. 6 of the infants who died had >1wk of data (8-20 days). I
>> was hoping we could find those infants as they would be useable for
>> this analysis.
>> 2. 39 infants survived with all infants having 50+ days of data
>> (52-291 days). Can you please look this list over and verify that you
>> do not have these infants?
>>
>> Lastly, in the Excel files, ihdatarequest20140107.xlsx and
>> ihdatarequest_forJulie.xlsx infant (b)(6) is missing. (This infant
>> is included in the raw waveform files on the DVD) Would you please
>> send me the information for that infant?
>>
>> Thanks!
>>
>> Julie
>>
>>
>> with the the On 12/23/2013 3:23 PM, Pickett, James wrote:
>>> Hello Juliann,
>>> No, there were no additional discs to send. You have all the data
>>> that is available. With regards to infant count vs. recording
>>> availability, not all infants will have recordings. For example,
>>> there are 28 infants on that subject listing that met status (death)
>>> at day of life 1 that we are unlikely to have any oximeter data for
>>> -- I have verified that is the case for 3 via spot check. That one
>>> example covers approximately 50% of your missing data. I will be
>>> more than happy to work with you after the holidays to assist you
>>> with the remaining subjects in question.
>>>
>>> Regards,
>>>
>>> J
>>>
>>> James Pickett - Res. Programmer / Analyst - Clinical Research
>>> Informatics * (919) 541-1253 * Haynes 399L *
>>> japickett@rti.org

>>> RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research
>>> Triangle Park, NC 27709-2194
>>>
>>>
>>> -----Original Message-----
>>> From: Juliann DiFiore [mailto:jmd3@case.edu]
>>> Sent: Monday, December 23, 2013 2:47 PM
>>> To: Pickett, James
>>> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele
>>> Subject: IH and mortality data
>>>
>>> Hello James,
>>>
>>> I have been working through the data sent on the DVD for the IH and
>>> mortality secondary study. I noticed that there are infants missing
>>> in the zipped files. There are 1316 infants listed in the
>>> IHdatarequest.xlsx spreadsheet but only 1255 zipped files are
>>> enclosed on the DVD. The missing infants seem to be random by site.
>>> (ie missing per site: 4-site J, 8-site I, 1- site M, 5-site F...).
>>> Was there a 2nd DVD that was not enclosed in the envelope you sent
>>> in september?
>>>
>>> Regards,
>>>
>>> Julie
>>>
>>> --
>>> 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
>>> ----------
>>> The enclosed information is STRICTLY CONFIDENTIAL and is intended
>>> for the use of this address only.
>>> Case Western Reserve University and University Hospitals of
>>> Cleveland and its affiliates disclaim any responsibility for
>>> unauthorized disclosure of this information to anyone other than the
>>> addressee.
>>>
>>> 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 regulations (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
>>> whome it pertains, or as otherwise permitted.
>>>
>>>
>>
>> --
>> 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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>> email. Federal regulations (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 whome it
>> pertains, or as otherwise permitted.
>>
>
>

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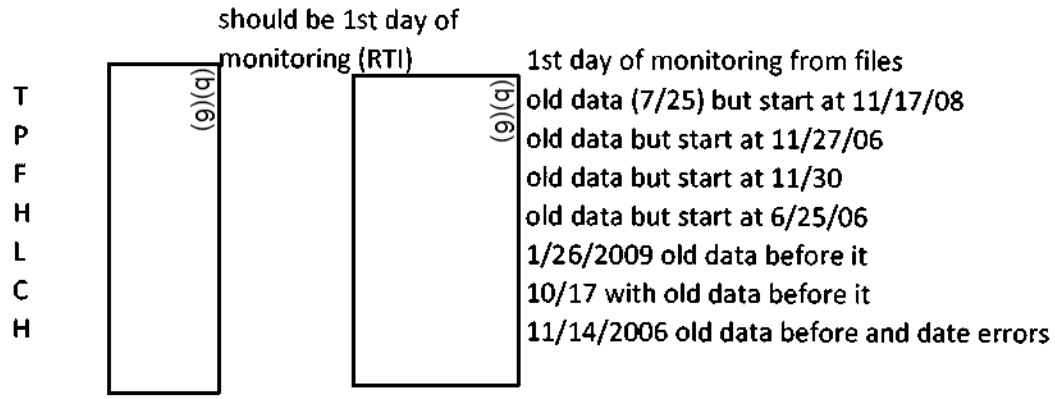
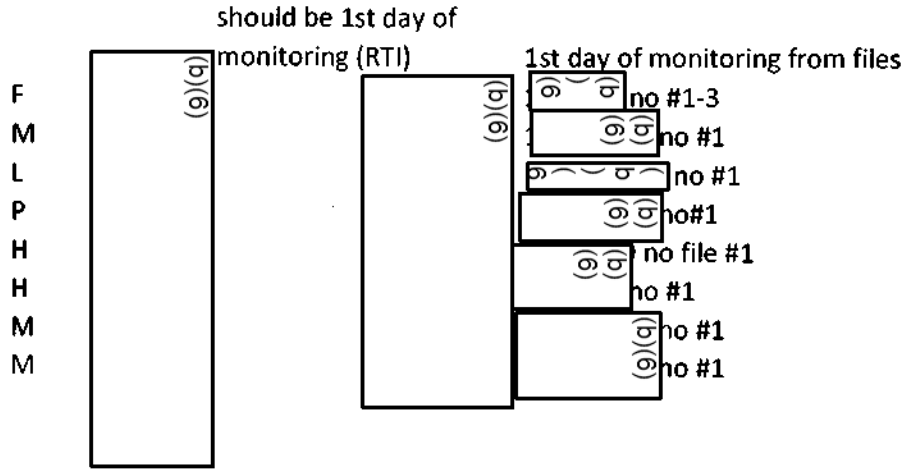
Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V.) test results, A.I.Ds-related conditions
alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulations (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit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

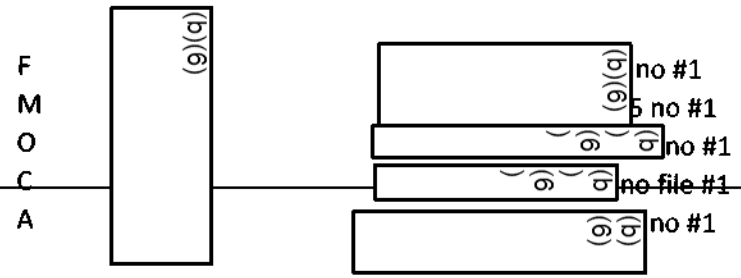
Infants with OLD DATA but still Started late



Infants with Missing File #1



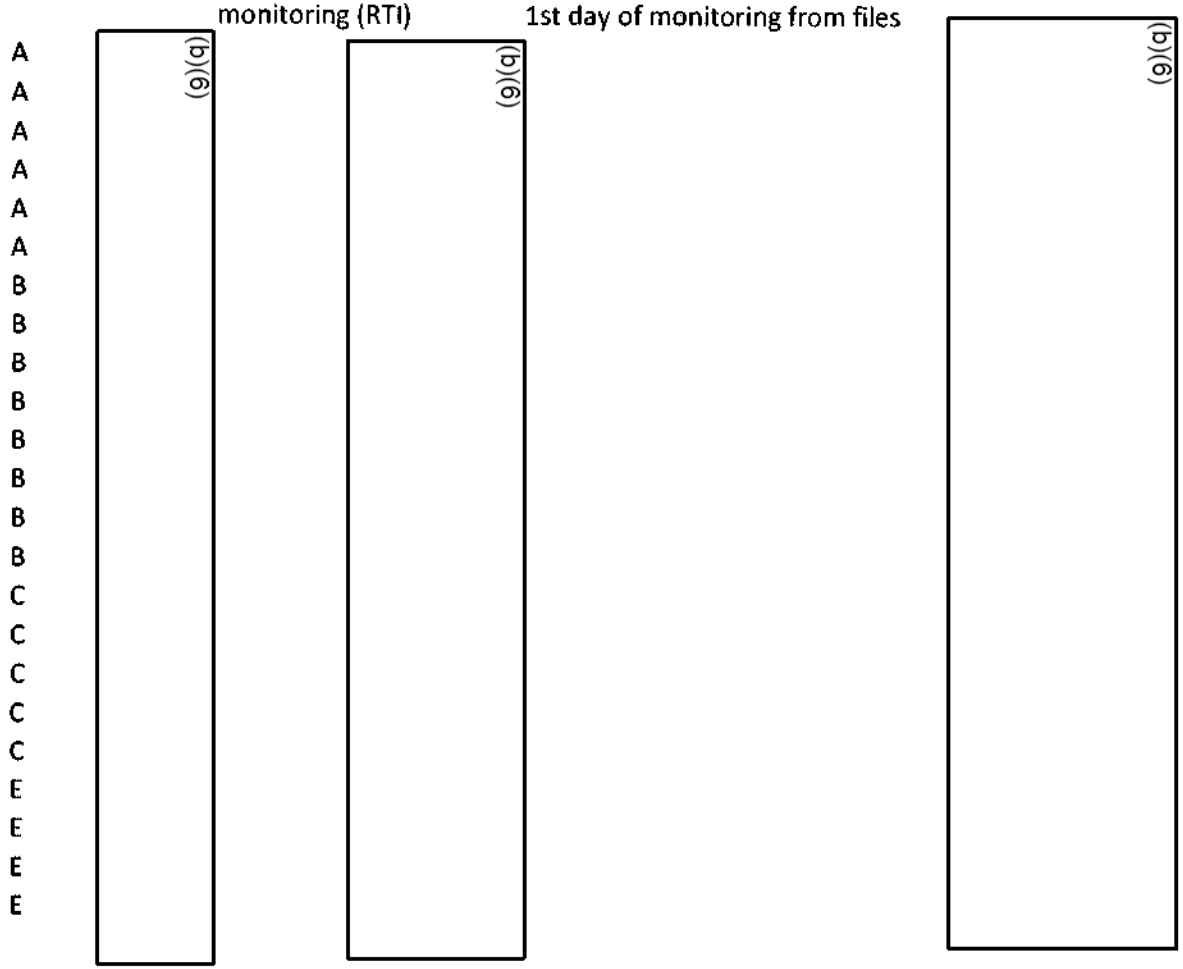
4-01027



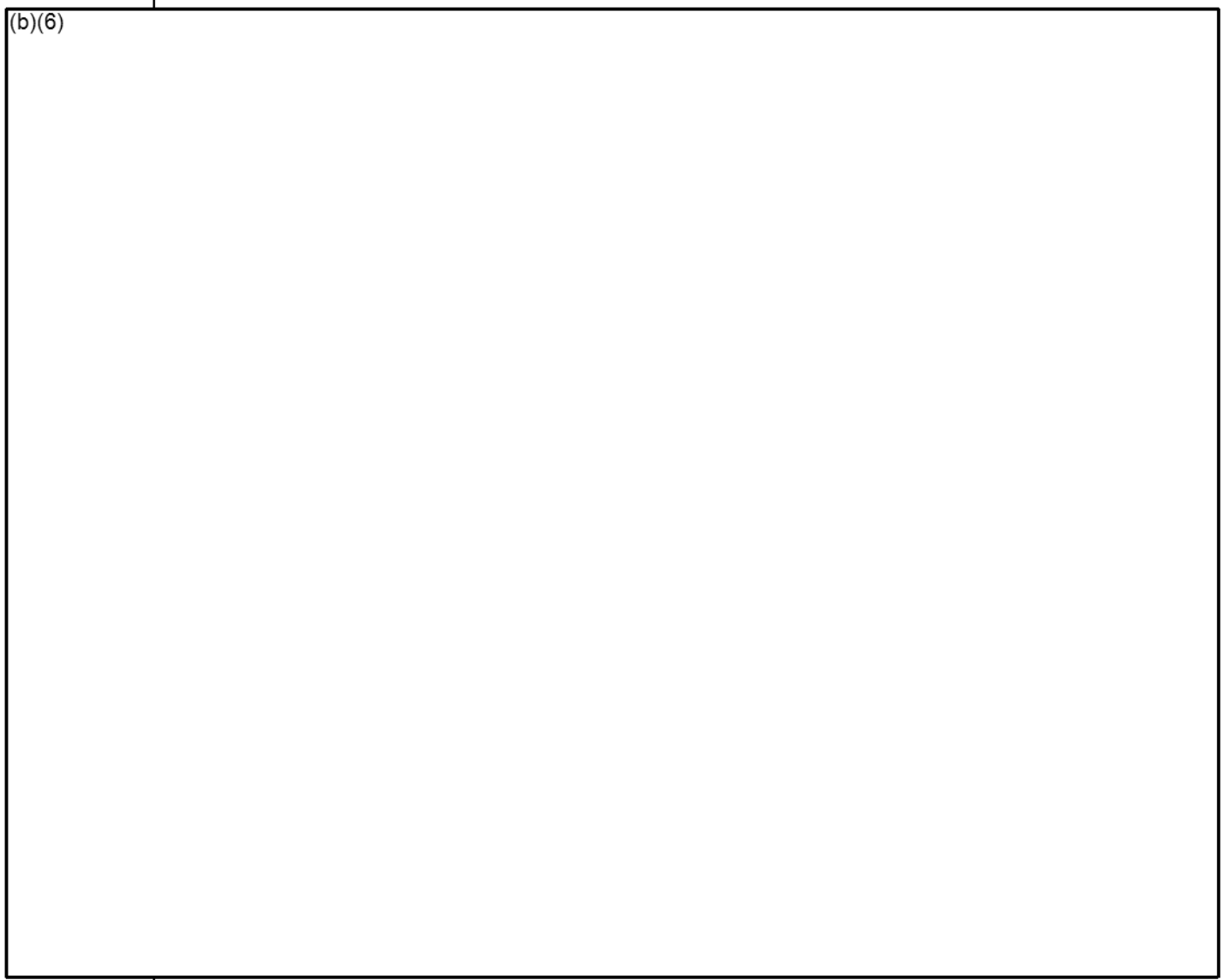
Infants with No Explanation

should be 1st day of monitoring (RTI)

1st day of monitoring from files

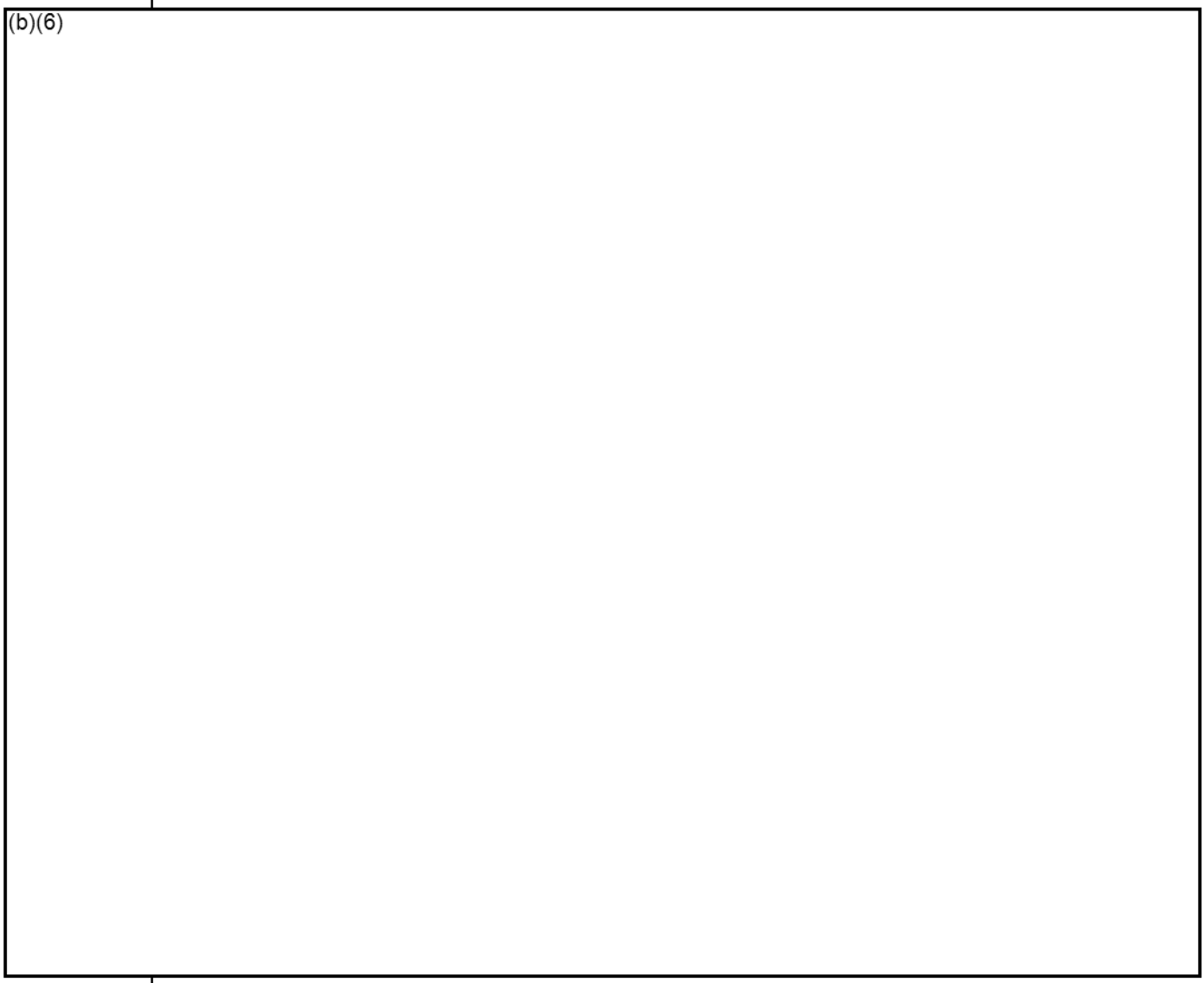


(b)(6)

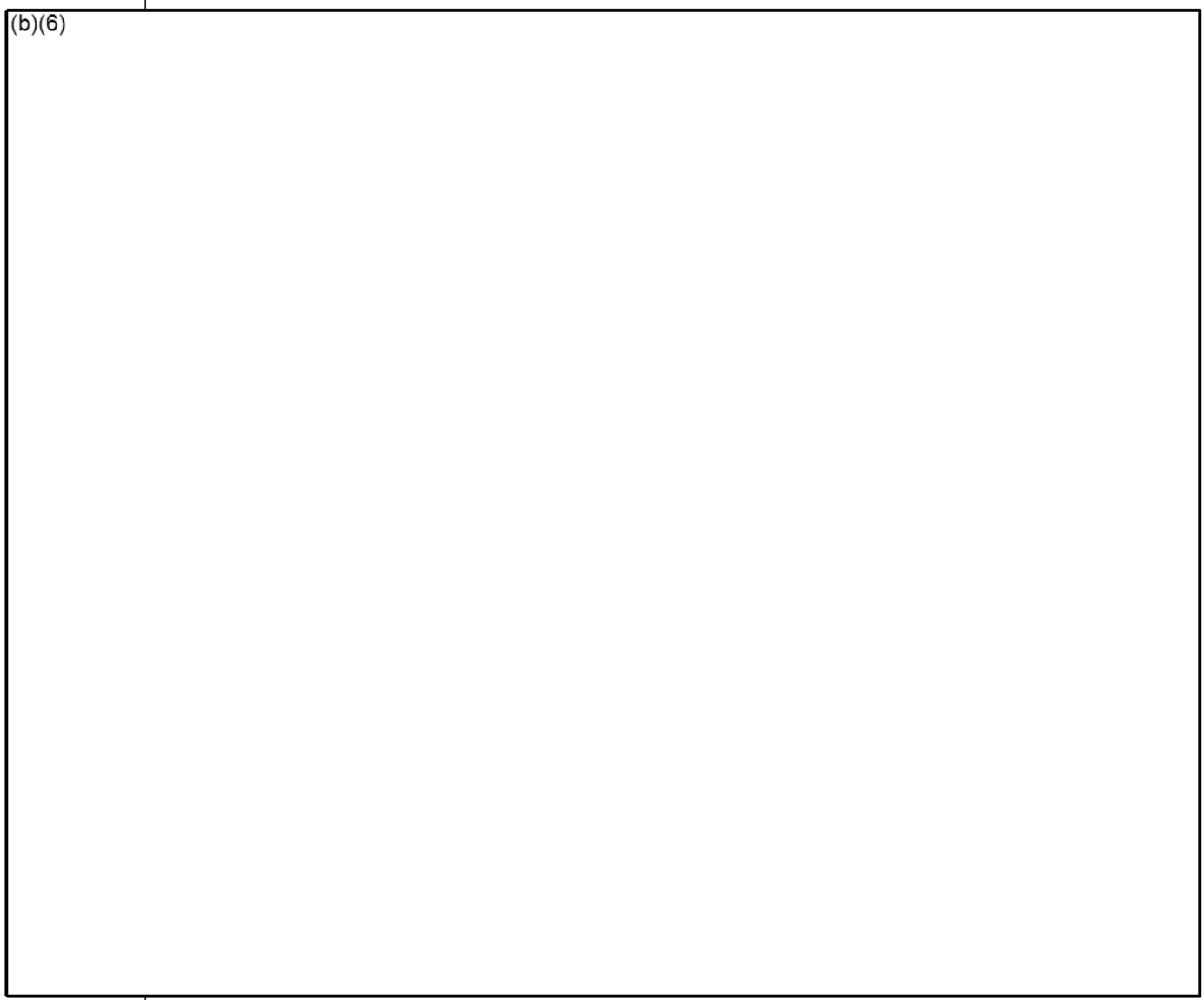


E E E E E E E E E E E E E E E E E F F F F F G G G G G H H H H H H H

(b)(6)



(b)(6)



L M M O O P P P P P P P P P P P P Q Q Q Q Q S S S S T T T T T T T

the infants below are missing the first days of monitoring and are split into the following 3 categories:

1. The first file contains old data followed by a string of empty days then the first day of monitoring for the correct infant. However, the first day of monitoring is off. Are 1st days of monitoring from RTI correct?

2. Infants with missing download file #1. Does RTI have it?

3. No explanation. Processed with both Textrac and ProcessPulseOxData. One or 2 infants have token error but not at beginning of file. Are 1st days of monitoring correct from RTI?

missing days
4
4
4
13
6
3
50
22
20
4
6
17
9
5
8
3
8
14
5
2
8
5
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21
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13
11
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5
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11
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8
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8
6
6
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42
30
17
40
17
8
11

8
41
2
9
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11
38
43
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3
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9
5
4
25
8
7
12
10
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6
19
13
14
11
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5
5
11
17
17
9

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Fwd: Follow-up letter regarding the SUPPORT study
Date: Monday, January 27, 2014 8:21:27 AM
Attachments: 140127_Letter to HHS Secretary re Monitoring of SUPPORT Trial_FINAL.pdf
ATT00001.htm

FYI. No reply necessary.

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

Begin forwarded message:

From: Michael Carome <mcarome@citizen.org>
Date: January 27, 2014 at 6:48:35 AM EST
To: "Kathleen.Sebelius@hhs.gov" <Kathleen.Sebelius@hhs.gov>
Cc: "'Bill.Corr@hhs.gov'" <Bill.Corr@hhs.gov>, "Howard.Koh@hhs.gov" <Howard.Koh@hhs.gov>, "jerry.menikoff@hhs.gov" <jerry.menikoff@hhs.gov>, "kristina.borror@hhs.gov" <kristina.borror@hhs.gov>, "francis.collins@nih.hhs.gov" <francis.collins@nih.hhs.gov>, "Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov)" <guttmach@mail.nih.gov>
Subject: Follow-up letter regarding the SUPPORT study

Dear Secretary Sebelius:

Attached please find a follow-up letter from Public Citizen's Health Research Group regarding the NIH-funded SUPPORT study involving extremely premature infants. 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.
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

From: Collins, Francis (NIH/OD) [E]
To: Hudson, Kathy (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Subject: RE: SUPPORT case dismissed against investigators and IRB
Date: Friday, January 24, 2014 5:04:42 AM

Wow, this is great!

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, January 23, 2014 12:09 PM
To: Bonham, Valerie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Subject: Re: SUPPORT case dismissed against investigators and IRB

Fantastic!!!!

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

On Jan 23, 2014, at 11:03 AM, "Bonham, Valerie (NIH/OD) [E]" <bonhamva@od.nih.gov> wrote:

Court Dismisses Claims Against IRB, PI
In SUPPORT Trial Wrongful Death Suit

Posted January 23, 2014, 11:38 A.M. ET

By John T. Aquino

Class action plaintiffs alleging their children were injured during participation in a clinical research study on oxygen therapy for premature infants failed to meet the heightened pleading standard for malpractice claims, a federal district court ruled Jan. 22 (Looney v. Moore, N.D. Ala., No. 2:13-cv-00733-KOB, dismissed in part 1/22/14).

The U.S. District Court for the Northern District of Alabama dismissed negligence and lack of informed consent claims against the study's principal investigator, Dr. Waldemar A. Carlo, and individual members of the institutional review board and the wrongful death claim against all defendants.

The claims were dismissed without prejudice, which allows the plaintiffs to re-plead, although the court warned them to "take special care when re-pleading the specific, malpractice-type claims" in their complaint.

The court denied the motions to dismiss the product liability and negligence claims against Masimo Corp., which had designed the pulse oximeter used in the study to monitor the infants' blood oxygen saturation and which argued that the claims against it were preempted by federal statutes.

The premature infants were enrolled in the Surfactant, Positive Pressure and Oxygenation Randomized Trial (SUPPORT) at the University of Alabama-Birmingham, which tested two oxygen treatments for chronic lung disease. The complaint alleged that two children of the plaintiffs who initially brought the suit were permanently impaired and one died as a result of the study (12 MRLR 345, 5/15/13).

The court agreed with the IRB defendants and Carlo that the plaintiffs' arguments made it "impossible to discern exactly what illegal conduct Plaintiffs are alleging for each particular action" and that, since the negligence and lack of informed consent allegations were malpractice claims, the plaintiffs failed to provide the detailed specification and factual description of each act and omission alleged required under the Alabama Medical Liability Act. The wrongful death claim was barred by the two-year statute of limitation, the court concluded.

The opinion is at
http://www.bloomberglaw.com/public/document/BILLY_RYAN_LOONEY_ET_AL_Plaintiffs_v_SHEILA_D_MOORE_ET_AL_Defenda/1

Valerie Bonham, J.D.
Senior Attorney
Office of the General Counsel
Public Health Division
National Institutes of Health
Building 31, Room 2B-50
31 Center Drive
Bethesda, MD 20892
301-451-8351 (direct)
301-496-6043 (main)

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT case dismissed against investigators and IRB
Date: Thursday, January 23, 2014 2:43:10 PM

Ok. I did give more detail below.

On Jan 23, 2014, at 1:35 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Change from

- (b)(5)

To

- (b)(5)

If someone wants the details, they can read the court decision.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, January 23, 2014 1:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT case dismissed against investigators and IRB

Hi Rose I inserted the comments in yellow

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, January 23, 2014 12:11 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: Fwd: SUPPORT case dismissed against investigators and IRB

FYI

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

From: "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>
Date: January 23, 2014 at 12:08:35 PM EST
To: "Bonham, Valerie (NIH/OD) [E]" <bonhamva@od.nih.gov>, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Cc: "Devaney, Stephanie (NIH/OD) [E]" <stephanie.devaney@nih.gov>, "Carr, Sarah (NIH/OD) [E]" <CarrS@OD.NIH.GOV>, "McGarey, Barbara (NIH/OD) [E]" <MCGAREYB@od.nih.gov>
Subject: Re: SUPPORT case dismissed against investigators and IRB

Fantastic!!!!

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
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On Jan 23, 2014, at 11:03 AM, "Bonham, Valerie (NIH/OD) [E]" <bonhamva@od.nih.gov> wrote:

Court Dismisses Claims Against IRB, PI
In SUPPORT Trial Wrongful Death Suit

Posted January 23, 2014, 11:38 A.M. ET

By John T. Aquino

Class action plaintiffs alleging their children were injured during participation in a clinical research study on oxygen therapy for premature infants failed to meet the heightened pleading standard for malpractice claims, a federal district court ruled Jan. 22 (Looney v. Moore, N.D. Ala., No. 2:13-cv-00733-KOB, dismissed in part 1/22/14).

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The claims were dismissed without prejudice, which allows the plaintiffs to re-plead, although the court warned them to "take special care when re-pleading the specific, malpractice-type claims" in their complaint.

The court denied the motions to dismiss the product liability and negligence claims against Masimo Corp., which had designed the pulse oximeter used in the study to monitor the infants' blood oxygen saturation and which argued that the claims against it were preempted by federal statutes.

The premature infants were enrolled in the Surfactant, Positive Pressure and Oxygenation Randomized Trial (SUPPORT) at the University of Alabama-Birmingham, which tested two oxygen treatments for chronic lung disease. The complaint alleged that two children of the plaintiffs who initially brought the suit were permanently impaired and one died as a result of the study (12 MRLR 345, 5/15/13).

The court agreed with the IRB defendants and Carlo that the plaintiffs' arguments made it "impossible to discern exactly what illegal conduct Plaintiffs are alleging for each particular action" and that, since the negligence and lack of informed consent allegations were malpractice claims, the plaintiffs failed to provide the detailed specification and factual description of each act and omission alleged required under the Alabama Medical Liability Act. The wrongful death claim was barred by the two-year statute of limitation, the court concluded.

The opinion is at
http://www.bloomberglaw.com/public/document/BILLY_RYAN_LOONEY_ET_AL_Plaintiffs_v_SHEILA_D_MOORE_ET_AL_Defenda/1

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From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT case dismissed against investigators and IRB
Date: Thursday, January 23, 2014 1:29:50 PM
Attachments: NIH BRAIN - SUPPORT Study.docx

Hi Rose I inserted the comments in yellow

Mona

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Page 1043 of 2000

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of the Freedom of Information and Privacy Act

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From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: SUPPORT case dismissed against investigators and IRB
Date: Thursday, January 23, 2014 12:58:06 PM

Thanks Rose! I am back at the "ranch" and will revise SUPPORT briefing paper before resubmitting

Mona

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From: Luc Brion
To: (b)(6) @gmail.com; Wrage, Lisa Ann (wrage@rti.org); Pablo.Sanchez@nationwidechildrens.org; Das, Abhik (adas@rti.org); "Gantz, Marie" (mgantz@rti.org); Myra Wyckoff; Mambarambath Jaleel; Roy Heyne; nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Pablo.Sanchez@nationwidechildrens.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Updated submission to ADC: Jadyn LeVan"s paper
Date: Thursday, January 23, 2014 11:02:14 AM
Attachments: s1-ln1663468395844769-1939656818Hwf592991014IdV-152662589816634683PDF_HI0001 (1).pdf

Dear Colleagues:

I missed a few points yesterday, sorry.

I corrected the submitted document as requested by ADC Editorial Office to include

1. A licence statement (now included after the list of references)
2. A separate title for Contributorship Statement (I split the acknowldedgment section).
3. Type of manuscript: original research

Best regards,

Luc

UT Southwestern Medical Center
The future of medicine, today.

Archives of
DISEASE IN CHILDHOOD

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Journal:	*Archives of Disease in Childhood*
Manuscript ID:	Draft
Article Type:	Original article
Edition:	not in use
Date Submitted by the Author:	n/a
Complete List of Authors:	LeVan, Jaclyn; Pediatrix Medical Group, Pediatrics Brion, Luc; University of Texas Southwestern Medical Center, Pediatrics Wrage, Lisa; Research Triangle Institute, Social, Statistical and Environmental Sciences Unit, RTI International, Gantz, Marie; Research Triangle Institute, Social, Statistical and Environmental Sciences Unit, RTI International, Wyckoff, Myra; University of Texas Southwestern Medical Center, Pediatrics Sanchez, Pablo; The Ohio State University - Nationwide Children's Hospital, Pediatrics Heyne, Roy; University of Texas Southwestern Medical Center, Pediatrics Jaleel, Mambarambath; University of Texas Southwestern Medical Center, Pediatrics Finer, Neil; University of California, Pediatrics Carlo, Waldemar; , University of Alabama at Birmingham, Pediatrics Das, Abhik; Research Triangle Institute, Social, Statistical and Environmental Sciences Unit, RTI International, Stoll, Barbara; 7Emory University School of Medicine, Pediatrics Higgins, Rose; Eunice Kennedy Shriver National Institute of Child, Health and Human Development,, NICHD
Keywords:	Neonatology, Respiratory, Clinical Procedures, Data Collection

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD, [1] Pablo J. Sánchez, MD, [1,4] Roy Heyne, MD, [1] Mambarambath Jaleel, [1] MD, Neil N. Finer, MD,[5] Waldemar A. Carlo, MD, [6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital, Columbus, OH; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

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No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 250 words
Article length: 2,499 words
Revised 1/23/2014

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NICHD, National Institute of Child Health and Human Development;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

ABSTRACT

Objective: To test the hypothesis that the proportion of endotracheal intubation in the delivery room (DR ETI) decreased in Neonatal Research Network (NRN) centers after the National Institute of Child Health and Human Development NRN SUPPORT trial

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85-89% or 91-95%. The prior NRN feasibility trial had assessed the feasibility of randomization to CPAP versus ETI.

Patients: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before and after the SUPPORT trial at 11 centers that participated in the SUPPORT trial and remained part of the NRN, excluding infants with syndromes or major malformations and those on comfort care only.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, p <0.0001) but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusion: This study shows that process of care changed after SUPPORT only in NRN centers that had not participated in a similar trial.

INTRODUCTION:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with early surfactant administration followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled.[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the ETI groups.[1] The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups.

The NRN previously conducted another trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in the SUPPORT Trial and the GA range that would be most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the feasibility trial demonstrated that clinical practice, specifically the proportion of DR ETI, changed among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after

the SUPPORT trial in participating centers. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the trial. We speculated that the decrease in proportion of DR ETI in each center after the trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the feasibility trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.

METHODS

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT

trial and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trial, i.e., physiological definition of BPD, and severe ROP (with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred).[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following variables: other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] (GA, antenatal corticosteroids, gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary and secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should

be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of DR ETI during the first period.

Sample size analysis

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough for multivariate analysis with 10 patients per covariate.

IRB

The IRB of each participating center has approved the Survey of Morbidity and Mortality Among High Risk Preterm Infants (GDB) and the SUPPORT Trial.

RESULTS

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial.

The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant (p = 0.01). This indicates that the change in proportion of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT in the subgroup of infants from centers that had participated in the feasibility trial (61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (95% CI 0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (95% CI 0.83-0.89), p<0.0001).

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

DISCUSSION:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the feasibility trial. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had already decreased in 200, when neonatologists prospectively introduced routine, early, bubble nasal CPAP.[17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients, which limits incomplete/missing data and information bias; the use of multivariate analysis to take into account confounding variables; inclusion and exclusion criteria that were similar to those used in the SUPPORT trial; inclusion of centers with or without prior participation in a similar trial; and inclusion of centers that remained in the NRN during the entire study period, thereby limiting bias due to large inter-institutional differences.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions; lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends and of the exact time when DR ETI changed in each center. Nevertheless, in another study we have shown that the proportion of DR ETI in one NRN center (which did not participate in the Feasibilty Trial) decreased in non-enrolled patients from baseline before the SUPPORT trial to epochs during the SUPPORT trial and before its publication, in the absence of any changes in DR policy or practice guidelines.[4] In that center, DR ETI decreased by 22% during/after the SUPPORT Trial (before release of the trial results), but only by 1.6% in a large comparable contemporaneous cohort of infants participating in the Vermont Oxford Network .[4] Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. This study was not designed to test whether any change in other variables were associated with a change in DR ETI, in oxygen management, or in practice based on the SUPPORT trial or other studies.[18-27] We

decided against conducting a survey of clinical practices because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results of the present study.

This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial.

CONCLUSION

The proportion of a process of care, DR ETI, decreased significantly after the SUPPORT Trial in the group of infants from centers that had not participated in the feasibility trial but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial. This study provides additional evidence to suggest that participation of a center in randomized trials may affect process of care of non-enrolled patients.

CONTRIBUTORSHIP STATEMENT

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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The Study Sponsor, the National Institute of Child Health and Human Development (NICHD), did not have any role in the study design; in the collection, analysis and interpretation data; in the writing of the report; and in the decision to submit the paper for publication.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.

WHAT THIS STUDY ADDS

A change in process of care after the SUPPORT trial was observed only among infants born in centers that had not participated previously in a related trial. This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

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LICENCE FOR PUBLICATION STATEMENT

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FIGURE LEGENDS

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval
[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial
[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
BPD	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Appendix- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth, °C	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[5]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[5]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and

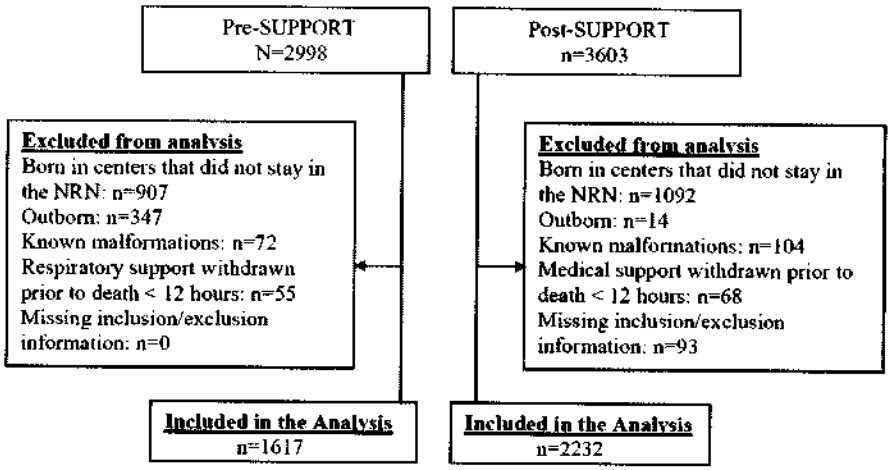
length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apgar at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those in the pre-SUPPORT cohort. The difference in distribution is shown on the next line in the Table (percentage of Apgar scores < 3).

[5]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.



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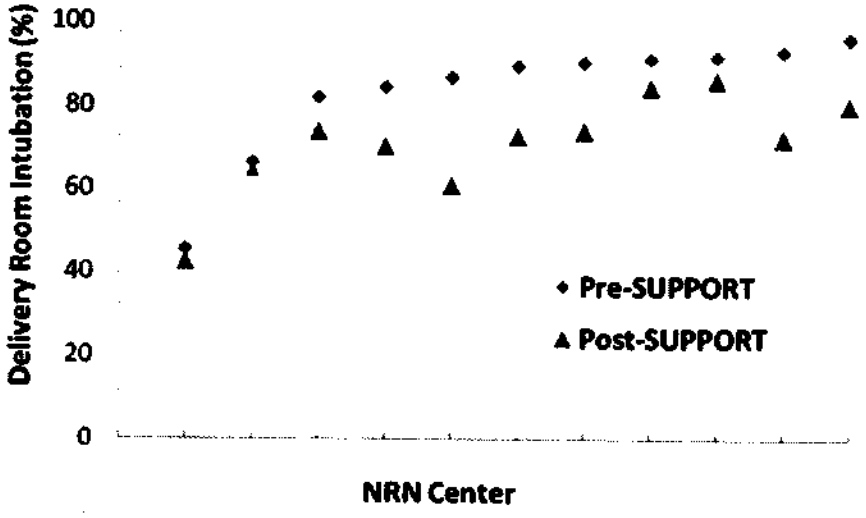

204x144mm (72 x 72 DPI)

From:	Luc Brion
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Subject:	Manuscript Submitted to ADC Fetal and Neonatal Edition
Date:	Wednesday, January 22, 2014 6:28:26 PM
Attachments:	s1-in1663468395844769-1939656818Hwf592991014IdV-152662589816634683PDF_HI0001.pdf

Dear Colleagues:

Thanks for all your responses and suggestions.

I submitted the attached manuscript to ADC Fetal and Neonatal Edition

Best regards,

Luc

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FYI - Redacted Congressional Response: OIG SUPPORT Pediatric Clinical Trial Review (OEI-01-13-00420)
Date: Wednesday, January 22, 2014 12:00:25 PM

Thanks Rose ! Alan simply comments that the OIG review is done—perhaps we can simply say that the (b)(5)

Mona

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 22, 2014 9:09 AM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: Fwd: FYI - Redacted Congressional Response: OIG SUPPORT Pediatric Clinical Trial Review (OEI-01-13-00420)

FYI - should the support document be updated? This came last week

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

From: "Stein, Meredith (NIH/OD) [E]" <steinme@od.nih.gov>
To: "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Carr, Sarah (NIH/OD) [E]" <CarrS@OD.NIH.GOV>, "Gordon, Valery (NIH/OD) [E]" <gordonv@od.nih.gov>, "Jarman, John (NIH/NICHD) [E]" <jarmanj2@mail.nih.gov>
Cc: "Devaney, Stephanie (NIH/OD) [E]" <stephanie.devaney@nih.gov>, "Barros, Colleen (NIH/OD) [E]" <BarrosC@od.nih.gov>, "Servis, Suzanne (NIH/OD) [E]" <ServisS@OD.NIH.GOV>, "Brown, Tiffany (NIH/OD) [E]" <browntv1@mail.nih.gov>
Subject: FYI - Redacted Congressional Response: OIG SUPPORT Pediatric Clinical Trial Review (OEI-01-13-00420)

Good Afternoon,

This afternoon, I received the attached OIG Congressional response, SUPPORT Pediatric Clinical Trial Review, OEI-01-13-00420. The OIG redacted the name of the requestor in the PDF file.

The OIG found that OHRP followed its procedures and exercised discretion throughout its evaluation of SUPPORT. There are no recommendations directed to HHS or NIH. There is no action required from your office as a result of this OIG review.

NOTE FROM OIG: "This is a non-public report, produced pursuant to Congressional request, that is being provided – CLOSE HOLD – as a courtesy to your agency. Do not reproduce, release, or further disseminate to any party outside your agency without express prior written approval of the Office of Inspector General."

Please let me know of any questions.
Meredith
301-402-8482

From: Rowe, Mona (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: SUPPORT paper
Date: Wednesday, January 22, 2014 9:09:51 AM

Thanks for the comments – very helpful

BTW I am going to transition from my home setting to the office – just finished shoveling driveway – We are completing two new bullets for the TBI piece and will send once I reach the office

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, January 22, 2014 8:59 AM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: SUPPORT paper

See attached.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
31 Center Drive
Building 31, Room 2A03
Bethesda, MD 20892-2425

Phone: 301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, January 21, 2014 8:53 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: SUPPORT paper

Here is the SUPPORT briefing paper for BRAIN --- it is an update of one that was finished last year. If you don't have time tomorrow –please feel free to get me comments later – we will ask to send in later in the week if we need be.

- Unfortunately, the format of the briefing paper leads to some redundancy – the first three sections act as "summaries" of the following, more in-depth sections. It is contains many references –enough to cover the major points, even if not fully comprehensive.
- Rose was my consultant – as I wanted to make sure we covered most of the research and other updates. She also checked the new verbiage, and we received comments from OER.

- Finally – the papers are internal and even as internal write-ups they can be classified as "Sensitive" – not to share . We were going to mark this sensitive so that it will not be widely available to other ICs.

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: SUPPORT paper
Date: Wednesday, January 22, 2014 8:58:45 AM
Attachments: NIH BRAIN - SUPPORT StudyAG.docx

See attached.

Alan E. Guttmacher, M.D.
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31 Center Drive
Building 31, Room 2A03
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Phone: 301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, January 21, 2014 8:53 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]
Subject: SUPPORT paper

Here is the SUPPORT briefing paper for BRAIN --- it is an update of one that was finished last year. If you don't have time tomorrow –please feel free to get me comments later – we will ask to send in later in the week if we need be.

- Unfortunately, the format of the briefing paper leads to some redundancy – the first three sections act as "summaries" of the following, more in-depth sections. It is contains many references –enough to cover the major points, even if not fully comprehensive.
- Rose was my consultant – as I wanted to make sure we covered most of the research and other updates. She also checked the new verbiage, and we received comments from OER.
- Finally – the papers are internal and even as internal write-ups they can be classified as "Sensitive" – not to share . We were going to mark this sensitive so that it will not be widely available to other ICs.

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PAM14-0083 Decision Letter
Date: Tuesday, January 21, 2014 11:00:53 PM

Rose:

Please advise:

Should we try collaborating with VON or the Canadian Network, or else keep trying this other journal including ADC, Early Human Development and Journal of Perinatology first?

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) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Tuesday, January 21, 2014 9:58 PM
To: Luc Brion
Subject: RE: PAM14-0083 Decision Letter

Hi Luc

You have had a rough ride

I am OK with whatever journal you choose

In addition the comparison with VON sounds good to me-It worked before

Neil

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, January 21, 2014 2:13 PM
To: doctorlevan@gmail.com; Wrage, Lisa Ann (wrage@rti.org); Pablo.Sanchez@nationwidechildrens.org; Das, Abhik (adas@rti.org); 'Gantz, Marie' (mgantz@rti.org); Myra Wyckoff; Mambarambath Jaleel; Roy Heyne; Finer, Neil; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll

(Barbara.Stoll@oz.ped.emory.edu); Luc Brion; Pablo.Sanchez@nationwidechildrens.org
Subject: FW: PAM14-0083 Decision Letter

Sorry about this.

How about going down the list that follows, starting by ADC Fetal/Neonatal. This is what I would do.

ADC Fetal Neonatal: 2.971
Early Human Development 2.394
Journal of Perinatology 1.960

One alternative would be to compare NRN data to those from VON; this is the critical step that led to publication of the other manuscript (attached).

Luc

From: jamapeds@msubmit.net [mailto:jamapeds@msubmit.net]
Sent: Tuesday, January 21, 2014 3:46 PM
To: Luc Brion
Cc: lucbrion@gmail.com
Subject: PAM14-0083 Decision Letter

January 21, 2014

Dr. Luc P Brion
University of Texas Southwestern Medical Center
Pediatrics
5323 Harry Hines Blvd, Stop 9063
Dallas, TX 75390-9063

RE: Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Dear Dr. Brion:

We have completed our review of your manuscript and after a review by our editors have decided not to consider it further for publication in JAMA Pediatrics. We are able to accept less than one of every five submissions for publication due to limitations on the number of manuscripts we can publish and the numerous high quality submissions we receive each year. Given the very competitive nature of submissions to the Journal, we often notify authors quickly that we are declining to publish papers that we are not likely to accept, without sending them to outside reviewers.

Over the past years, we have done this for about 40% of all submissions. Our reasons for doing this are not only related to the quality of the manuscript, but include a range of other reasons such as, the publication is well written, but better suited to a different type of journal (for example, papers that have an appeal to a more narrow subspecialty audience) or those that duplicate topics or findings from papers that were recently published within JAMA Pediatrics.

This rapid decision allows authors to have a quick, even though not desirable, response that helps them move forward quickly to find a more suitable journal for their work. It also allows us to maintain a reviewer panel that is more able to respond to the large number of submissions that we do ask them to review.

We appreciate that you provided JAMA Pediatrics the opportunity to review your work and to consider it for publication in our journal. We can think of no higher sign of respect from authors and hope that you will consider this journal for your next manuscript.

Sincerely,

Ron Keren, MD, MPH
Associate Editor
JAMA Pediatrics
University of Washington, Box 354920
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6200 NE 74th Street, Suite 120B
Seattle, WA 98115-8160
Phone: 206-685-3573
eFax: (866) 541-3890
E-mail: jamapeds@jamanetwork.org

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: checking another item
Date: Tuesday, January 21, 2014 8:38:41 PM

That's good – (b)(6) -BTW—Alan said that he would like to look at the SUPPORT write-up – so I am going to send it to him this evening –that's why I wanted to check on the TOP trial – I have added a few sentences in addition to the ones that you looked at –based upon things already written -but I was trying to get to Alan shortly.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 21, 2014 8:06 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: checking another item

(b)(6)

Rosemary D Higgins, MD

Sent from my iPhone

On Jan 21, 2014, at 7:59 PM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

(b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 21, 2014 7:30 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: checking another item

Transfusion of prematures

Feel free to bother.

(b)(6)

Rose

Rosemary D Higgins, MD

Sent from my iPhone

On Jan 21, 2014, at 7:04 PM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

Rose is this the correct name for the TOP trials – the Transfusion of Prematures (TOP)

I have seen it also referred to as the Transfusion of Prematurity – guidance appreciated

Sorry to keep bothering you

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: another look at a few paragraphs
Date: Tuesday, January 21, 2014 4:40:55 PM

Thanks Rose !

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 21, 2014 4:38 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: another look at a few paragraphs

See below in italics

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, January 21, 2014 4:32 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: another look at a few paragraphs

HI Rose—Building 1 asked that I add some things to the SUPPORT briefing paper – first to spell out the acronyms in the beginning and then to discuss the folks that sided with OHRP (I told them there were not too many) Anyway –to be responsive – I am suggesting the following changes—(b)(5)
(b)(5)
—would you please mind checking the verbiage in yellow? Is that Ok any changes or comments welcome -- as ever -- thanks for your time and help, Mona

(b)(5)

Page 1102 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Vohr, Betty
To: Halbrook, Andrea M; Newman, Jamie
Cc: Susan Hintz; Carrie Rau; Manndi Loertscher; sarah.winter@hsc.utah.edu; Bradley Yoder; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Utah SUPPORT pt seen at Brown at 18 months - plan for SUPPORT NEURO School Age
Date: Friday, January 17, 2014 2:52:56 PM

Thanks Andrea.

From: Halbrook, Andrea M
Sent: Friday, January 17, 2014 1:36 PM
To: Newman, Jamie
Cc: Susan Hintz; Carrie Rau; Manndi Loertscher; sarah.winter@hsc.utah.edu; Bradley Yoder; Higgins, Rosemary (NIH/NICHD) [E]; Vohr, Betty
Subject: RE: Utah SUPPORT pt seen at Brown at 18 months - plan for SUPPORT NEURO School Age

Hi Jamie,

This patient is indeed on my tracking list, with the window opening on (b)(6) However, when I pulled the patients current information, it appears as though someone updated the address to one in Iowa since their last visit here (but there are no notes associated with this change of address). I have contacted a family friend that is going to call me back with more information either today or Tuesday. Will update all at that point.

Thanks,

Andrea

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Friday, January 17, 2014 12:56 PM
To: Halbrook, Andrea M
Cc: Susan Hintz; Carrie Rau; Manndi Loertscher; sarah.winter@hsc.utah.edu; Bradley Yoder; Higgins, Rosemary (NIH/NICHD) [E]; Vohr, Betty
Subject: Utah SUPPORT pt seen at Brown at 18 months - plan for SUPPORT NEURO School Age

Andrea,
Network # (b)(6) (DOB (b)(6) is a SUPPORT pt that was enrolled at Utah but seen for the 18-22 months Follow-up on (b)(6) at Brown. The 3-4 year status form indicates that the family is planning on attending the school age visit. The SUPPORT NEURO School Age window opens on (b)(6) and closes on (b)(6) for this child. I'm checking in to make sure this child is on your radar to see for the SUPPORT NEURO School Age visit.

Please let me know if you have any questions.

Thanks, Jamie

Jamie E. Newman, PhD, MPH
RTI International
3040 Cornwallis Road (PO Box 12194)
RTP, NC 27709 USA
Telephone: (919) 485-5719

Fax: (919) 485-7762
newman@rti.org

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: CONFIRMING Grand Rounds: Rethinking Clinical Research presentation - Jan 31
Date: Friday, January 17, 2014 1:46:43 PM

Hi Rose:

I have told you about this DCRI NIH Grand Rounds and you thought it would be ok to present SUPPORT.

I have selected a title that on purpose does not focus on SUPPORT but wanted to check with you.

The title would be: Comparative effectiveness research in oxygenation trials in neonates.

What do you think? I was going to use the Hot Topic slides which have been publicly used multiple times and maybe add a few from the NIH presentation I did in June.

Let me know what you 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: (b)(6)

From: DCRI NIH Collaboratory [mailto:nih-collaboratory@dm.duke.edu]
Sent: Wednesday, January 15, 2014 3:39 PM
To: Wally Carlo, M.D.
Cc: Gloria Carter; Asba Tasneem, Ph.D.; Tammy Reece; Sandi McDaniel
Subject: CONFIRMING Grand Rounds: Rethinking Clinical Research presentation - Jan 31

Dear Dr. Carlo,

We thank you for agreeing to give a presentation at the Grand Rounds: Rethinking Clinical Research scheduled for Friday, January 31st, 1:00 PM Eastern.

Kindly provide the title of your presentation as soon as possible so we may update the Collaboratory website. You may change your presentation title at a later date if needed.

Our audience is comprised of basic and clinical researchers, all manner of healthcare providers and staff involved in clinical trials research. The presentation is video streamed over the web for participants

across the medical research community. Please let us know if there is any objection to your presentation being streamed and archived to the web.

Please plan to be logged in to the Grand Rounds not later than 12:45 PM Eastern time on the day of your presentation. You will have 30 minutes for your presentation, and 30 minutes for Q&A discussion from the audience.

Please don't hesitate to contact me if you have any questions. Additional information will be sent in the coming days.

Sincerely,

Sandi McDanel
919-668-8001
NIH Collaboratory Coordinating Center
www.nihcollaboratory.org

From: Rowe, Mona (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: SUPPORT related paper submitted to JAMA Pediatrics
Date: Friday, January 17, 2014 11:06:39 AM

Thanks

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
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Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 17, 2014 10:58 AM
To: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: SUPPORT related paper submitted to JAMA Pediatrics

Hi
This paper has gone through NICHD clearance and has just been submitted to JAMA Pediatrics (It was rejected by pediatrics). Will keep you posted as to its status

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: SUPPORT related paper submitted to JAMA Pediatrics
Date: Friday, January 17, 2014 10:58:22 AM
Attachments: 13375_0_merged_1389971996.pdf

Hi

This paper has gone through NICHD clearance and has just been submitted to JAMA Pediatrics (It was rejected by pediatrics). Will keep you posted as to its status

Thanks

Rose

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD,[1] Pablo J. Sánchez, MD,[1,4] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil N. Finer, MD,[5] Waldemar A. Carlo, MD,[6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

No reprints needed

Conflicts of interest: There are no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 350 words
Article length: 2,936 words
Revised 1/17/2014

Formatted: Numbering: Continuous

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.

Objective: To test the hypothesis that endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial within NICUs in NRN centers.

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a feasibility trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% versus 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, $p < 0.0001$) but not in the group

of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the trial (61% before versus 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusions and Relevance: A change in process of care after the SUPPORT trial was observed only among infants born in NRN centers that had not participated previously in a related trial. This study provides additional evidence suggesting that participation of a center in unblinded randomized trials may affect process of care of non-enrolled patients.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of DR ETI and postnatal steroids for BPD, fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven of life. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the

risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN previously conducted a feasibility trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the feasibility trial demonstrated that participation in the SUPPORT Trial affected clinical practice, specifically the proportion of DR ETI among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the feasibility trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical

166 estimate, delivered at an NRN center participating in the SUPPORT trial, and included in
167 the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis
168 were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd
169 cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion
170 was different from the SUPPORT trial, where patients were included if a decision had
171 been made to provide full resuscitation.
172
173 Baseline variables
174 Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity,
175 prenatal steroid use (any type or betamethasone, any or full course), mode of delivery,
176 multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or
177 antibiotic use before delivery.
178
179 Outcome variables:
180 The primary outcome variable was a practice variable, i.e., DR ETI.
181 Secondary outcomes of prime interest included (1) the composite of death or BPD
182 (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of
183 severe ROP (defined as ROP surgery or retinal detachment) or death before discharge,
184 and (3) death before discharge. Additional secondary outcomes included death by 36
185 weeks PMA, BPD at 36 weeks PMA, severe ROP, mechanical ventilation on day 7, and
186 days on ventilator until discharge for survivors. The definitions of BPD and ROP were
187 based on those used in the GDB; they were similar but not identical to those used for the
188 primary outcomes of the SUPPORT trial, i.e., physiological definition of BPD defined as

receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post versus pre-SUPPORT) and pre-specified prenatal covariates (based on the

literature) shown to affect outcomes in very preterm infants[6] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton versus multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in proportion of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of DR ETI during the first period.

Results

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI during the first period and the change in proportion of DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial was significant ($p = 0.01$). This indicates that the change in proportion

of DR ETI varied across these subgroups, thus results for DR ETI are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT in the subgroup of infants from centers that had participated in the Feasibility Ttrial (61.3% before versus 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)), p<.0001.

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial. The proportion of DR ETI

significantly decreased in the subgroup of infants from centers that had not participated in the feasibility trial. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP versus ETI in the DR. In one of these 3 centers, the proportion of ETI had decreased before the feasibility trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000.[17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients, which limits incomplete/missing data and information bias; the use of multivariate analysis to take into account confounding variables; inclusion and exclusion criteria that were similar to those used in the SUPPORT trial; inclusion of centers with or without prior participation in a similar trial with unblinded randomization to DR CPAP versus DR ETI; and inclusion of study centers that remained in the NICHD NRN during the entire study period, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (which were similar to those in SUPPORT); lack of serial data in each center and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends. Nevertheless, in another study we have shown that the proportion of DR ETI in one of these centers (which did not participate in the Feasibilty Trial) decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010).[4] In that

304 center, DR ETI decreased by 22% during/after the SUPPORT Trial (before release of the
305 trial results to NRN centers), in contrast to only by 1.6% in a large comparable
306 contemporaneous cohort of infants born in level IIIb or IIIc North American centers
307 participating in the Vermont Oxford Network (VON).[4] That study excluded VON centers
308 participating in SUPPORT or in the Network Delivery Room Management Trial, as well
309 as neonates who received comfort care in the DR (ETI), or had severe congenital
310 anomalies.[4]
311 Additional limitations of the present study include lack of information on the history of
312 changes in policies and practice guidelines in each participating NRN center; and lack of
313 information in the GDB on DR CPAP or oxygen saturation. Nevertheless, our prior study
314 showed that DR ETI decreased and DR CPAP increased in one NRN center during and
315 after SUPPORT in the absence of any changes in DR policy or practice guidelines.[4] It is
316 also possible that additional unknown biases or confounding variables, such as changes in
317 personnel, could have affected the rationale used for each practice in each infant and thus
318 the results of the present study.
319 Mortality before discharge decreased in the post-SUPPORT group. Earlier studies from
320 the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in
321 ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight
322 infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in
323 mortality.[20] Similarly, mortality in very low birth weight infants decreased in the
324 Vermont Oxford Network between 2000 and 2009.[21]
325 This study was not designed to test whether any change in secondary or tertiary variables
326 were associated with a change in DR ETI, with changes in oxygen delivery or oxygen

saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

The proportion of a process of care, DR ETI, decreased significantly after the SUPPORT Trial in the group of infants from centers that had not participated in the feasibility trial but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial. This study provides additional evidence to suggest that participation of a center in randomized trials may affect process

of care of non-enrolled patients.

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Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

553 **Table 2. Primary Outcome**

554

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

555
556
557 Abbreviations: RR, relative risk; CI, confidence interval
558 [1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the
559 Feasibility Trial
560 [2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests
561 [3]Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight
562 (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture
563 of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
564 [4] Adjusted p-values from robust Poisson model
565

566
567 **Table 3. Secondary Outcomes[1]**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
BPD	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

568
569 Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA,
570 patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk
571 [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
572 [2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
573 [3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g
574 increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of
575 membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these
576 same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA
577 indomethacin treatment, and late onset sepsis.
578 [4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).
579
580

Appendix- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth, °C	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[5]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[5]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and

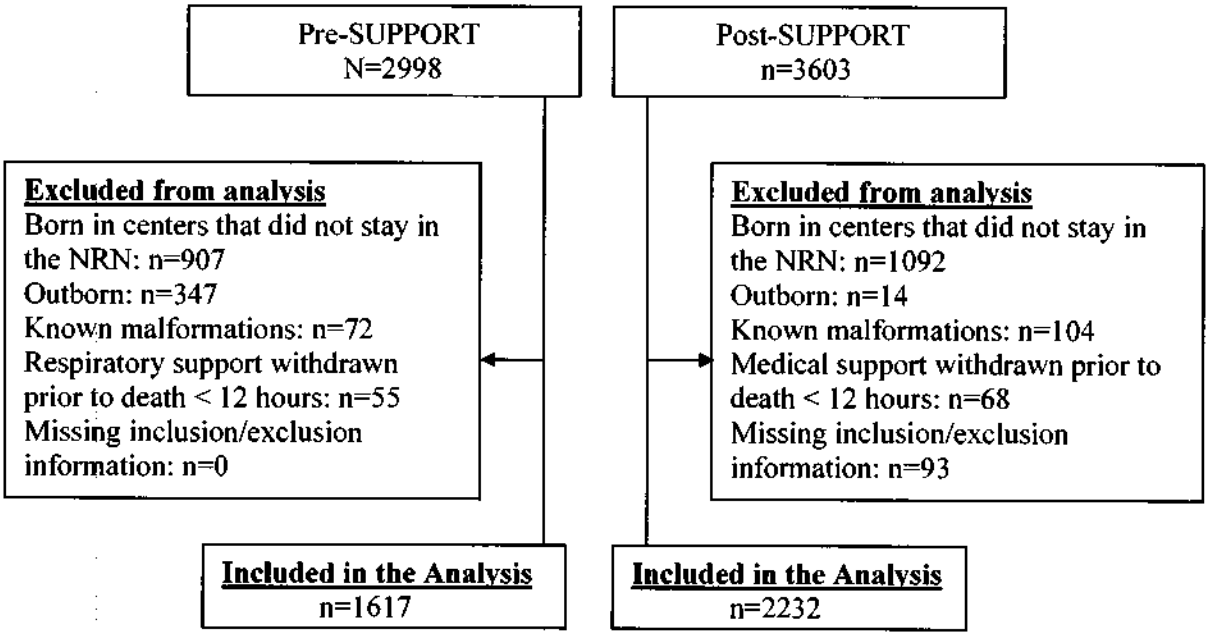
length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

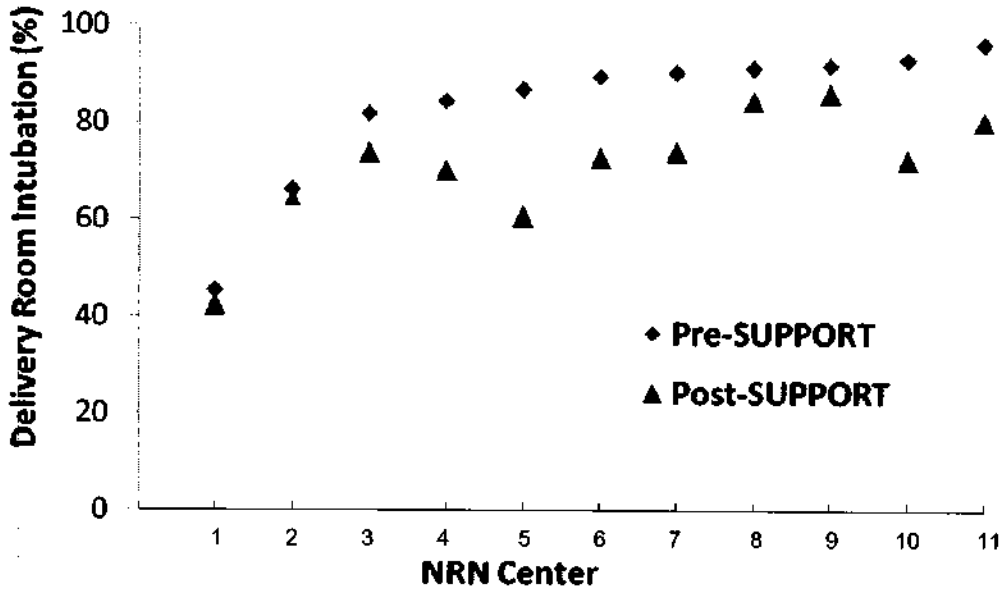
[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apgar at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those in the pre-SUPPORT cohort. The difference in distribution is shown on the next line in the Table (percentage of Apgar scores < 3).

[5]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.


Pre-SUPPORT
N=2998
Post-SUPPORT
n=3603
Excluded from analysis
Born in centers that did not stay in the NRN: n=907
Outborn: n=347
Known malformations: n=72
Respiratory support withdrawn prior to death < 12 hours: n=55
Missing inclusion/exclusion information: n=0
Excluded from analysis
Born in centers that did not stay in the NRN: n=1092
Outborn: n=14
Known malformations: n=104
Medical support withdrawn prior to death < 12 hours: n=68
Missing inclusion/exclusion information: n=93
Included in the Analysis
n=1617
Included in the Analysis
n=2232


Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

From:	Luc Brion
To:	Higgins, Rosemary (NIH/NICHD) [E]; doctorlevan@gmail.com; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); "Gantz, Marie" (mgantz@rti.org); Wrage, Lisa Ann (wrage@rti.org); Das, Abhik (adas@rti.org); nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Luc Brion; Pablo.Sanchez@nationwidechildrens.org
Subject:	Manuscript submittted to JAMA Pediatrics
Date:	Friday, January 17, 2014 10:50:42 AM
Attachments:	13375_0_merged_1389971996.pdf

Dear Colleagues:

Here is the PDF file of the manuscript that was submitted to JAMA Pediatrics.

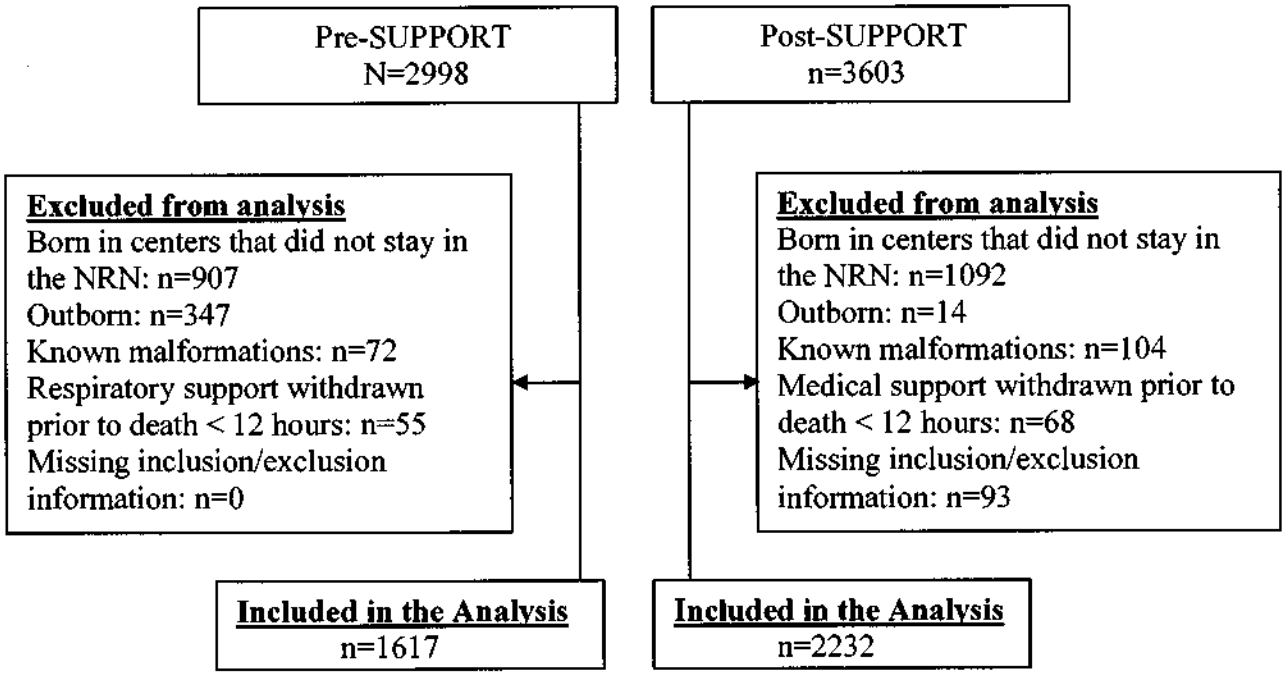
Thanks a lot for your help and collaboration.

Best regards,

Luc

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; (b)(6) gmail.com; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); "Gantz, Marie" (mgantz@rti.org); Wrage, Lisa Ann (wrage@rti.org); Das, Abhik (adas@rti.org); nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Luc Brion; Pablo.Sanchez@nationwidechildrens.org
Subject: Manuscript version 1-16-14 rev
Date: Thursday, January 16, 2014 6:27:56 PM
Attachments: Appendix.docx
Figure 1 rev 12-12-13.docx
Figure 2.docx
Table 1 12-12-13.docx
Table 2_edlw10Jan14.docx
Table 3.docx
Jackie LeVan Manuscript NRN 1-16-14 rev.docx

This version includes additional changes suggested by Lisa and Roy.
Thanks a lot for all the comments and suggestions.
As mentioned previously, I am planning to submit this tomorrow to JAMA Pediatrics.
Best regards,
Luc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Included in the Analysis
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Appendix- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
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Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
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Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
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Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
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Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[5]	59.2 (36.4)	56.6 (37.5)	0.06
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ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
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PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
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PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
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Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

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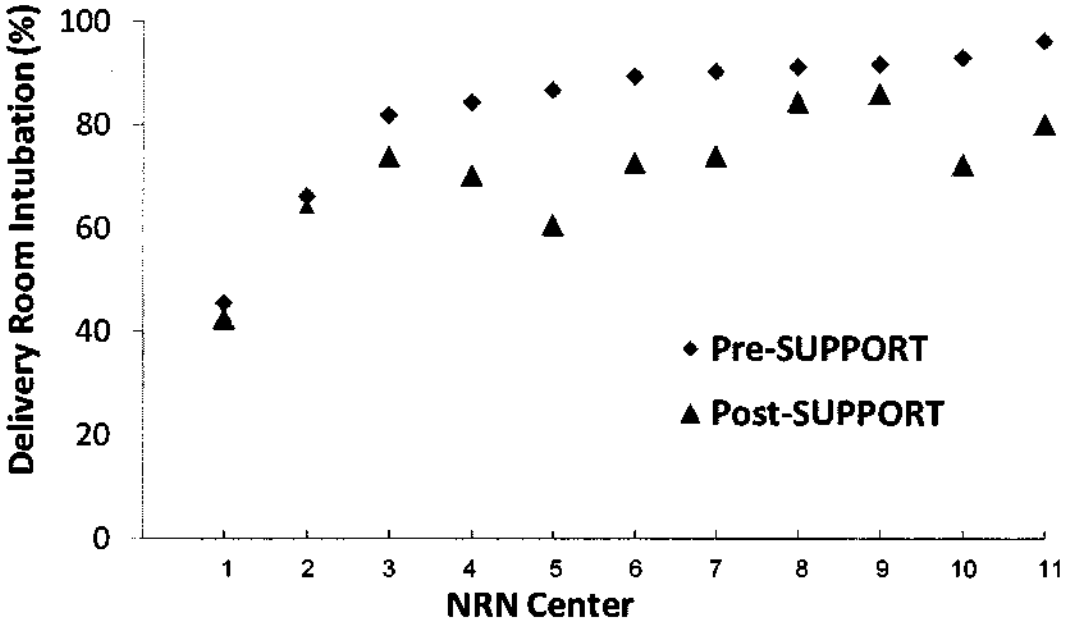
in the pre-SUPPORT cohort. The difference in distribution is shown on the next line in the Table (percentage of Apgar scores < 3).

[5]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.


Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
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9
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11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD, [1] Pablo J. Sánchez, MD, [1,4] Roy Heyne, MD, [1] Mambarambath Jaleel, [1] MD, Neil N. Finer, MD,[5] Waldemar A. Carlo, MD, [6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

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No reprints needed

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 3~~3~~50 words
Article length: 2,93~~8~~4 words
Revised 1/16~~5~~/2014 5:26 PM

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients during the trial and before release of its results. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related randomized trial.

Objective: To test the hypothesis that endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial within NICUs in NRN centers.

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a feasibility trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the feasibility trial (91% vs. 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, $p < 0.0001$) but not in the group

of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the trial (61% before vs. 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusions and Relevance: A change in process of care after the SUPPORT trial was observed only among infants born in NRN centers that had not participated previously in a related randomized trial. This study provides additional evidence ~~to~~ suggesting that participation of a center in randomized trials may affect process of care of non-enrolled patients.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of DR ETI and postnatal steroids for BPD, fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven of life. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the

risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN previously conducted a feasibility trial in 5 centers, to determine the feasibility of randomization to DR CPAP versus DR ETI in the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the feasibility trial demonstrated that participation in the SUPPORT Trial affected clinical practice, specifically the proportion of DR ETI among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the feasibility trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the feasibility trial.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical

estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge ~~from the hospital~~, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP ~~at status~~ or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trial, i.e.,

physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included an indicator for study

group (post vs. pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as DR ETI~~intubation in the DR~~, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in rate of DR ETI varied across the subgroups of infants in centers who did and did not participate in the feasibility trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR ETI ~~intubation~~ model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of DR ETI ~~delivery room intubations~~ from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of DR ETI ~~intubation~~ during the first period.

Results

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, with a total n of 1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of DR ETI ~~intubations in the DR~~ during the first period and the change in proportion of ~~intubations in the~~ DR ETI from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the feasibility trial.

In the model for DR ETI the interaction term between the pre versus post-SUPPORT indicator and the indicator for the subgroups of centers that did and did not participate in the feasibility trial ~~with the pre vs. post-SUPPORT indicator,~~ was significant (p = 0.01). This ~~,~~indicate~~sing~~ that the change in proportion ~~rate~~ of DR ETI varied across these subgroups, thus results for DR ETI ~~intubation~~ are presented within subgroup (Table 2). The proportion of DR ETI did not decrease significantly after SUPPORT in the subgroup of infants from centers that had participated in the Feasibility Ttrial (61.3% before vs. 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)), p<.0001.

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the feasibility trial. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the feasibility trial, and thus already had experience with unblinded randomization to CPAP vs. ETI in the DR. In one of these 3 centers, the proportion of ETI had decreased before the feasibility trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000.[17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients, which limits incomplete/missing data and information bias; the use of multivariate analysis to take into account confounding variables; inclusion and exclusion criteria that were similar to those used in the SUPPORT trial; inclusion of centers with or without prior participation in a similar trial with unblinded randomization to DR CPAP vs. DR ETI; and inclusion of study centers that remained in the NICHD NRN during the entire study period, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (which were similar to those in SUPPORT); lack of serial data in each center and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of

secular trends. Nevertheless, in another study we have shown that the proportion of DR ETI in one of these centers (which did not participate in the Feasibilty Trial) decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010).[4] In that center, DR ETI decreased by 22% during/after the SUPPORT Trial (before release of the trial results to NRN centers), in contrast to only by 1.6% in a large comparable contemporaneous cohort of infants born in level IIIb or IIIc North American centers participating in the Vermont Oxford Network (VON).[4] That study excluded VON centers participating in SUPPORT or in the Network Delivery Room Management Trial, as well as neonates who received comfort care in the DR (ETI), or had severe congenital anomalies.[4]

Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. Nevertheless, our prior study showed that DR ETI decreased and DR CPAP increased in one NRN center during and after SUPPORT in the absence of any changes in DR policy or practice guidelines.[4] It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the rationale used for each practice in each infant and thus the results of the present study.

Mortality before discharge decreased in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in

mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

The proportion of a process of care, DR ETI, decreased significantly after the SUPPORT Trial in the group of infants from centers that had not participated in the feasibility trial but not in the group of infants from the other centers, where the proportion of ETI was already lower prior to initiation of the SUPPORT trial. This study provides additional evidence to suggest that participation of a center in randomized trials may affect process of care of non-enrolled patients.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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12.

Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviations: RR, relative risk; CI, confidence interval

[1] Results are shown for groups defined by combining subjects from centers that had or had not participated in the Feasibility Trial

[2] Unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] Adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] Adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hirschfeld, Steven (NIH/NICHD) [E]
Subject: Fwd: SUPPORT results
Date: Thursday, January 16, 2014 3:01:54 PM

Steven
Do you know when the support rests will be posted on clinical trials.gov?
Thanks
Rose

Rosemary D Higgins, MD

Sent from my iPhone
N
Begin forwarded message:

From: "Crawford, Meg" <mcrawford@rti.org>
Date: January 16, 2014 at 2:49:04 PM EST
To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Subject: SUPPORT results

Rose,

Do you have an update on the SUPPORT results?

Meg

Meg Crawford, CCRP
RTI International
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Crawford, Meg
Subject: Re: SUPPORT results
Date: Thursday, January 16, 2014 3:00:32 PM

No update . I will ask dr. Hirschfeld again

Rosemary D Higgins, MD

Sent from my iPhone

On Jan 16, 2014, at 2:52 PM, "Crawford, Meg" <mcrawford@rti.org> wrote:

Rose,

Do you have an update on the SUPPORT results?

Meg

Meg Crawford, CCRP
RTI International
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From: Luc Brion
To: Gantz, Marie; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Jackie LeVan"s manuscript
Date: Thursday, January 16, 2014 2:32:40 PM

Thanks a lot, Marie, for all your help
Luc

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, January 16, 2014 1:31 PM
To: Luc Brion; Mambarambath Jaleel; Rose Higgins
Subject: RE: Jackie LeVan's manuscript

I agree with submitting. I like the addition of the analysis splitting out centers who participated in the feasibility study.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, January 15, 2014 11:02 PM
To: Mambarambath Jaleel; Rose Higgins ; Gantz, Marie
Subject: Jackie LeVan's manuscript

Rose, Marie, Jaleel:
Could you please let me know if you agree with me submitting Jackie Levan's manuscript to JAMA Pediatrics on Friday.
Thanks
Luc

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Subject:	Revised manuscript
Date:	Thursday, January 16, 2014 12:59:44 PM
Attachments:	Appendix.docx Figure 1 rev 12-12-13.docx Figure 2.docx Jackie LeVan Manuscript NRN 1-16-14.docx Table 1 12-12-13.docx Table 2_edlw10Jan14.docx Table 3.docx

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Here is a revised version, which takes into account all Myra's suggestions.
I tracked the changes versus the 1/15/14 version.
The main change is in the conclusion and relevance in the abstract and the text.
Luc

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised Jackie LeVan"s manuscript
Date: Thursday, January 16, 2014 12:41:51 PM

Rose et al:

Thanks for all your comments, suggestions and collaboration.

Luc

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 16, 2014 7:21 AM
To: Luc Brion
Subject: RE: Revised Jackie LeVan's manuscript

Luc

I am fine with resubmission. Once you submit, please send me a copy of all of the submitted items.

Thanks so much for your diligence and commitment with this manuscript.

Rose

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, January 15, 2014 6:16 PM
To: Barbara Stoll
Cc: Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; wrage@rti. org; Mambarambath Jaleel; Gantz,

Marie; Finer, Neil; Das, Abhik; " <WCarlo@peds.uab.edu>"@ws-mr3.cc.emory.edu
Subject: RE: Revised Jackie LeVan's manuscript

Barbara et al:

Thanks a lot for all the comments.

I attach the next version, taking into account all your comments, as well as further comments from Lisa.

I made some additional changes (mostly fixed duplications and abbreviations).

All marked changes are those beyond Lisa's version.

I am sorry: I realize I had attached previous drafts of some tables and figures; this is th correct version.

I am waiting for the latest comments

Best regards and thanks a lot.

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

From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Wednesday, January 15, 2014 2:56 PM
To: Luc Brion
Cc: Roy Heyne; <doctorlevan@gmail.com>, Myra Wyckoff <Myra.Wyckoff@utsouthwestern.edu>, ; wrage@rti. org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; Das, Abhik; "_ <WCarlo@peds.uab.edu>"@ws-mr3.cc.emory.edu
Subject: Re: Revised Jackie LeVan's manuscript

A few minor edits
Ready to go
Fingers crossed
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Sent from my iPad

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To: Roy Heyne; doctorlevan@gmail.com; Myra Wyckoff; higginsr@mail.nih.gov; wrage@rti.org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; doctorlevan@gmail.com; Das, Abhik; _WCarlo@peds.uab.edu; Barbara Stoll; Luc Brion
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From: Luc Brion
Sent: Tuesday, January 21, 2014 12:17 AM
To: Sanchez, Pablo; 'Barbara Stoll'; Roy Heyne; 'Wally Carlo, M.D.'; 'Ganz, Marie'; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]; 'nfinnet@ucsd.edu'; Myra Wyckoff; Mambarambath Faleel; 'Mcclevelevan@gmail.com'
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George W. Brumley, Jr., Professor and Chair
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bstoll@emory.edu

Confidential - Please do not forward.

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To:	Barbara Stoll
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Subject:	RE: Revised Jackie LeVan"s manuscript
Date:	Wednesday, January 15, 2014 6:16:43 PM
Attachments:	Appendix.docx Figure 1 rev 12-12-13.docx Figure 2.docx Jackie LeVan Manuscript NRN 1-15-14.docx Table 1 12-12-13.docx Table 2_edlw10Jan14.docx Table 3.docx

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UT Southwestern Medical Center
The future of medicine, today.

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair
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Confidential - Please do not forward.

Blansfield, Earl (NIH/NICHD) [E]

From: Jarman, John (NIH/NICHD) [E]
Sent: Wednesday, January 15, 2014 5:09 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: FYI - Redacted Congressional Response: OIG SUPPORT Pediatric Clinical Trial Review (OEI-01-13-00420)
Attachments: Enclosure_OHRP Procedures.pdf; Style Enclosure_SUPPORT Timeline.pptx; ex_60450_64387 (2)_Redacted.pdf

Importance: High

FYI

John S. Jarman
Associate Director for Administration/Executive Officer
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institutes of Health, DHHS
301-496-0648

From: Stein, Meredith (NIH/OD) [E]
Sent: Wednesday, January 15, 2014 4:33 PM
To: Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Carr, Sarah (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Jarman, John (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Barros, Colleen (NIH/OD) [E]; Servis, Suzanne (NIH/OD) [E]; Brown, Tiffany (NIH/OD) [E]
Subject: FYI - Redacted Congressional Response: OIG SUPPORT Pediatric Clinical Trial Review (OEI-01-13-00420)
Importance: High

Good Afternoon,

This afternoon, I received the attached OIG Congressional response, *SUPPORT Pediatric Clinical Trial Review*, OEI-01-13-00420. The OIG redacted the name of the requestor in the PDF file.

The OIG found that OHRP followed its procedures and exercised discretion throughout its evaluation of SUPPORT. There are no recommendations directed to HHS or NIH. There is no action required from your office as a result of this OIG review.

NOTE FROM OIG: "This is a non-public report, produced pursuant to Congressional request, that is being provided – **CLOSE HOLD** – as a courtesy to your agency. Do not reproduce, release, or further disseminate to any party outside your agency without express prior written approval of the Office of Inspector General."

Please let me know of any questions.
Meredith
301-402-8482

NOTE: THIS GUIDANCE REPLACES OHRP'S OCTOBER 19, 2005 GUIDANCE ENTITLED "COMPLIANCE OVERSIGHT PROCEDURES FOR EVALUATING INSTITUTIONS" CLICK HERE

Office for Human Research Protections (OHRP) Department of Health and Human Services (HHS)

OHRP's Compliance Oversight Procedures for Evaluating Institutions

Date: October 14, 2009

Scope: This document summarizes the procedures used by OHRP in performing compliance oversight evaluations of institutions and human subjects research that are under OHRP's jurisdiction. In particular, OHRP offers guidance on the following topics:

- How OHRP conducts for-cause compliance oversight evaluations;
- How OHRP conducts not-for-cause compliance oversight evaluations;
- Possible outcomes of OHRP compliance oversight evaluations;
- Public and governmental access to OHRP compliance oversight evaluation records; and
- The Privacy Act is not applicable to OHRP compliance oversight evaluation records.

Target Audience: Institutions and investigators that conduct human subjects research, institutional review boards (IRBs), HHS agencies that fund human subjects research, and members of the public.

Legal Authority:

Section 289 of the Public Health Service Act authorizes OHRP to, on behalf of HHS, establish a compliance oversight process regarding violations of the rights of human subjects of research conducted or supported by HHS. Pursuant to this authority, OHRP may receive reports of such violations and take appropriate action.

OHRP also derives compliance authority from the HHS regulations for the protection of human research subjects at 45 CFR part 46 (hereinafter referred to as "the HHS regulations"). HHS regulations at 45 CFR 46.103(a) require each institution engaged in non-exempt human subjects research that is conducted or supported by HHS to provide written assurance that it will comply with the requirements of the HHS regulations. On behalf of HHS, OHRP reviews and approves these written agreements, called assurances of compliance (Federalwide assurances or FWAs). An FWA approved by OHRP commits the entire institution (including institutional officials, IRBs designated in the FWA, research investigators, and all other employees or agents) to full compliance with the HHS regulations whenever the institution is engaged in HHS-conducted or -supported human subjects research.

How OHRP Conducts For-Cause Compliance Oversight Evaluations:

For-cause evaluations occur, at OHRP's discretion, in response to OHRP's receipt of substantive written allegations or indications of non-compliance with the HHS regulations. Sources of such allegations or indications of noncompliance include, but are not limited to, research subjects and their family members, individuals involved in the conduct of research such as investigators and study coordinators, institutional officials, and research publications. OHRP may choose to use other mechanisms to address allegations or indications of noncompliance rather than conducting a for-cause evaluation. Complainants may submit allegations of noncompliance by mail, e-mail, or fax to OHRP's Director of the Division of Compliance Oversight, 1101 Wootton Parkway, Suite 200, Rockville, MD, 20852 (email ohrp@hhs.gov; fax (240) 453-6909). OHRP accepts complaints submitted anonymously, and asks complainants who identify themselves to OHRP whether OHRP may reveal their identity to the institution where the alleged noncompliance may have occurred.

When OHRP receives an allegation or indication of noncompliance, OHRP proceeds as follows:

(1) OHRP determines whether our office has jurisdiction to evaluate the allegations or indications of noncompliance at the relevant institution(s), based on whether the possible noncompliance involves non-exempt human subjects research that is HHS-conducted or -supported, or covered by an applicable OHRP-approved FWA. If an institution through its FWA voluntarily applies the HHS regulations to all research regardless of support, OHRP has the authority to evaluate allegations or indications of noncompliance pertaining to all research to which the FWA applies, including research that is not Federally conducted or supported. Where OHRP and another agency both have jurisdiction, OHRP and the other agency will confer as to what arrangement to utilize in responding to the allegation in the particular case. If OHRP receives an allegation or indication of noncompliance related to human subjects research that is covered by an OHRP-approved FWA and is conducted or supported solely by a Federal department or agency other than HHS, OHRP will refer the matter to the other department or agency for review and action as appropriate.

(2) OHRP notifies any complainant who provides contact information as to whether OHRP will open a compliance oversight evaluation of the allegations raised.

(3) If OHRP has jurisdiction to evaluate the possible noncompliance, and chooses to conduct a for-cause evaluation, OHRP sends officials at the institution(s) engaged in the research an initial inquiry letter informing them that our office is evaluating human subjects research protections at their institution(s). The initial inquiry letter:

(a) describes the allegations or indications of noncompliance, and potential regulatory violations;

(b) asks the institution to conduct an investigation of the potential noncompliance;

(c) asks for a written response to the allegations or indications of noncompliance, and for submission of supporting documentation (including relevant IRB and research records) by a specified date;

(d) asks the institution to develop and submit a corrective action plan if the investigation conducted by the institution reveals any noncompliance; and

(e) provides an explanation of OHRP's compliance oversight evaluation procedures.

OHRP does not take any action against an institution without first affording the institution an opportunity to offer information that might refute the allegations or indications of noncompliance, except in very rare circumstances where serious concerns about subject safety require an immediate suspension of research activities.

(4) OHRP sends copies of the initial inquiry letter to the principal investigator(s) of the specific research project(s) at issue.

(5) OHRP evaluates the documentation submitted by the institution in response to OHRP's initial inquiry letter to determine whether additional information is needed for OHRP to determine whether there is evidence of noncompliance with the HHS regulations.

(6) OHRP engages external expert consultants to assist in for-cause compliance oversight evaluations as needed.

(7) If OHRP has specific additional questions or concerns that can be addressed by the institution in writing, OHRP will present these questions and concerns in additional written correspondence to the institution. If additional questions and concerns are raised by the previous institutional response, there may be multiple letters sent to the institution by OHRP and thus more than one institutional response. In general, all questions and concerns are to be resolved before the case is closed. If OHRP feels that discussion of pertinent issues with institutional employees, IRB members, research investigators, or others would assist OHRP's decision making, OHRP staff may conduct interviews via telephone or videoconference or an on-site visit of the institution's human subject protection program. On-site visits also are conducted when IRB record review, or evaluation of institutional facilities, is relevant to OHRP's determinations, or if OHRP has serious concerns about an institution's system for protecting human subjects.

(8) Based on the institution's responses and any relevant information received from the complainant or other sources, OHRP issues one or more letters to the institution containing OHRP's determinations (determination letter) pertaining to (a) the complainant's specific allegations or indications of noncompliance with the HHS regulations and (b) the institution's program for protecting human subjects, including IRB operating procedures and policies. If OHRP makes determinations of noncompliance, OHRP will describe in such letters any relevant corrective actions proposed or implemented by the institution and the extent to which these corrective actions adequately address the noncompliance. If the institution has not proposed an adequate corrective action plan to address one or more of OHRP's findings of noncompliance, OHRP will require the institution to develop and submit in writing an appropriate corrective action plan by a specified date. OHRP expects institutions to tailor their corrective actions both

to the specific facts under evaluation and to OHRP's conclusions regarding the strength of the institution's program for protecting human subjects. OHRP evaluates all corrective action plans proposed in response to OHRP's determinations of noncompliance, and assesses how institutions have progressed with implementation of the corrective action plans, before deciding whether to conclude the compliance oversight evaluation. OHRP is available for assistance in developing a corrective action plan. OHRP may also make recommendations to an institution for specific improvements to its human subjects protections system; the institution is free to implement these recommendations or not.

(8) If OHRP makes no determinations of noncompliance, or if OHRP makes determinations of noncompliance but also determines that they have been adequately addressed through corrective action, OHRP concludes the evaluation and informs the institution of this final outcome in writing.

(9) If OHRP's compliance oversight evaluation was initiated by a complainant who provided contact information, OHRP informs the complainant in writing of OHRP's determinations and any corrective actions taken by the institution upon completion of the evaluation.

(10) An institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation.

How OHRP Conducts Not-For-Cause Compliance Oversight Evaluations:

Not-for-cause compliance oversight evaluations are conducted in the absence of substantive allegations or indications of noncompliance. Institutions are selected for not-for-cause evaluation based on a range of considerations, including: (a) the volume of HHS-conducted or -supported research in which they are engaged; (b) whether they have a history of a relatively low level of reporting to OHRP under the requirements of HHS regulations at 45 CFR 46.103(b)(5); (c) the need to evaluate implementation of corrective actions following a previous for-cause compliance oversight evaluation; (d) geographic location; (e) status of accreditation by professionally recognized human subject protection program accreditation groups; and (f) status of recent human subject protection evaluations or audits by other regulatory agencies (such as the Food and Drug Administration) or recent participation in quality improvement programs (such as OHRP's Quality Improvement program).

When OHRP decides to undertake a not-for-cause compliance oversight evaluation, OHRP proceeds as follows:

(1) OHRP advises institutional officials in writing that our office intends to conduct an evaluation of human subject protections at the institution. OHRP's notice requests that the institution provide to OHRP by a specified date relevant information concerning the institution's human subject protection program, including:

(a) IRB policies and procedures;

(b) minutes from recent IRB meetings; and

(c) a list of active IRB protocols.

OHRP's initial written notice also indicates whether the evaluation will include interviews with institutional officials, IRB members, and research investigators, and whether OHRP intends to conduct an on-site evaluation of human subject protections at the institution.

(2) OHRP may decide as a not-for-cause evaluation progresses that additional information is needed to determine whether there is evidence of noncompliance with the HHS regulations. Hence, not-for-cause compliance oversight evaluations initially based on interviews or mailed documents may subsequently expand to include an on-site evaluation.

(3) OHRP engages external expert consultants to assist in not-for-cause compliance oversight evaluations as needed.

(4) Following the evaluation, OHRP issues a letter to the institution containing OHRP's determinations, concerns and recommendations regarding the institution's compliance with the HHS regulations with respect to its human subject protection program, including its IRB operating policies and procedures. In addition, if OHRP makes determinations of noncompliance, OHRP will describe in the letter any relevant corrective actions proposed or implemented by the institution and the extent to which these corrective actions adequately address the noncompliance. If the institution has not proposed an adequate corrective action plan to address one or more of OHRP's determinations of noncompliance, OHRP will require the institution to develop and submit in writing an appropriate corrective action plan by a specified date. OHRP expects institutions to tailor their corrective actions both to the specific facts under evaluation and to OHRP's conclusions regarding the strength of the institution's program for protecting human subjects. OHRP evaluates all corrective action plans proposed in response to OHRP determinations of noncompliance, and assesses how institutions have progressed with implementation of the corrective action plans before deciding whether to conclude the evaluation. OHRP is available for assistance in developing a corrective action plan.

(5) If OHRP makes no determinations of noncompliance, or if OHRP makes determinations of noncompliance but determines that they have been adequately addressed through corrective action, OHRP concludes the evaluation and informs the institution in writing of this final outcome.

(6) An institution may request that the Director of OHRP reconsider any determinations resulting from a not-for-cause compliance oversight evaluation.

Possible Outcomes of OHRP Compliance Oversight Evaluations:

OHRP for-cause and not-for-cause compliance oversight evaluations will result in one or more of the following outcomes, in accordance with OHRP's authority under 45 CFR 46.103(e):

(1) OHRP does not identify any areas of noncompliance with the HHS regulations.

(2) OHRP recommends improvements to the institution's human subject protection policies and procedures, such as better documentation of actions or communications in IRB protocol records, or clearer description of operational details in IRB written procedures. The institution is free to implement these recommendations or not.

(3) OHRP determines that the institution's policies and procedures for protecting human subjects in general are not in compliance with one or more requirements of the HHS regulations, or that the IRB review (or IRB records related to the review) or conduct of one or more specific research projects are not in compliance with one or more of the requirements of the HHS regulations. In these circumstances, OHRP requires that the institution develop and implement corrective actions. Examples of corrective actions that institutions have undertaken to address OHRP determinations include:

(a) re-review by the IRB of research for which IRB determinations required for approval were not previously made;

(b) implementing a new IRB database management strategy to ensure timely continuing review or review of amendments; and

(c) increasing education and training for investigators and IRB members.

(4) OHRP determines that there is noncompliance with the HHS regulations and, as a result, restricts or attaches conditions to its approval of the institution's FWA based on the nature and scope of the institution's noncompliance. Despite such restrictions or conditions, OHRP may allow some or all research projects to which the FWA applies to continue while the institution satisfies the terms of the restriction or conditions placed upon OHRP's approval of the institution's FWA.

Examples of such conditions include, but are not limited to:

(a) requiring special reporting (such as quarterly reports) to OHRP;

(b) requiring that IRB members, institutional officials, investigators, or others receive appropriate education and training regarding human subjects research protections;

Examples of such restrictions include, but are not limited to:

(a) requiring prior OHRP review of some or all research projects to be conducted under the FWA; and

(b) suspending the conduct of a specific research project until specified protections or corrective actions have been implemented (in these circumstances, research activities involving subjects already enrolled in the affected project may continue if it is in the best interests of the subjects to do so).

(5) OHRP determines that there is noncompliance with the HHS regulations and, as a result, suspends its approval of an institution's FWA. In these circumstances, all Federally-conducted

or -supported research activities to which the FWA applies must be suspended until OHRP approval of the FWA is reinstated, except that research activities involving already enrolled subjects in such research may continue if it is in the best interests of the subjects to do so. If an FWA is suspended, research funded by any other Federal agency that relies on the FWA also must stop unless the other Federal agency issues its own assurance to cover such research.

(6) OHRP determines that there is noncompliance with the HHS regulations and, as a result, recommends to appropriate HHS officials: (a) that an institution or an investigator be temporarily suspended or permanently removed from participation in specific projects, or (b) that HHS scientific peer review groups be notified of an institution's or an investigator's past noncompliance prior to review of new projects.

(7) OHRP determines that there is noncompliance with the HHS regulations and, as a result, recommends to appropriate HHS officials that institutions or investigators be debarred in accordance with the procedures specified at 45 CFR part 76. Debarment is a government-wide sanction.

(8) OHRP refers the matter to another Federal department or agency for further review and action, if appropriate.

Public and Governmental Access to Compliance Oversight Evaluation Documents:

Under HHS regulations at 45 CFR part 5, documents related to OHRP compliance oversight evaluations may be subject to the provisions of the Freedom of Information Act (FOIA). In most cases, such documents are exempt from the disclosure provisions of the FOIA while the evaluation is in progress, and OHRP treats them confidentially. However, determination letters are available for release under FOIA at the time they are provided to the institution. Each determination letter will be made accessible on the OHRP website once a request for the letter under FOIA is received or ten working days after the letter is issued to the institution, whichever occurs first. Sections of determination letters that discuss unresolved concerns, questions, or allegations related to an ongoing compliance oversight evaluation will be redacted from the posted letters. Nonredacted determination letters, and other documents related to OHRP's compliance oversight evaluation, become publicly available once the compliance oversight evaluation is closed.

OHRP routinely advises appropriate HHS agencies and officials (for example, NIH, FDA, CDC) concerning the status of its evaluations and may share compliance documents with other Federal agencies as appropriate. Additionally, OHRP may be required to inform members of Congress about its compliance evaluations, and to provide Congress some or all of the information or documents in its files.

The Privacy Act Is Not Applicable to OHRP Compliance Oversight Evaluation Records:

Under HHS regulations at 45 CFR part 5b, records that are retrieved by an individual's name or other personal identifier are subject to the provisions of the Privacy Act of 1974. OHRP maintains compliance oversight evaluation information in a system of records identifying the

institution under evaluation. Records can be retrieved by an institution's name or FWA number, but not by any individual's name or other personal identifier. Therefore, the Privacy Act does not apply to information OHRP obtains in the course of a compliance oversight evaluation.

Questions:

For questions about compliance oversight procedures, please contact OHRP at (240) 453-6900 or 1-866-447-4777 (toll free within the U.S.), or by email at ohrp@hhs.gov.

Chronology of OHRP's Evaluation of SUPPORT

(from OHRP's 5/24/11 receipt of complaint to UAB's 3/22/13 response to OHRP's determination letter)

2011

May 24 OHRP receives an email complaint alleging that SUPPORT was unethical and researchers did not obtain informed consent from participants.

May 25 OHRP confirms SUPPORT is funded by Eunice Kennedy Shriver National Institute of Child Health (NICHD) Neonatal Research Network and that OHRP has jurisdiction to conduct an evaluation.

May 31 OHRP responds to the complainant acknowledging that the complaint was received and is under review.

June 6 OHRP receives the SUPPORT protocol and informed-consent template from NICHD and conducts a preliminary review. OHRP identifies some preliminary concerns with the informed-consent document.

July 7 OHRP initiates a conference call with NICHD to discuss the complaint.

July 18 OHRP opens an evaluation by sending an inquiry letter to UAB (the lead institution) and RTI (the data-coordinating center) of SUPPORT.

OHRP informs the complainant of its action the same day.

Aug. 26 UAB responds to OHRP's inquiry letter, stating that it found no violations during its investigation.

2012

Jan. OHRP requests additional information from UAB, such as DSMC documents and clarification on aspects of SUPPORT.

June OHRP drafts its determination letter to UAB. OHRP asks for additional information from UAB and redrafts a few versions before finalizing.

2013

Feb. 11 OHRP sends its final determination letter to UAB and RTI.

Mar. 7 In response to RTI's request, OHRP removes RTI and reissues its determination letter.

Mar. 22 UAB responds to OHRP's determination letter with corrective actions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201

JAN 09 2014

[redacted]

Dear [redacted]

I am writing in response to your letter of May 20, 2013, requesting that the Department of Health and Human Services (HHS) Office of Inspector General (OIG) conduct a review to determine whether the Office for Human Research Protections (OHRP) followed its procedures in its compliance evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). In that letter, you asked us to review relevant SUPPORT and compliance evaluation documents and to conduct interviews to assess OHRP's response to an allegation regarding the use of informed consent in SUPPORT. Specifically, you asked OIG to:

1. Ensure that OHRP followed procedures and exercised reasonable discretion in the compliance evaluation of SUPPORT.
2. Provide specific recommendations for how OHRP or HHS can strengthen its review, approval, and monitoring procedures if any violation is found.

We found that OHRP followed its procedures and exercised discretion throughout its evaluation of SUPPORT. Generally, OHRP sees its role as educational and sees such evaluations as opportunities to strengthen human subjects protections in future research. The events following OHRP's determination in SUPPORT have raised important questions about the protection of human subjects in research that compares two treatments within the current standard of care.

BACKGROUND

OHRP. Section 491 of the Public Health Service Act (42 U.S.C. § 289) authorizes the Secretary to establish a process to respond to alleged violations of human subjects protection in research conducted or supported by HHS. The Secretary has delegated this authority to OHRP.[1] Pursuant to this authority, when OHRP receives allegations of violations it may conduct for-cause compliance evaluations.[2]

[1] 65 Fed. Reg. 37136, 37136–37 (June 13, 2000).

[2] OHRP also conducts not-for-cause evaluations in the absence of allegations or indications of noncompliance. OHRP selects institutions for not-for-cause evaluations on the basis of a range of factors, including volume of supported research, history of low-level reporting to OHRP, and geographic location.

OHRP has developed an 11-step procedure for conducting a for-cause compliance evaluation. In general, OHRP's process involves notifying the institution and requesting that it investigate the allegation, provide a written response with supporting documents, and develop a corrective action plan if any noncompliance is revealed. OHRP evaluates the institution's response and issues a determination letter addressing the allegations of noncompliance. If OHRP identifies noncompliance with human subjects protections regulations, it can (1) require the institution to take corrective measures, such as developing a corrective action plan or improving institutional policies; (2) restrict or suspend research at the institution; and/or (3) recommend that an institution or investigator be debarred from receiving Federal funds for research.

OHRP has considerable discretion in this process. For example, OHRP is able to determine whether to conduct a for-cause compliance evaluation; how to assess the institution's investigation; whether to consult with experts; and what, if any, are appropriate corrective actions.

SUPPORT. SUPPORT was a randomized multisite study that enrolled about 1,300 premature infants between 2005 and 2009. The National Institute of Child Health and Human Development (NICHD) within the National Institutes of Health (NIH) funded SUPPORT. The University of Alabama, Birmingham (UAB), was the lead coordinating institution of the 23 sites in the study.[3] Research Triangle Institute (RTI) was the data-coordinating center responsible for collecting, storing, and analyzing study data for all sites.

One purpose of the study was to determine the appropriate levels of oxygen saturation in infants with extremely low birth weights by comparing lower and higher levels of oxygen saturation in them.[4] Enrolled infants were randomized into two groups and maintained in one of two oxygen saturation target ranges (85–89 percent or 91–95 percent).[5] At the time of the study, the standard of care was to treat premature infants within an oxygen saturation range of 85–95 percent. In practice, clinicians adjust oxygen saturation levels within that range according to an infant's individual needs and characteristics.[6]

One objective of the study was to test the hypothesis that a lower target range of oxygen saturation compared to a higher range would reduce the incidence of severe retinopathy of prematurity (a disease that causes abnormal blood vessel growth in the eye, leading to blindness

[3] Other institutions involved in SUPPORT were Case Western Reserve University, Duke University, Wake Forest University, Women and Infants Hospital of Rhode Island, Brown University, the University of Utah, the University of Cincinnati, Tufts Medical Center, the University of Texas Southwestern Medical Center, Emory University, the University of Rochester, Indiana University, Stanford University, the University of Miami, Wayne State University, the University of Iowa, Yale University, the University of California, Sharp Mary Birch Hospital for Women & Newborns, and the University of New Mexico.

[4] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, "Target Ranges of Oxygen Saturation in Extremely Preterm Infants." *The New England Journal of Medicine*, 2010; 362: 1959–1969, May 27, 2010.

[5] Ibid.

[6] J.M. Drazen et al., "Informed Consent and SUPPORT." *The New England Journal of Medicine*, 2013; 368: 1929–1930, May 16, 2013.

and other visual impairments) or death among infants with extremely low birth weights. A second objective of the study was to compare two ventilation treatments in such infants.

Allegation of Violation and OHRP's Determination Letter. In May 2011, OHRP received an email about SUPPORT alleging that (1) the study design was unethical because some infants received "severely reduced" oxygen and (2) the researchers had not obtained informed consent. In response, OHRP conducted a for-cause compliance evaluation of SUPPORT at UAB (see enclosed chronology of OHRP's evaluation). OHRP issued a determination letter to UAB in March 2013 stating 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."

OUR REVIEW

We reviewed OHRP's procedures in conducting its for-cause compliance evaluation of SUPPORT. We assessed how OHRP followed its 11 procedural steps and how the agency exercised its discretion.

We reviewed the following documents provided by OHRP:

- Emailed allegation regarding SUPPORT.
- Email and written communication of relevant OHRP staff involved in the SUPPORT compliance evaluation, including communication among staff from OHRP, NIH, other HHS offices, UAB, and RTI.
- Study documents that OHRP requested from UAB as part of its evaluation, including SUPPORT's Data Safety Monitoring Committee (DSMC) documents and approved informed-consent documents.[7]
- Summary report of previous OHRP investigations or actions involving UAB.

We also reviewed the minutes for both open and closed DSMC meetings and adverse event data provided by RTI. In addition, we conducted structured interviews with OHRP and NIH staff involved with SUPPORT.

LIMITATIONS

We did not review the appropriateness of OHRP's determination or actions in its SUPPORT evaluation.

[7] A DSMC is an independent committee of experts responsible for reviewing clinical trial data on an ongoing basis to ensure the safety of study subjects and validity and integrity of the data.

RESULTS

We found that OHRP followed its for-cause compliance evaluation procedures, which are broadly drawn and provide the office with substantial discretion.
OHRP's activities to ensure institutions' compliance are not codified in Federal statute or regulations; rather, they appear in compliance procedures issued by the agency. These procedures give OHRP considerable discretion in how it conducts such evaluations. For reference, we enclose a copy of these procedures.[8] OHRP specifies 11 steps in a for-cause compliance evaluation, and we found that after receiving the allegation, OHRP followed its procedures for each step. Below, we restate each step and describe what actions OHRP took and how it exercised its discretion.

Step 1: OHRP determines whether it has jurisdiction to evaluate allegations.

After receiving the emailed allegation on May 24, 2011, OHRP reviewed the published results of SUPPORT in a *New England Journal of Medicine* article referenced in the allegation and determined that the study fell within its jurisdiction.[9] The article stated that SUPPORT was an NIH-funded study; OHRP confirmed this fact by contacting NIH. OHRP has the authority to evaluate allegations pertaining to human subject research that HHS conducts or supports.[10] According to officials at OHRP, the agency receives between 80 and 100 allegations per year, of which 5 to 10 fall within its jurisdiction.[11]

Step 2: OHRP notifies complainant as to whether it will open an evaluation.

OHRP notified the complainant by email on July 18, 2011, saying: "OHRP will be evaluating the allegations related to informed consent/parental permission."

Step 3: If OHRP chooses to conduct a for-cause compliance evaluation, OHRP sends an inquiry letter to the institution.

Step 4: OHRP sends copies of the inquiry letter to the principal investigator(s) involved in the research.

OHRP sent an inquiry letter to UAB and RTI on July 18, 2011, copying the principal investigator for SUPPORT along with relevant individuals at NIH, NICHD, and the Food and Drug

[8] The copy of OHRP's procedures that are enclosed are as they appear on OHRP's Web site at http://www.hhs.gov/ohrp/compliance/evaluation/ as accessed on January 8, 2014.
[9] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, "Target Ranges of Oxygen Saturation in Extremely Preterm Infants." *The New England Journal of Medicine*, 2010; 362: 1959–1969, May 27, 2010.
[10] 42 U.S.C. § 289(b)(2); 65 Fed. Reg. 37136, 37136-37 (June 13, 2000).
[11] In addition, OHRP has authority to evaluate allegations when an institution is covered by an applicable OHRP-approved Federal Wide Assurance. A Federal Wide Assurance is a written document that commits the institution to full compliance with HHS regulations whenever the institution is engaged in human subject research that HHS conducts or supports.

Administration (FDA).[12] OHRP's inquiry letter included all required information outlined in its procedures. It explained OHRP's compliance procedures, described the allegations, and requested that UAB investigate and respond in writing with corrective actions if the investigation revealed a violation.

OHRP discretion in initiating the evaluation. Within 2 weeks of receiving the allegation, OHRP had conducted preliminary analysis to determine whether the allegation warranted an evaluation. OHRP first obtained from NIH the research protocol and the template for informed-consent documents. OHRP's initial decision was that the template did not include all reasonably foreseeable risks. OHRP staff told us that OHRP chose to initiate an evaluation even though enrollment in SUPPORT had ended and therefore the element of ongoing risk to human subjects was absent. OHRP considered the evaluation important because NIH has increasingly funded research of similar design (i.e., human subjects assigned to receive different treatments within the current standard of care). OHRP staff reported that in deciding to initiate an evaluation, they consider primarily the level of risk to human subjects. Because each compliance evaluation requires OHRP to commit significant human resources, new evaluations may require OHRP to reprioritize ongoing or planned evaluations.

OHRP discretion in defining the scope of the evaluation. OHRP reviewed the allegation and relevant study documents and chose to focus its evaluation on one institution, one study objective, and informed consent only.

OHRP chose to focus its evaluation on the lead institution, UAB, rather than all of the institutions involved in the study. OHRP staff told us that they expected the outcomes among the multiple sites would be similar, so focusing the review on the lead institution seemed appropriate.

OHRP staff also explained that they chose to focus the evaluation on one of the two research objectives of SUPPORT because the allegation referred specifically to the comparison of different oxygen saturation ranges.[13]

Lastly, OHRP focused its evaluation on the initial informed-consent document that UAB used to determine whether that document appropriately described the research purpose and all reasonably foreseeable risks to human subjects. OHRP did not assess whether any new risks were identified throughout the trial that should have been communicated to human subjects as required by 45 CFR 46.116(b). According to OHRP staff, their concern was that known risks at the start of SUPPORT were not set out in the informed-consent document that UAB used.

[12] OHRP staff indicated that they also included RTI because data-coordinating centers "often have access to materials that the individual sites don't have." OHRP later determined that RTI had limited involvement in the conduct of SUPPORT and only collected, stored, and analyzed data for SUPPORT. OHRP communicated to RTI that it need not respond.

[13] The other arm of the study compared different ventilation treatments.

Step 5: OHRP evaluates the documentation submitted by the institution in response to its inquiry letter to determine whether additional information is needed.

Step 6: OHRP engages external expert consultants as needed.

Step 7: OHRP presents any questions and concerns in additional written correspondence to the institution. OHRP can conduct interviews and onsite visits at institutions if relevant.

UAB responded to OHRP's inquiry letter on August 26, 2011, stating that it had reviewed the institutional review board (IRB) file for SUPPORT and interviewed relevant study staff. UAB found that its informed-consent document complied with 45 CFR § 46.116(a). Specifically, UAB stated that "there were no data from evidence-based trials to indicate increased risk or benefits between the two ranges of oxygen saturations tested." It also stated that the DSMC had reviewed study data several times and found no concerns with increased risk or benefit.

OHRP started its review of UAB's response in January 2012 when it assigned the case to a specific coordinator in its Division of Compliance Oversight. OHRP did not engage experts external to HHS in its evaluation, but did consult experts in NIH before issuing its inquiry letter to UAB. OHRP did not conduct interviews or site visits in its evaluation of SUPPORT. OHRP requested additional information from both NICHD and UAB via email between January 2012 and April 2012. OHRP requested informed-consent documents from all SUPPORT-involved sites to conduct a comparative analysis of all the documents.[14] OHRP also requested additional DSMC documents from UAB after receiving only some of the open meeting minutes. OHRP received no additional DSMC documents because UAB had none. OHRP also requested clarification regarding oxygen saturation practices for premature infants at UAB at the time of the study.

OHRP discretion in prioritizing evaluations. Although OHRP received a response from UAB to its inquiry letter on August 26, 2011, it did not begin its review until January 2012. OHRP staff stated they were unable to commit resources in the interim because of ongoing evaluations and insufficient staffing. In addition, SUPPORT had completed enrollment, results had been published, and the element of ongoing risk to human subjects was absent.

OHRP discretion in engaging experts. According to OHRP staff, OHRP's review of SUPPORT was based on information included in the SUPPORT protocol and informed-consent documents written by the principal investigators themselves and no external expert was needed. OHRP staff explained that they rarely consult outside experts during an evaluation, but often contact NIH or FDA to obtain more information about specific research and related clinical practices, medical devices, or drugs. OHRP discussed handling the SUPPORT allegation in a manner similar to that of past allegations by identifying experts at NICHD who could discuss the trial and by requesting a copy of the protocol and model parental permission form. In addition, OHRP staff

[14] OHRP's analysis of all informed-consent documents found that none of the documents listed death as a risk and two listed blindness as a risk.

told us that OHRP had in-house expertise and was familiar with the science and debate regarding retinopathy and premature infants.

OHRP discretion in conducting interviews or site visits. According to OHRP staff, OHRP conducts site visits when it has concerns of systemic issues at an institution; when certain events occur, such as an unexpected death of a study subject; or when correspondence with the institution has been difficult. None of these issues was present during its SUPPORT evaluation.

Step 8: On the basis of the institution's responses and any relevant information received from the complainant or other sources, OHRP issues its determination letter(s) to the institution pertaining to the allegations and the institution's program for protecting human subjects.

OHRP issued a determination letter to UAB and RTI on February 11, 2013. RTI contacted OHRP and requested that OHRP remove it from the determination letter because of its limited involvement in the trial. OHRP removed RTI from the letter and reissued it on March 7, 2013. In its determination letter, OHRP copied UAB's principal investigator on SUPPORT along with the principal investigators at each institution in the multisite trial.

OHRP's determination letter addressed in detail the specific noncompliance with Federal regulations at 45 CFR 46.11(a)(2) that require a description in the informed-consent document of any reasonably foreseeable risks and discomforts to the subject. According to OHRP staff, the determination letter included significant detail so that it could serve as a resource for the research community.

OHRP's procedures specify eight possible outcomes for evaluations, ranging from identifying no issues of noncompliance to recommending suspension and debarment of an institution or investigator. The determination letter to UAB aligns with one possible outcome that OHRP described in its procedures, i.e., a determination that the research project as conducted was out of compliance with one or more requirements of the Federal regulations. OHRP procedures require that in such an instance the institution develop and implement corrective actions. Specifically, OHRP required UAB to provide a plan to its IRB to ensure that its approved informed-consent documents include the elements of 45 CFR § 46.116(a).

OHRP discretion in copying all institutions. OHRP conducted its evaluation at the lead institution only, but for educational purposes, OHRP copied all institutions involved in the study. OHRP staff told us that OHRP's determination letters are commonly reviewed by the broader research community. OHRP staff reported that the agency's primary purpose in overseeing federally funded research is educational rather than punitive. Furthermore, staff referenced OHRP's common practice of limiting evaluations to one or two institutions in multisite studies and copying the others. They said that conducting one evaluation and making one determination is more efficient and achieves the same impact as conducting 23 separate but similar evaluations.

OHRP discretion in focusing on one regulatory concern. In its original inquiry letter, OHRP listed two concerns with SUPPORT informed-consent documents' not adequately addressing two basic elements required by Federal regulations: (1) a description of any reasonably foreseeable

risks and discomforts and (2) an explanation of the purposes of the research. In its determination letter, OHRP staff reported that they chose to focus only on the failure to describe any reasonably foreseeable risks and discomforts within the informed-consent document. The staff stated that they made this decision because they thought highlighting both concerns would be confusing. OHRP staff explained that OHRP letters tend to focus on the central regulatory issue, which they believed, in this case, was that human subjects were not adequately informed of the risks of participating in the study.

Step 9: If OHRP makes no determinations of noncompliance or determines that noncompliance has been adequately addressed through corrective action, OHRP concludes the evaluation and informs the institution of this final outcome in writing.

OHRP issued a determination letter, so this step was not applicable.

Step 10: OHRP informs the complainant in writing of OHRP's determinations and any corrective actions taken by the institution upon completion of the evaluation.

At the time of our review, OHRP's evaluation of SUPPORT was not final and OHRP had not informed the complainant of its determination.

Step 11: An institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation.

No evidence exists that UAB asked the Director of OHRP to reconsider OHRP's determination. Rather, UAB responded to OHRP's determination on March 22, 2013, with a list of corrective actions that the institution had implemented to ensure that approved informed-consent documents would include and would adequately address the basic elements of consent as required by Federal regulations. These corrective actions included a revision to UAB's template for informed-consent documents; the creation of a new protocol checklist; and a reminder to UAB staff of the IRB that all risks must be described, even when treatment falls within the parameters of standard of care.

OHRP discretion in maintaining its determination. In mid-April 2013, NIH contacted OHRP and raised concerns regarding OHRP's determination letter. Later that month, NIH encouraged OHRP to reverse its determination. OHRP maintained its determination but suspended all corrective actions directed to UAB. In a followup letter to UAB on June 4, 2013, OHRP committed to providing guidance to address the appropriate way to communicate risks to human subjects enrolled in research on different treatments within the standard of care. On August 28, 2013, HHS held a public meeting to discuss the protection of human subjects in such research.

SUMMARY OF EVENTS FOLLOWING OHRP'S DETERMINATION

In the time since OHRP issued its determination letter in March 2013, additional important events and discussion have taken place. On April 10, 2013, the advocacy group Public Citizen brought the determination letter to the attention of the public by sending an open letter to HHS Secretary Kathleen Sebelius. Public Citizen agreed with OHRP's finding that the informed-consent document was inadequate, but alleged that OHRP had "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."

After Public Citizen released its letter, SUPPORT and OHRP's determination received significant attention in the popular media and in professional journals. Prominent scholars, physicians, and bioethicists wrote to the editor of *The New England Journal of Medicine* expressing a range of views. Some argued that randomizing infants to different oxygen-saturation ranges within a standard of care may increase risk for study subjects.[15] These individuals agreed with OHRP that the informed-consent documents used in SUPPORT were inadequate. Others argued that treatments within a standard of care, by definition, cannot increase risk; that the risk of death in SUPPORT was not supported by current research; and that all premature infants have an increased risk of death as a result of their condition.[16, 17] These individuals considered OHRP's determination regarding the informed-consent document to be inappropriate.[18]

NIH encouraged OHRP to withdraw its determination letter on SUPPORT, arguing that at the start of SUPPORT, researchers did not have scientific evidence to expect a difference in mortality between the two target ranges for oxygen saturation. Furthermore, NIH acknowledged that OHRP's determination letter has raised a larger issue: the question of how risks should be conveyed when the purpose of the research is to compare interventions that are all considered to be within the standard of care. According to NIH officials, the outcome of this debate "could affect how we conduct and communicate about critical research on interventions that are within the standard of care for all disease and conditions."[19]

In response to the concerns of the research community and NIH, OHRP issued a followup letter to UAB on June 4, 2013. OHRP reaffirmed its decision that the informed-consent document was inadequate, but acknowledged the difficulty in defining reasonably foreseeable risks in research involving interventions considered to be within the standard of care. OHRP put on hold

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[15] R. Macklin et al., "The OHRP and SUPPORT—Another View." *The New England Journal of Medicine*, 2013; 369: e3, June 26, 2013.
[16] J.M. Drazen et al., "Informed Consent and SUPPORT." *The New England Journal of Medicine*, 2013; 368: 1929–1930, May 16, 2013.
[17] D. Magnus and A.L. Caplan, "Risk, Consent, and SUPPORT." *The New England Journal of Medicine*, 2013; 368: 1864–1865, May 16, 2013.
[18] B.S. Wilfond et al., "The OHRP and Support." *The New England Journal of Medicine, 2013;* 368: e36, June 20, 2013.
[19] K.L. Hudson et al., "In Support of SUPPORT—A View from the NIH." *The New England Journal of Medicine*, 2013; 368: 2349–2351, June 20, 2013.

compliance actions against UAB relating to SUPPORT and committed to providing guidance on this topic.

On June 26, 2013, HHS announced a public meeting to be held August 28, 2013, on how regulations on human subjects protections should be applied to research on interventions within the standard of care. Issues for consideration included defining reasonably foreseeable risks and what should be disclosed to research subjects in such research.[20] The announcement also stated that HHS was considering changes to OHRP's compliance oversight procedures, including the use of experts during compliance reviews and the establishment of an administrative process for appealing OHRP's determinations.[21] HHS held this public meeting to gather input as it considered developing guidance on the topic. Twenty-seven individuals, including SUPPORT subjects' parents, bioethicists, physicians, and researchers, presented a range of views and provided feedback to OHRP on ways to improve oversight of human subjects protections.

FURTHER DISCUSSION

We offer the following observations based on this review and the events that have occurred since OHRP issued its determination letter in March 2013. Our observations relate to the retrospective nature of OHRP's compliance review of SUPPORT, OHRP's flexibility in its procedures for conducting reviews, and research involving the current standards of medical care.

Retrospective nature of the SUPPORT review

OHRP's ability to influence directly the informed-consent process for a particular study is limited. Federal regulations rely on IRBs and research institutions, as well as the funders of research, to protect human subjects through initial determination of the ethics and merits of any particular study and through the informed-consent process.

OHRP received the complaint about the SUPPORT trial 2 years after patient enrollment in the trial had concluded. The study was complete and the results had already been published. As a result, any actions that OHRP took could not have affected the course of the research, the informed-consent documents, or the enrollment of individual subjects in the study. Although OHRP's review of SUPPORT was retrospective, its determination letter addressed the institution's failure to include or adequately address reasonably foreseeable risks. The letter required the institution to provide a plan that the IRB will use to ensure and adequately address the basic elements of consent in future research involving human subjects, as required by Federal regulations. OHRP shared this determination letter with the other 22 institutions involved in the research and posted it on its Web site to educate those institutions about expectations for this type of research.

[20] 78 Fed. Reg. 38343, 38345 (June 26, 2013).
[21] Ibid.

Flexibility in conducting compliance reviews.

OHRP's 11-step process for conducting evaluations and the considerable discretion provided therein allow it to prioritize and shape its reviews in response to the specific circumstances of each allegation. OHRP can largely choose the specific allegations that it evaluates, as well as the content of any determination letters that it issues. Its compliance activities are not codified in Federal statute or regulations; rather, they appear in procedures issued by the agency.

In its review of SUPPORT, OHRP exercised its discretion to focus the evaluation on risks known at the start of the trial and on whether those risks had been communicated in the initial informed-consent document. Furthermore, in focusing its evaluation on the initial informed-consent documents, OHRP exercised its discretion to not review other aspects, such as whether any new risks were identified during the trial that should have been communicated to human subjects. Such risks might be found, for example, by the DSMC, which reviews data that might not be available to the funders of the research or to OHRP.[22]

Differing views on research involving current standards of care.

Finally, the discussions about SUPPORT have drawn attention to the protection of human subjects in research that compares treatments within the current standard of medical care. The goal of such research is to improve current knowledge and practice by determining the more effective intervention for diseases and conditions. OHRP's evaluation and determination made public fundamental differences on this topic, not just within the research and patient advocacy community, but also among government agencies that fund and oversee this research.

For example, in an article published in *The New England Journal of Medicine*, NIH leadership wrote: "[W]e respectfully disagree with the conclusions of the OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPPORT study commenced."[23] Given the differing perspectives of NIH and OHRP, HHS is reexamining this issue to better ensure that appropriate protections of human subjects are in place, while not discouraging progress in scientific research.

CONCLUSION

Our review of OHRP's for-cause compliance evaluation of SUPPORT found that it followed its published procedures in conducting that evaluation. Those procedures are broad, meaning that the office has substantial discretion in how it carries out any one evaluation.

[22] In our review, we became aware that OHRP may not have access to the minutes and records from the closed DSMC meetings. We are following up with OHRP to seek clarification on its authority to obtain all DSMC records when needed.

[23] K.L. Hudson et al., "In Support of SUPPORT—A View from the NIH." *The New England Journal of Medicine*, 2013; 368:2349-2351, June 20, 2013.

If you have any questions, please contact me or your staff may contact Chris Hinkle, Director of Congressional and Regulatory Affairs, at (202) 401-2206 or through email at Christina.Hinkle@oig.hhs.gov.

Sincerely,

Daniel R. Levinson

Daniel R. Levinson
Inspector General

Enclosures

From:	Barbara Stoll
To:	Luc Brion
Cc:	Roy Heyne; Higgins, Rosemary (NIH/NICHD) [E]; wrage@rti. org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; Das, Abhik; "_<WCarlo@peds.uab.edu>"@ws-mr3.cc.emory.edu
Subject:	Re: Revised Jackie LeVan"s manuscript
Date:	Wednesday, January 15, 2014 3:56:35 PM
Attachments:	Jackie LeVan Manuscript NRN 1-14-14 bjs.docx

A few minor edits
Ready to go
Fingers crossed
BJS**Luc Brion <Luc.Brion@utsouthwestern.edu> writes:**
Data from all centers together were removed from the text and this first row was removed by Lisa; please see discussion with Lisa and Abhik
I will send the revised version soon, integrating Wally's and Lisa's changes.
Bill

Sent from my iPad

On Jan 15, 2014, at 1:21 PM, "Roy Heyne" <Roy.Heyne@UTSouthwestern.edu> wrote:

This looks good and ready to go, except for one thing: the revised Table 2 does not include the row of data for overall group, though the Results-Primary Outcome narrative still references Table 2 in conjunction with the sentence presenting overall before/after data.

From: Luc Brion
Sent: Wednesday, January 15, 2014 8:38 AM
To: Roy Heyne; doctorlevan@gmail.com; Myra Wyckoff; higginsr@mail.nih.gov; wrage@rti. org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; doctorlevan@gmail.com; Das, Abhik; "WCarlo@peds.uab.edu"; Barbara Stoll; Luc Brion
Subject: RE: Revised Jackie LeVan's manuscript

Roy, thanks a lot

Dear Collaborators,

Please let me know ASAP if I may submit this revised manuscript to JAMA Pediatrics.

I would like to submit this manuscript on Friday!

Thanks and best regards,

Lue

From: Roy Heyne
Sent: Tuesday, January 14, 2014 10:18 AM
To: Lue Brion
Subject: RE: Revised Jackie LeVan's manuscript

Looks good. Only missed one typo in second sentence of results in the abstract. "no" should be not."

From: [redacted] Luc Brion
Sent: Tuesday, January 14, 2014 12:17 AM
To: Sanchez, Pablo; [redacted]; Roy, Hayne; Wally Carlo, M.D.; Gantz, Marie'; 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]; 'nfinet@ucsd.edu'; Myra Wyckoff; Manjbaramban, Jaleel; 'doctorlevan@gmail.com'
Subject: Revised Jackie LeVan's manuscript

Here's a revised manuscript, thanks all the suggestions and comments I have received, thanks Pablo, Roy, Neil and Lisa.

I made several additional changes to streamline the discussion.

Best regards,

Luc P. Brion, MD

Professor of Pediatrics

Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern Medical Center at Dallas

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bstoll@emory.edu

privileged or confidential information. If you have received it in error, please notify the sender immediately and delete the original.

From: Luc Brion
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Cc: doctorlevan@gmail.com; Myra Wyckoff; Higgins, Rosemary (NIH/NICHD) [E]; wrage@rti. org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; Das, Abhik; WCarlo@peds.uab.edu; Barbara Stoll
Subject: Re: Revised Jackie LeVan"s manuscript
Date: Wednesday, January 15, 2014 2:47:24 PM

Data from all centers together were re moved from the text and this first row was removed by Lisa; please see discussion with Lisa and Abhik
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> **Subject:** RE: Revised Jackie LeVan's manuscript
>
> Roy, thanks a lot
> Dear Collaborators:
> Please let me know ASAP if I may submit this revised manuscript to JAMA Pediatrics.
> I would like to submit this manucript on Friday.
> Thanks and best regards,
> Luc
>
> ---
>
> **From:** Roy Heyne
> **Sent:** Tuesday, January 14, 2014 10:18 AM
> **To:** Luc Brion
> **Subject:** RE: Revised Jackie LeVan's manuscript
>
> Looks good. Only missed one typo in second sentence of results in the abstract: "no" should be "not"
>
> ---
>
> **From:** Luc Brion
> **Sent:** Tuesday, January 14, 2014 12:17 AM
> **To:** Sanchez, Pablo; 'Barbara Stoll'; Roy Heyne; 'Wally Carlo, M.D.'; 'Gantz, Marie'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'nfiner@ucsd.edu'; Myra Wyckoff; Mambarambath Jaleel; 'doctorlevan@gmail.com'
> **Subject:** Revised Jackie LeVan's manuscript
>
> Here is a revised manuscript, thanks all the suggestions and comments I have received,

thanks Pablo, Roy, Neil and Lisa.
I made several additional changes to streamline the discussion.
Best regards,

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

Short title: Clinical practice changes after SUPPORT

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related trial.

Objective: To test the hypothesis that endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial within NICUs in NRN centers.

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a Feasibility Trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly in the group of infants from centers that had not participated in the Feasibility Trial (91% vs. 75%, adjusted relative risk (RR) 0.86, 95% confidence interval (CI) 0.83-0.89, p <0.0001) but not in the group

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of infants from the other centers, where rates of intubation were already lower prior to initiation of the trial (61% before vs. 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusions and Relevance: After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after release of the results of the SUPPORT trial to NRN centers had significantly lower percentages of DR ETI compared to infants born before the SUPPORT trial. This result was limited to the subgroup of infants from centers that had not participated in the Feasibility Trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of DR ETI and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN previously conducted a Feasibility Trial in 5 centers, to determine the feasibility of randomization to DR CPAP vs. DR ETI in the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the Feasibility Trial demonstrated~~has shown~~ that participation in the SUPPORT Trial affected clinical practice, specifically the proportion of DR ETI among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the Feasibility Trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the Feasibility Trial.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical

estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

~~The most important~~ Secondary outcomes of prime interest included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT

trial, i.e., physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included an indicator for study

group (post vs. pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] ~~[treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids]~~ (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in rate of DR ETI varied across the subgroups of infants in centers who did and did not participate in the Feasibility Trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR intubation model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, with a total ~~of~~ n of ~ 1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the Feasibility Trial.

~~The overall proportion of DR ETI decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, p<.0001. Within the subgroup of centers participating in the Feasibility trial, however, there was not a significant decrease: 326/532 (61%) before vs. 454/789 (58%) after, p=0.18, , while in the subgroup of center not participating there was: 987/1085 (91%) before vs. 1086/1443 (75%) after, p<0.0001.~~ In the model for DR ETI the interaction term between the indicator for the subgroups of centers that ~~who~~ did and did not participate in the Feasibility Trial with the pre vs. post-SUPPORT indicator, was significant ($p \leq 0.0001$), indicating that the change in rate of DR ETI varied across these subgroups, thus results for DR intubation are presented within subgroup (Table 2). ~~The~~ proportion of DR ETI ~~intubation rate~~ did not decrease significantly after SUPPORT in the subgroup of infants from centers that had participated in the Feasibility Trial (61.3% before vs. 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)), p<.0001.

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the Feasibility Trial. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the Feasibility Trial, and thus already had experience with unblinded randomization to CPAP vs. ETI in the DR. In one of these 3 centers, the proportion of ETI had decreased before the Feasibility Trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000.[17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients, which limits incomplete/missing data and information bias; the use of multivariate analysis to take into account confounding variables; inclusion and exclusion criteria that were similar to those used in the SUPPORT trial; inclusion of centers with or without prior participation in a similar trial with unblinded randomization to DR CPAP vs. DR ETI; and inclusion of study centers that remained in the NICHD

NRN during the entire study period, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (which were similar to those in SUPPORT); lack of serial data in each center and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends. Nevertheless, in another study we have shown that the proportion of DR ETI in one of these centers (which did not participate in the Feasibilty Trial) decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010).[4] In that center, DR ETI decreased by 22% during/after the SUPPORT Trial (before release of the trial results to NRN centers), in contrast to only by 1.6% in a large comparable contemporaneous cohort of infants born in level IIIb or IIIc North American centers participating in the Vermont Oxford Network (VON).[4] That study excluded VON centers participating in SUPPORT or in the Network Delivery Room Management Trial, as well as neonates who received comfort care in the DR (ETI~~death without endotracheal intubation~~), or had severe congenital anomalies.[4]

Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. Nevertheless, our prior study showed that DR ETI decreased and DR CPAP increased in one NRN center during and after SUPPORT in the absence of any changes in DR policy or practice guidelines.[4] It is also possible that additional unknown biases or confounding variables, such as changes in

personnel, could have affected the rationale used for each practice in each infant and thus rhe results of the present study.

Mortality before discharge decreased in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight

oxygen monitoring during the SUPPORT trial and might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial. This result was limited to the subgroup of infants from centers not included in the Feasibility Trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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12.

Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

From: Luc Brion
To: Das, Abhik; Wrage, Lisa Ann; Wrage, Lisa Ann; Roy Heyne; doctorlevan@gmail.com; Myra Wyckoff; Higgins, Rosemary (NIH/NICHD) [E]; wrage@rti.org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; doctorlevan@gmail.com; Das, Abhik; WCarlo@peds.uab.edu; "Barbara Stoll"; Luc Brion
Cc: Gantz, Marie
Subject: RE: Revised Jackie LeVan"s manuscript
Date: Wednesday, January 15, 2014 12:41:46 PM
Attachments: Table 2 edlw10Jan14.docx

Abhik;
Thanks for your email and for the clarification.

Dear collaborators:
Here is table 2 edited by Lisa we should then use for the submission.
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
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luc.brion@utsouthwestern.edu

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, January 15, 2014 11:25 AM
To: Luc Brion; Wrage, Lisa Ann
Cc: Gantz, Marie
Subject: RE: Revised Jackie LeVan's manuscript

The problem is that if we have a significant interaction, then talking about an overall effect is not meaningful any more, because there is no consistent overall effect. For example, if a drug has a significant interaction with gender, it works differently in men and women, so it does not make sense to talk about its overall effect any more.

Thanks

Abhik

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, January 15, 2014 11:58 AM
To: Wrage, Lisa Ann
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Revised Jackie LeVan's manuscript

Lisa;
Thanks for your email.
I am having serious concern about not presenting the overall significant change in the entire group. This would require discussion. Pablo and Neil strongly argued with this as well.
In trials the overall group is presented with later subgroup analyses as secondary outcomes. I think we must keep as primary outcome the overall effect in the entire group; subgroup analysis should then remain a secondary outcome.
Luc

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luc.brion@utsouthwestern.edu

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, January 15, 2014 10:32 AM
To: Luc Brion
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Revised Jackie LeVan's manuscript

Hi Luc,
Could you please also share the tables that you plan to submit. Table 2 has changed and I would like to see if the way we are now describing results is clear to everyone. Or if we need to clear it up some more. I've made some edits in this version, since we are now including that interaction term between the feasibility trial subgroup indicator and post/pre SUPPORT indicator, and since it is significant, the overall adjusted result is not relevant anymore (it is from the previous version of the model that did not include the feasibility study indicator). If you'd like to present the overall result in Table 2 and in the paper we can put the overall unadjusted result in there, but otherwise the focus would be on the two subgroup results. I've tried to clear that up with the edits. Let me know if this makes sense.
Thanks.
Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, January 15, 2014 9:38 AM
To: Roy Heyne; doctorlevan@gmail.com; Myra Wyckoff; higginsr@mail.nih.gov; Wrage, Lisa Ann; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; doctorlevan@gmail.com; Das, Abhik; WCarlo@peds.uab.edu; 'Barbara Stoll'; Luc Brion
Subject: RE: Revised Jackie LeVan's manuscript

Roy, thanks a lot
Dear Collaborators:
Please let me know ASAP if I may submit this revised manuscript to JAMA Pediatrics.
I would like to submit this manucript on Friday.
Thanks and best regards,
Luc

From: Roy Heyne
Sent: Tuesday, January 14, 2014 10:18 AM
To: Luc Brion
Subject: RE: Revised Jackie LeVan's manuscript

Looks good. Only missed one typo in second sentence of results in the abstract: "no" should be "not"

From: Luc Brion
Sent: Tuesday, January 14, 2014 12:17 AM
To: Sanchez, Pablo; 'Barbara Stoll'; Roy Heyne; 'Wally Carlo, M.D.'; 'Gantz, Marie'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'nfiner@ucsd.edu'; Myra Wyckoff; Mambarambath Jaleel; 'doctorlevan@gmail.com'
Subject: Revised Jackie LeVan's manuscript

Here is a revised manuscript, thanks all the suggestions and comments I have received, thanks Pablo, Roy, Neil and Lisa.
I made several additional changes to streamline the discussion.
Best regards,

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The

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Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviation: RR, relative risk

[1] results are shown for groups defined by combining subjects from centers who did or did not participate in the Feasibility Trial

[2] unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] adjusted p-values from robust Poisson model

From: Luc Brion
To: Wrage, Lisa Ann; Roy Heyne; doctorlevan@gmail.com; Myra Wyckoff; Higgins, Rosemary (NIH/NICHD) [E]; wrage@rti.org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; doctorlevan@gmail.com; Das, Abhik; WCarlo@peds.uab.edu; "Barbara Stoll"; Luc Brion
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Revised Jackie LeVan"s manuscript
Date: Wednesday, January 15, 2014 11:52:12 AM
Attachments: Table 2.docx
Appendix.docx
Table 3.docx
Table 1.docx
Figure 2.docx
Figure 1.docx

Lisa:
Thanks for your email.
Here are the current tables and figures
Luc

From: Wrage, Lisa Ann [wrage@rti.org]
Sent: Wednesday, January 15, 2014 10:31 AM
To: Luc Brion
Cc: Das, Abhik; Gantz, Marie
Subject: RE: Revised Jackie LeVan's manuscript

Hi Luc,
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Thanks.
Lisa

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Subject: RE: Revised Jackie LeVan's manuscript

Roy, thanks a lot
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Luc

From: Roy Heyne
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Looks good. Only missed one typo in second sentence of results in the abstract: "no" should be "not"

From: Luc Brion
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Subject: Revised Jackie LeVan's manuscript

Here is a revised manuscript, thanks all the suggestions and comments I have received, thanks Pablo, Roy, Neil and Lisa.
I made several additional changes to streamline the discussion.
Best regards,

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Appendix. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.0025
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.0028
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

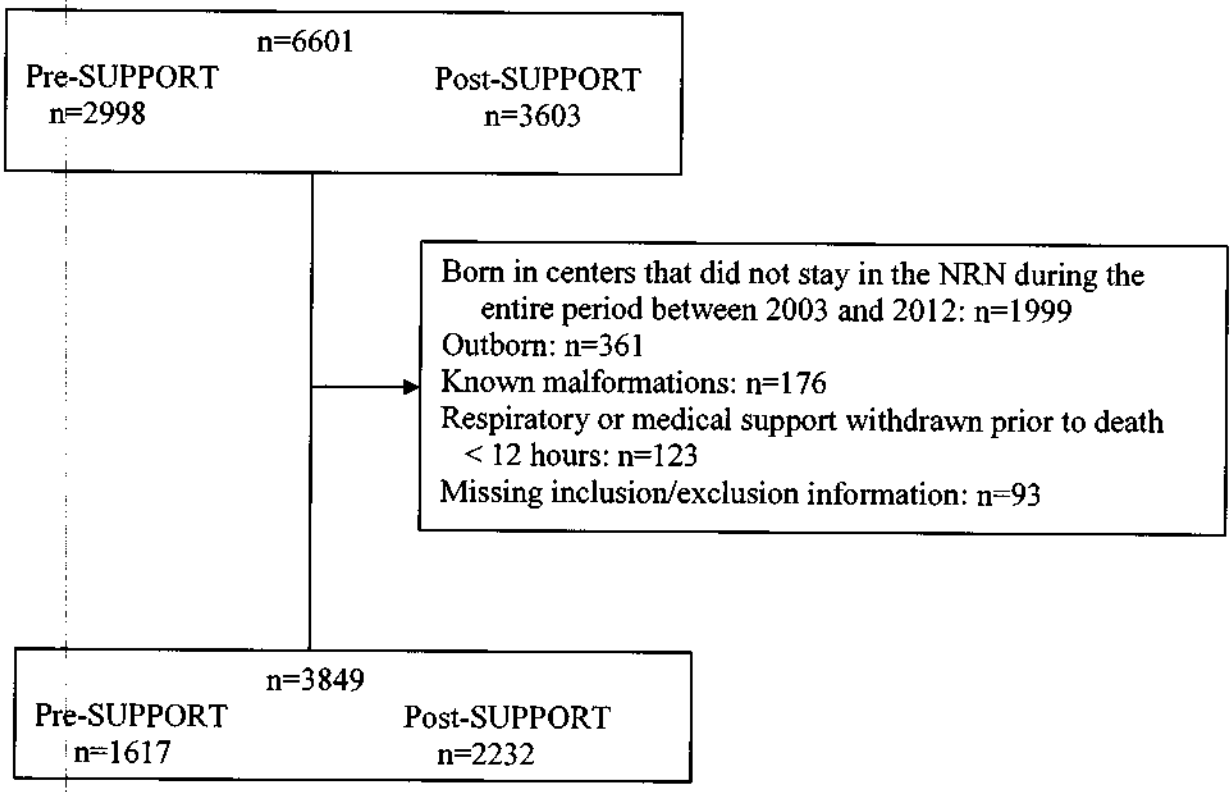
n=6601
Pre-SUPPORT
n=2998
Post-SUPPORT
n=3603
Born in centers that did not stay in the NRN during the entire period between 2003 and 2012: n=1999
Outborn: n=361
Known malformations: n=176
Respiratory or medical support withdrawn prior to death < 12 hours: n=123
Missing inclusion/exclusion information: n=93
n=3849
Pre-SUPPORT
n=1617
Post-SUPPORT
n=2232

Figure 2

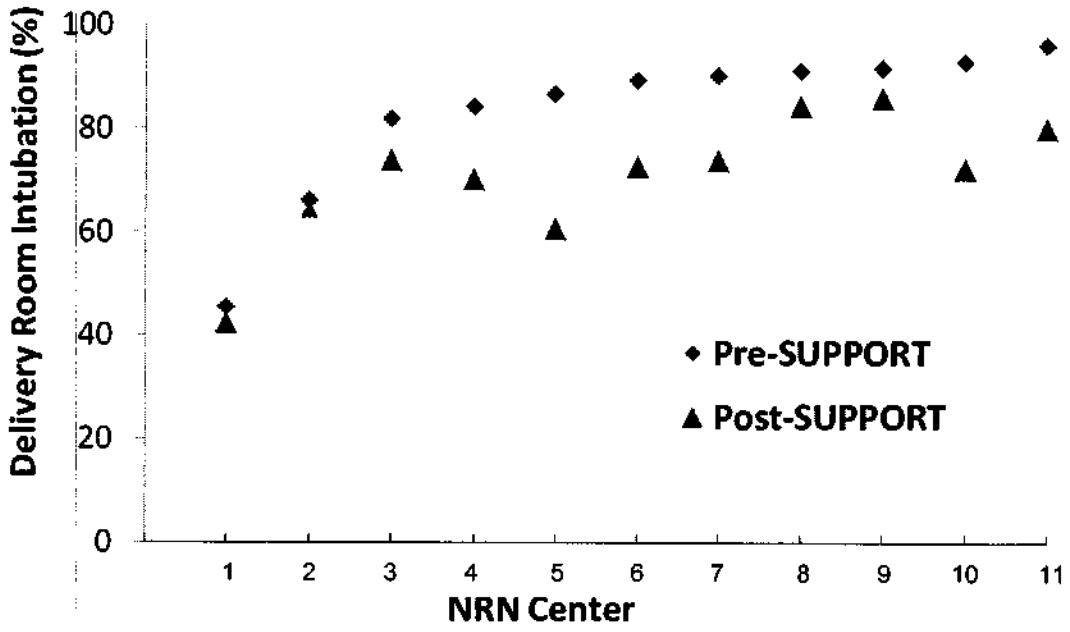
Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[4]
All subjects	1313/1617 (81%)	1539/2232 (69%)	<0.0001	0.88 (0.85-0.91)	<0.0001
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviation: RR, relative risk

[1] results are shown for groups defined by combining subjects from centers who did or did not participate in the Feasibility Trial

[2] unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: could you please review this briefing paper on the SUPPORT ttial?
Date: Wednesday, January 15, 2014 10:32:31 AM

Sure
Thanks
Rose

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

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, January 15, 2014 10:29 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: could you please review this briefing paper on the SUPPORT ttial?

Didn't get a chance to say – about the OIG – Sarah informs me that we can keep this paper confidential – would that do the trick?

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, January 15, 2014 8:57 AM
To: Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: could you please review this briefing paper on the SUPPORT ttial?

Here you go

Thanks
Rose

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, January 14, 2014 8:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: could you please review this briefing paper on the SUPPORT ttial?

Hi Rose – could you please review this updated briefing paper on the SUPPORT trial. Hope I got the updates correct after our discussion.

Lisa –to save time—can you please look at the leg section and see if it needs updating
To facilitate this I've attached the updated version
Thanks all!!

From: Luc Brion
To: Roy Heyne (b)(6) gmail.com; Myra Wyckoff; Higgins, Rosemary (NIH/NICHD) [E]; wrage@rti.org; Mambarambath Jaleel; Gantz, Marie; Finer, Neil; doctorlevan@gmail.com; Das, Abhik; WCarlo@peds.uab.edu; "Barbara Stoll"; Luc Brion
Subject: RE: Revised Jackie LeVan"s manuscript
Date: Wednesday, January 15, 2014 9:37:43 AM
Attachments: Jackie LeVan Manuscript NRN 1-14-14.docx

Roy, thanks a lot
Dear Collaborators:
Please let me know ASAP if I may submit this revised manuscript to JAMA Pediatrics.
I would like to submit this manucript on Friday.
Thanks and best regards,
Luc

From: Roy Heyne
Sent: Tuesday, January 14, 2014 10:18 AM
To: Luc Brion
Subject: RE: Revised Jackie LeVan's manuscript

Looks good. Only missed one typo in second sentence of results in the abstract: "no" should be "not"

From: Luc Brion
Sent: Tuesday, January 14, 2014 12:17 AM
To: Sanchez, Pablo; 'Barbara Stoll'; Roy Heyne; 'Wally Carlo, M.D.'; 'Gantz, Marie'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'nfiner@ucsd.edu'; Myra Wyckoff; Mambarambath Jaleel; 'doctorlevan@gmail.com'
Subject: Revised Jackie LeVan's manuscript

Here is a revised manuscript, thanks all the suggestions and comments I have received, thanks Pablo, Roy, Neil and Lisa.
I made several additional changes to streamline the discussion.
Best regards,

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Short title: Clinical practice changes after SUPPORT

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in a related trial.

Objective: To test the hypothesis that endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial within NICUs in NRN centers.

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a Feasibility Trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: Proportion of DR ETI

Results: The proportion of DR ETI decreased significantly after SUPPORT, adjusted relative risk (RR) 0.89, 95% confidence interval (CI) 0.86-0.93. DR ETI decreased significantly in the group of infants from centers that had not participated in the

Feasibility Trial (91% vs. 75%, adjusted RR 0.86, 95% CI 0.83-0.89, p <0.0001) but not in the group of infants from the other centers (61% before vs. 58% after SUPPORT, adjusted RR 0.96, 95% CI 0.89-1.05, p=0.40).

Conclusions and Relevance: After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after release of the results of the SUPPORT trial to NRN centers had significantly lower percentages of DR ETI compared to infants born before the SUPPORT trial. This result was limited to the subgroup of infants from centers that had not participated in the Feasibility Trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of DR ETI and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN previously conducted a Feasibility Trial in 5 centers, to determine the feasibility of randomization to DR CPAP vs. DR ETI in the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the Feasibility Trial has shown that participation in the SUPPORT Trial affected clinical practice, specifically the proportion of DR ETI among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the Feasibility Trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the Feasibility Trial.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical

estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trial, i.e.,

physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included an indicator for study

group (post vs. pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in rate of DR ETI varied across the subgroups of infants in centers who did and did not participate in the Feasibility Trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR intubation model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, a total of n=1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

The primary outcome, the proportion of DR ETI, decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. The adjusted risk of DR ETI significantly decreased after the SUPPORT trial, RR 0.89, 95% confidence interval 0.86-0.93 (Table 2). Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

The 3 centers with the lowest baseline proportion were those that had participated in the Feasibility Trial.

The indicator for the subgroups of centers who did and did not participate in the Feasibility Trial, and its interaction with the pre vs. post-SUPPORT indicator, was significant, so results for DR intubation are presented within these subgroups (Table 2). The DR intubation rate did not decrease after SUPPORT in the subgroup of infants from centers that had participated in the feasibility trial (61.3% before vs. 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)).

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the Feasibility Trial. In contrast, the proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the Feasibility Trial, and thus already had experience with unblinded randomization to CPAP vs. ETI in the DR. In one of these 3 centers, the proportion of ETI had decreased before the Feasibility Trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000.[17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients, which limits incomplete/missing data and information bias; the use of multivariate analysis to take into account confounding variables; inclusion and exclusion criteria that were similar to those used in the SUPPORT trial; inclusion of centers with or without prior participation in a similar trial with unblinded randomization to DR CPAP vs. DR ETI; and inclusion of study centers that remained in the NICHD NRN during the entire study period, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (which were similar to those in SUPPORT); lack of serial data in each center and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of

secular trends. Nevertheless, in another study we have shown that the proportion of DR ETI in one of these centers (which did not participate in the Feasibilty Trial) decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010).[4] In that center, DR ETI decreased by 22% during/after SUPPORT (before release of the trial results to NRN centers), in contrast to only by 1.6% in a large comparable contemporaneous cohort of infants born in level IIIb or IIIc North American centers participating in the Vermont Oxford Network (VON).[4] That study excluded VON centers participating in SUPPORT or in the Network Delivery Room Management Trial, as well as neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies.[4]

Additional limitations of the present study include lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or oxygen saturation. Nevertheless, our prior study showed that DR ETI decreased and DR CPAP increased in one NRN center during and after SUPPORT in the absence of any changes in DR policy or practice guidelines.[4] It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the rationale used for each practice in each infant and thus the results of the present study.

Mortality before discharge decreased in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in

mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial. This result was limited to the subgroup of infants from centers not included in the Feasibility Trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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12.

Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

From: Kaeser, Lisa (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: could you please review this briefing paper on the SUPPORT ttial?
Date: Wednesday, January 15, 2014 9:26:29 AM

Hi – just looked, and no, there has been no further legislative activity or inquiry on this since last summer. So I think you can just note that in the legislative section and send forward.

Thanks,

Lisa

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 15, 2014 8:57 AM
To: Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: could you please review this briefing paper on the SUPPORT ttial?

Here you go

Thanks
Rose

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, January 14, 2014 8:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: could you please review this briefing paper on the SUPPORT ttial?

Hi Rose – could you please review this updated briefing paper on the SUPPORT trial. Hope I got the updates correct after our discussion.

Lisa –to save time—can you please look at the leg section and see if it needs updating
To facilitate this I've attached the updated version
Thanks all!!

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
Subject: RE: could you please review this briefing paper on the SUPPORT ttial?
Date: Wednesday, January 15, 2014 8:57:07 AM
Attachments: NIH BRAIN - SUPPORT Studymrclean.docx

Here you go

Thanks
Rose

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, January 14, 2014 8:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]
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From: Luc Brion
To: Sanchez, Pablo; "Barbara Stoll"; Roy Heyne; "Wally Carlo, M.D."; "Gantz, Marie"; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"; Myra Wyckoff; Mambarambath Jaleel; (b)(6) @gmail.com"
Subject: Revised Jackie LeVan"s manuscript
Date: Tuesday, January 14, 2014 1:16:50 AM
Attachments: Jackie LeVan Manuscript NRN 1-13-14.docx

Here is a revised manuscript, thanks all the suggestions and comments I have received, thanks Pablo, Roy, Neil and Lisa.
I made several additional changes to streamline the discussion.
Best regards,

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in ~~to~~ a related trial.

Objective: To test the hypothesis that endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial ~~SUPPORT trial~~ within NICUs in NRN centers.

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the ~~NICHD Neonatal Research Network (NRN)~~ SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a Feasibility Trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: Proportion of DR ETI

Results: The proportion ~~rate~~ of DR ETI decreased significantly after SUPPORT, adjusted relative risk (RR) 0.89, 95% confidence interval (CI) 0.86-0.93. DR ETI decreased significantly in the group of infants from centers that had not participated in the

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Feasibility Trial (91% vs. 75%, adjusted RR 0.86, 95% CI 0.83-0.89, p <0.0001) but no in ~~did not decrease after SUPPORT in~~ the group of infants from the other centers ~~previously participating in the Feasibility Trial~~ (61% before vs. 58% after SUPPORT-, adjusted ~~relative risk~~ (RR) 0.96, 95% CI ~~confidence interval (CI)~~ 0.89-1.05, p=0.40).~~, but decreased significantly in the group of infants from the other centers (91% vs. 75%, adjusted RR 0.86, 95% CI 0.83-0.89, p <0.0001).~~

Conclusions and Relevance: After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after release of the results of the SUPPORT trial to NRN centers had significantly lower percentages of DR ETI compared to infants born before the SUPPORT trial. This result was limited to the subgroup of infants from centers that ~~had~~did not participate ~~dnot included~~ in the Feasibility Trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of DR ETI and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN previously conducted a Feasibility Trial in 5 centers, to determine the feasibility of randomization to DR CPAP vs. DR ETI in the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the Feasibility Trial has shown that participation in the SUPPORT Trial affected clinical practice, specifically the proportion of DR ETI among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the Feasibility Trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003-2012). Of these centers, three had participated in the Feasibility Trial.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The

definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trial, i.e., physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence

intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included an indicator for study group (post vs. pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in rate of DR ETI varied across the subgroups of infants in centers who did and did not participate in the Feasibility Trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR intubation model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of delivery room intubations from

the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, a total of n=1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

The primary outcome, the proportion of DR ETI, decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. The adjusted risk of DR ETI significantly decreased after the SUPPORT trial, RR 0.89, 95% confidence interval 0.86-0.93 (Table 2). Using aggregate center data, Figure 2 shows the

proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the Feasibility Trial.

The indicator for the subgroups of centers who did and did not participate in the Feasibility Trial, and its interaction with the pre vs. post-SUPPORT indicator, was significant, so results for DR intubation are presented within these subgroups (Table 2). The DR intubation rate did not decrease after SUPPORT in the subgroup of infants from centers that had participated in the feasibility trial (61.3% before vs. 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)).

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before ~~initiation of~~ the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the Feasibility Trial. ~~Since we did not analyze serial changes in the proportion of DR ETI in this study, the data do not allow us to determine when DR ETI decreased in each center. However, in another study we have shown that the proportion of DR ETI in one of these centers that did not participate in the Feasibility Study decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[4] The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[4]~~ In contrast, the ~~p~~ proportion of DR ETI in the current study did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the Feasibility Trial, (and thus already had experience with unblinded randomization to CPAP vs. ETI ~~using T-piece resuscitators and CPAP~~ in the DR). In one of these 3 centers, the proportion of

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ETI had decreased before the Feasibility Trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000.[17]

The strengths of this study include the large sample size; the use of a prospective database of inborn patients, ~~and a large sample size of inborn patients~~ which limits incomplete/missing data and information bias; the use of multivariate analysis to take into account confounding variables; ~~the use of~~ inclusion and exclusion criteria that were similar to those used in the SUPPORT trial; inclusion of centers with or without prior participation in a similar trial with unblinded randomization to DR CPAP vs. DR ETI; and ~~the~~ inclusion of study centers that remained in the NICHD NRN during the entire study period ~~including the two cohorts~~, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (which were similar to those in ~~required to restrict the cohorts to match the~~ SUPPORT) ~~enrollment criteria as closely as possible~~); lack of serial data in each center and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends. Nevertheless, in another study we have shown that the proportion of DR ETI in one of these centers (which did not participate in the Feasibilty Trial) decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010).[4] In that center, DR ETI decreased by 22% during/after SUPPORT (before release of the trial results to NRN centers), in contrast to only by 1.6% in a large comparable contemporaneous cohort of infants born in level IIIb or IIIc North American centers

participating in the Vermont Oxford Network (VON).[1] That study excluded VON centers participating in SUPPORT or in the Network Delivery Room Management Trial, as well as neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies.[1]

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Additional limitations of the present study include : lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP or ; oxygen saturation, ~~or rationale used for each practice in each infant.~~ Nevertheless, our prior study showed that DR ETI decreased and DR CPAP increased in one NRN center during and after SUPPORT in the absence of any changes in DR policy or practice guidelines.[1] It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the ~~or~~ rationale used for each practice in each infant, and thus the results of the present study. Mortality before discharge decreased in ~~the group of infants in~~ the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after

the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. -We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial. This result was limited to the subgroup of infants from centers not included in the Feasibility Trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

From:	Luc Brion
To:	Sanchez, Pablo; "Barbara Stoll"; Roy Heyne; "Wally Carlo, M.D."; "Gantz, Marie"; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"; Myra Wyckoff; Mambarambath Jaleel; "doctorlevan@gmail.com"
Subject:	RE: Updated files
Date:	Sunday, January 12, 2014 10:52:46 AM
Attachments:	LeVan Pediatrics 2013 Change in Care Nonenrolled Patients.pdf Jackie LeVan Manuscript NRN 1-12-14 rev.docx

Here is a revised version in which I specifically address the issue of secular trends.
Luc

From: Sanchez, Pablo [Pablo.Sanchez@nationwidechildrens.org]
Sent: Saturday, January 11, 2014 9:17 PM
To: Luc Brion; 'Barbara Stoll'; Roy Heyne; 'Wally Carlo, M.D.'; 'Gantz, Marie'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'nfiner@ucsd.edu'; Myra Wyckoff; Mambarambath Jaleel; 'doctorlevan@gmail.com'
Subject: RE: Updated files

Hi Luc---see attached—some errors in the reference numbers –minor comments—interesting—you were right about the participation in the feasibility trial .. pablo

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Saturday, January 11, 2014 7:10 PM
To: 'Barbara Stoll'; Roy Heyne; 'Wally Carlo, M.D.'; 'Gantz, Marie'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'nfiner@ucsd.edu'; Sanchez, Pablo; Myra Wyckoff; Mambarambath Jaleel; 'doctorlevan@gmail.com'; Luc Brion
Subject: Updated files

I did some minor changes in the text and in Table 2.
Luc

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Change in Care Among Nonenrolled Patients During and After a Randomized Trial

WHAT'S KNOWN ON THIS SUBJECT: Participating in a trial may affect processes of care by participating physicians; however, no study has assessed whether it affects processes of care for nonenrolled patients.

WHAT THIS STUDY ADDS: Participation in a trial may affect processes of care for nonenrolled patients, even when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study.

OBJECTIVE: Parkland Memorial Hospital (PMH) participated in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded controlled trial, in which preterm neonates of $24^{0/7}$ to $27^{6/7}$ weeks' gestational age (GA) were randomized in the delivery room (DR) to endotracheal intubation or nasal continuous positive airway pressure. We hypothesized that DR intubation could change in nonenrolled patients at PMH and that the change would be larger than in comparable centers not participating in the trial.

METHODS: The PMH Cohort included eligible but nonenrolled neonates of $24^{0/7}$ to $27^{6/7}$ weeks (primary) and noneligible neonates of 28 to $34^{6/7}$ weeks (confirmatory). A subset ($24^{0/7}$–$29^{6/7}$weeks) of that cohort was compared with a contemporaneous cohort born in centers participating in the Vermont Oxford Network (VON). We used a Poisson regression model to obtain adjusted relative risks (RRs) of DR intubation (during/after SUPPORT versus before SUPPORT) for PMH and for VON along with the ratio of these RRs.

RESULTS: In the PMH cohort ($n = 3527$), the proportion of DR intubation decreased during/after SUPPORT in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96) and the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70). Compared with the RR for DR intubation in VON, the RR at PMH was smaller in the lower (ratio of RR 0.76, 95% CI 0.65–0.87) and the upper GA group (ratio of RR 0.52, 95% CI 0.39–0.68).

CONCLUSIONS: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. *Pediatrics* 2013;132:e960–e970

AUTHORS: Jaclyn M. LeVan, DO,[a] Myra H. Wyckoff, MD,[a] Chul Ahn, PhD,[b] Roy Heyne, MD,[a] Pablo J. Sánchez, MD,[a] Lina Chalak, MD,[a] Mambarambath A. Jaleel, MD,[a] P. Jeannette Burchfield, RN,[a] Lucy Christie, RN,[a] Roger Soll, MD,[c,d] Gary J. Badger, MS,[c] and Luc P. Brion, MD[a]

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KEY WORDS

randomized controlled trial, process of care, unblinded, preterm, endotracheal intubation, birth cohort study, non-enrolled patients

ABBREVIATIONS

BW—birth weight
CI—confidence interval
CPAP—continuous positive airway pressure
DR—delivery room
GA—gestational age
NNT—number needed to treat
NRN—Neonatal Research Network
PMH—Parkland Memorial Hospital
RCT—randomized controlled trial
RD—risk difference
RR—relative risk
SUPPORT—Surfactant, Positive Pressure, and Oxygenation Randomized Trial
VON—Vermont Oxford Network

Dr LeVan conceptualized and designed the study, merged data from all Parkland Memorial Hospital (PMH) databases, participated in the interpretation of the data, drafted the first version of the manuscript, and critically reviewed the revisions; Drs Wyckoff, Heyne, Sanchez, Chalak, and Jaleel conceptualized and designed the study, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Ahn conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Ms Burchfield and Ms Christie collected and entered data into the databases and extracted the data for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Soll conceptualized and designed the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Badger conceptualized, designed, and conducted the statistical analyses for the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Brion conceptualized and designed the study, conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

(Continued on last page)

4-01334

Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients.[1,2] Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.[1] Andersen et al showed that conducting a seeding trial (company-driven trial to entice doctors to prescribe a new drug being marketed by the company) changed some processes of care among participating physicians compared with nonparticipating physicians; however, processes of care for nonenrolled patients were not assessed.[3,4]

The objective of the current study was to evaluate whether a process of care of contemporaneous nonenrolled patients can change during and after recruitment to an unblinded randomized trial, when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study. We hypothesized (1) that participation of Parkland Memorial Hospital (PMH) in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded RCT comparing processes of care, could be associated with a reduction in the proportion of delivery room (DR) intubation in nonenrolled patients, and (2) that the local practice change would be larger than in comparable centers not participating in SUPPORT.

METHODS

Setting

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 × 2 factorial trial in which preterm neonates of $24^{0/7}$ to $27^{6/7}$ weeks' gestational age (GA) were randomized at birth to 2 interventions: (1) continuous positive airway pressure (CPAP) initiated in the DR and subsequent use of a protocol-driven limited ventilation strategy or DR intubation with surfactant administration, and (2) oxygen saturation targets of 85% to 89% or 91% to 95%.[5,6] The first intervention (CPAP versus DR intubation/surfactant) was unblinded, and its primary outcome was death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age.[5] PMH participated in SUPPORT from July 2005 until February 2009.

Data were compiled from 3 prospective databases, including detailed information about DR and NICU management with predetermined entry criteria and definitions: the Neonatal DR Resuscitation Registry (started in 1989), the NICU database (started in 1977), and SUPPORT registry. At PMH, all neonates <35 weeks' GA by obstetrical assessment are admitted to the NICU and included in the Resuscitation Registry and in the NICU database (unless triaged to the newborn nursery if pediatric assessment is >34 weeks' GA and the infant is otherwise well). These databases provide information on 99.8% of eligible neonates, with high interrater reliability (<1% error); most missing data points correspond to infants triaged to the newborn nursery (≤6%).

Data for an analysis cohort were abstracted by using a before–after study design during 3 consecutive epochs: (1) up to 30 months before SUPPORT initiation, (2) during SUPPORT participation, and (3) up to 15 months after trial completion. To account for secular trends in DR intubation, a subset of the PMH cohort was compared with a contemporaneous control population in the Vermont Oxford Network (VON), a voluntary collaboration of more than 900 NICUs around the world. The VON includes de-identified data by calendar year on infants with birth weight (BW) of 501 to 1500 g. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

Participants

The PMH cohort included neonates $24^{0/7}$ to $34^{6/7}$ weeks' GA born at PMH before SUPPORT (January 2003–June 2005), during SUPPORT (July 2005–February 2009), and after SUPPORT (March 2009–June 2010) until SUPPORT publication.[5,6] The study included (1) neonates $24^{0/7}$ to $27^{6/7}$ weeks' GA who were eligible for SUPPORT but not enrolled (lower GA group), and (2) noneligible neonates of $28^{0/7}$ to $34^{6/7}$ weeks' GA (upper GA group). The latter was used as a positive control for the lower GA group, in whom selection bias (due to exclusion of patients enrolled into SUPPORT) was possible.[7,8] Exclusion criteria were comfort care or major congenital anomalies known at birth, lack of patient record in the DR Resuscitation Registry or the NICU database, and enrollment in SUPPORT.

A subset of the PMH cohort, including all neonates $24^{0/7}$ to $29^{6/7}$ weeks' GA born in 2003 to 2004 (before SUPPORT) and 2006 to 2009 (during/after SUPPORT), was compared with inborn contemporaneous neonates born in level IIIb or IIIc North American centers participating in VON. The subset included (1) neonates $24^{0/7}$ to $27^{6/7}$ weeks' GA (lower GA group), and (2) neonates of $28^{0/7}$ to $29^{6/7}$ weeks' GA (upper GA group). We excluded centers participating in SUPPORT or in the VON Delivery Room Management Trial,[9] and neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies. This GA range was selected because infants in this GA range are included in the 501 to 1500 g BW range of VON. PMH was not a member of VON during the study period.

Comparisons of Interest

PMH Cohort

The primary analysis was the adjusted relative risk (RR) of DR intubation

during/after SUPPORT versus before SUPPORT in the lower GA group. The adjusted RR in the upper GA group was confirmatory and used as a positive control.

Univariate analyses in each GA group evaluated DR treatment (endotracheal intubation, positive pressure ventilation, CPAP), intubation (within the first 4 hours after admission to the NICU or during the first 24 hours of age), surfactant administration, pneumothorax, mortality to discharge from the hospital, chronic lung disease (chronic changes on chest radiograph and supplemental oxygen requirement for at least 28 days), duration of mechanical ventilation, patent ductus arteriosus, necrotizing enterocolitis (stage II or greater, modified Bell classification),[10] severe intraventricular hemorrhage (Papile grade III or IV),[11] periventricular leukomalacia, and severe retinopathy of prematurity (grade 3 or higher, international classification).[12]

Comparison With VON

The primary analysis was the comparison of RR (adjusted for baseline variables) of DR intubation (during/after SUPPORT versus before SUPPORT) in the subset of the PMH cohort in the lower GA group with the RR of DR intubation in the contemporaneous VON cohort.

The secondary analyses were (1) the adjusted ratio of RRs for DR intubation in the upper GA group and (2) the adjusted ratio of RRs for any invasive (endotracheal tube or tracheostomy) ventilation.

Statistical Analysis: PMH Cohort

Multivariate Analyses

In each GA group, the adjusted RRs for DR intubation during/after SUPPORT versus before SUPPORT were calculated using robust Poisson regression in a generalized estimating equation model adjusted for covariates that met the $P < .05$ criterion (backward selection). Candidate variables selected for modeling were characteristics preceding the decision of DR intubation and shown previously to associate with DR intubation.[13–27] To avoid collinearity with GA, BW was converted to BW *z*-score.[28] The adjusted risk difference (RD) and number needed to treat (NNT) were obtained from the adjusted RR and the proportion of DR intubation before SUPPORT. The Altman interaction test[29] was used to determine if the adjusted RRs for DR intubation were different between GA groups.

Univariate Analyses

Univariate analyses were performed by using χ^2 tests or Fisher's exact tests for categorical variables, and Student's *t* tests or analyses of variance followed by Tukey test, or Kruskal-Wallis test followed by Mann-Whitney test for continuous variables. We analyzed temporal patterns of DR intubation to determine how soon after initiating SUPPORT the proportion of DR intubation changed from baseline; we selected blocks of 15 to 16 months to limit fluctuation due to sample size.

Statistical analyses were performed by using SPSS version 19 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and SAS version 9.2 (SAS Institute, Cary, NC). Statistical significance (2-tailed) was determined based on $P < .05$, except for multiple pairwise nonparametric comparisons, for which we used the Bonferroni adjustment.

The time interval for data abstraction was set to ascertain a sufficient number of registered patients in the PMH cohort to detect changes in DR intubation in the lower GA subgroup using multivariate analysis. Given the ascertainment of data on 200 DR intubations, the analysis set was sufficient to conduct a multivariate analysis with up to 20 independent covariates tested as main effects, with a 2-sided α of 0.05. The duration of the study was set to recruit enough patients to detect changes in DR intubation in the lower GA group by univariate analysis. The effect size was selected as a 33% RR reduction in DR intubation, a conservative estimate compared with the 47% RR reduction in DR intubation in a center in which routine DR bubble CPAP was prospectively introduced in 2000.[21] A sample of 97 patients before SUPPORT and during/after SUPPORT yielded 80% power to detect a reduction in DR intubation from 60% to 40% with a 2-sided α of 0.05.

Comparison With VON

A Poisson regression model with robust variance was used for each GA group to obtain adjusted RRs (during/after SUPPORT versus before SUPPORT) for PMH and VON along with the ratio of their RRs.[30] Covariates in the model were infants' GA, gender, BW, *z*-score, and antenatal steroids. Location (PMH and VON) and epoch (before and during/after SUPPORT) were represented by a 4-level categorical variable in the model, with the appropriate linear contrasts constructed to obtain estimates of RRs and their ratio.

RESULTS

PMH Cohort

At PMH, a total of 3821 individual patient database records were reviewed, of which 3533 were eligible and 3527 (99.8%) had records in the 3 PMH databases (Fig 1). The analysis cohort comprised 3527 records. In the lower GA group, the percentage of multiple births was lower after SUPPORT (Table 1). In the upper GA group, exposure to antenatal steroids was more frequent after SUPPORT, maternal diabetes was more frequent during SUPPORT, and BW was greater during/after SUPPORT; other differences were clinically insignificant (Table 2).

During SUPPORT, patients in the lower GA group included in the current study

had a greater GA than contemporaneous patients enrolled in SUPPORT (excluded from the current study), were less likely to have been exposed to antenatal steroids, and were more likely to receive positive pressure ventilation in the DR (Appendix).

Multivariate Analysis

Among 3527 neonates, 649 (18%) were intubated in the DR. The proportion of DR intubation significantly decreased during/after SUPPORT versus before SUPPORT, in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96, $P = .02$) and in the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70, $P < .001$) (Tables 3 and 4). In the lower GA group, the proportion of DR intubation decreased from 85% before SUPPORT to 61% during/after SUPPORT (Table 5) (adjusted RD 0.21, 95% CI 0.03–0.34; NNT 5, 95% CI 3–33). In the upper GA group, the proportion decreased from 19% to 10% (Table 6) (adjusted RD 0.08, 95% CI 0.06–0.10; NNT 12, 95% CI 10–18). The decrease in DR intubation was not significantly different in the upper GA group compared with the lower GA group (adjusted ratio of RR 0.75, 95% CI 0.54–1.03).

Univariate Analyses

In the lower GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ($P = .01$) and that of CPAP increased ($P < .001$) (Table 5). Not surprisingly, the proportion of intubation in the NICU within 4 hours after admission increased over time ($P = .03$); however, intubation within 24 hours of life decreased during/after SUPPORT ($P = .002$). The proportion of surfactant administration decreased during SUPPORT ($P < .001$). The proportion of pneumothoraces increased after SUPPORT ($P = .03$). Most pneumothoraces occurred in neonates who were intubated in the DR.

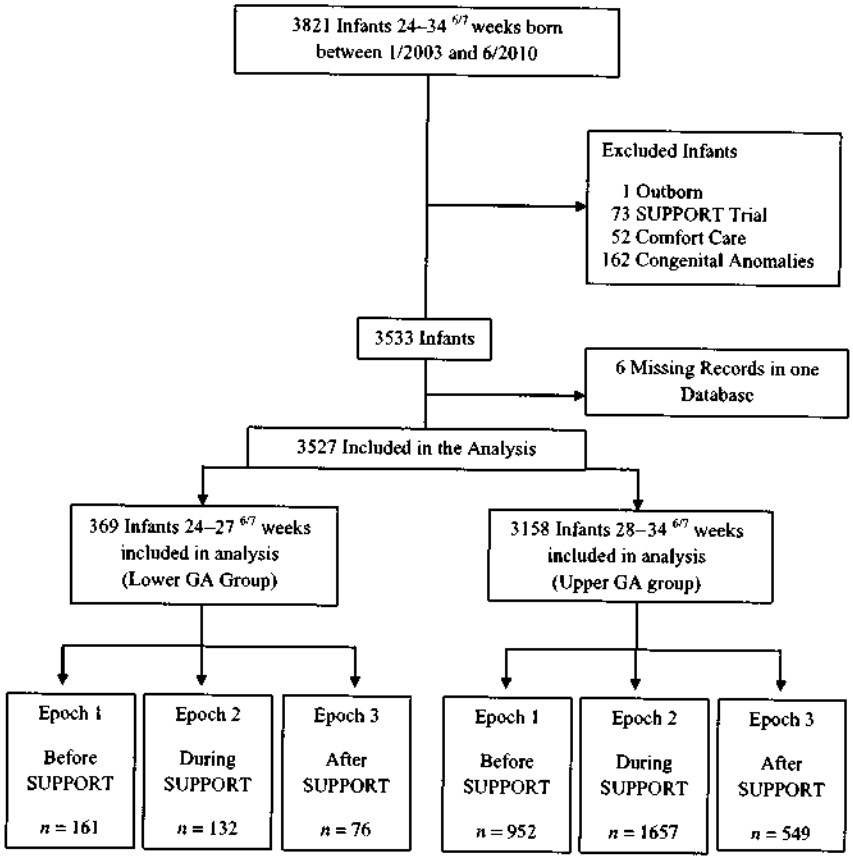

FIGURE 1
Flow diagram at PMH.

TABLE 1 Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Lower GA Group: $24^{0/7}$ to $27^{6/7}$ Weeks' Gestation

Characteristic[a]	Before SUPPORT, $n = 161$	During SUPPORT, $n = 132$	After SUPPORT, $n = 76$	*P* Value
GA, wk, mean (SD)	25.8 (1.0)	25.9 (1.1)	25.8 (1.1)	.42
BW, g, mean (SD)	858 (236)	908 (238)	874 (290)	.24
Size for age, *n* (%)				.52
Small for GA	19 (12)	14 (11)	10 (13)	
Large for GA	19 (12)	25 (19)	12 (16)	
Female, *n* (%)	74 (46)	61 (46)	36 (47)	.98
Multiple birth, *n* (%)	34 (21)	19 (14)	5 (7)*	.01
Antenatal steroids, *n* (%)	81 (50)	52 (39)	38 (50)	.14
Abruptio placentae, *n* (%)	6 (4)	11 (8)	4 (5)	.25
Placenta previa, *n* (%)	3 (2)	1 (1)	3 (4)	.25
Maternal diabetes mellitus, *n* (%)	6 (4)	10 (8)	8 (11)	.11
Gestational hypertension or preeclampsia, *n* (%)	25 (16)	28 (21)	19 (25)	.19
Clinic attendance, *n* (%)	146 (90)	113 (86)	67 (88)	.40

[a] Complete data were available for patients in the lower GA group and for GA. *P* values on the last column on the right are based on analyses of variance or χ^2 analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined using $P < .025$ and *P* values indicated as * $P < .025$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

In the upper GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ($P = .002$) (Table 6). The proportion of intubation within 24 hours of life decreased during/after SUPPORT ($P <$

TABLE 2 Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group: $28^{0/7}$ to $34^{6/7}$ Weeks' Gestation

Characteristic[a]	Before SUPPORT, $n = 952$	During SUPPORT, $n = 1657$	After SUPPORT, $n = 549$	*P* Value
GA, wk, mean (SD)	32.1 (1.8)	32.2 (1.8)	32.4 (1.8)*	.002
BW, g, mean (SD)	1824 (468)	1904 (486)*	1932 (472)*	<.001
Size for age, *n* (%)				.04
Small for GA	101 (11)	139 (9)	49 (9)	
Large for GA	103 (11)	239 (15)	64 (12)	
Female, *n* (%)	422 (46)	716 (44)	247 (46)	.64
Multiple birth, *n* (%)	182 (19)	333 (20)	122 (22)	.35
Use of antenatal steroids, *n* (%)	260 (27)	430 (26)	204 (37)**	<.001
Abruptio placentae, *n* (%)	23 (2)	41 (2)	11 (2)	.82
Placenta previa, *n* (%)	18 (2)	33 (2)	14 (3)	.66
Maternal diabetes mellitus, *n* (%)	88 (9)	216 (13)*	71 (13)	.01
Gestational hypertension or preeclampsia, *n* (%)	264 (28)	511 (30)	168 (31)	.23
Clinic attendance, *n* (%)	852 (90)	1530 (92)*	511 (93)*	.02

[a] In the upper GA group, 95% of data were available, we used the total number available as denominator. *P* values on the last column on the right are based on analyses of variance or χ^2 analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed by using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined using $P < .025$ and *P* values indicated as * $P < .025$, or ** $P < .001$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

TABLE 3 Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Lower GA Group: $24^{0/7}$ to $27^{6/7}$ Weeks' Gestation, $n = 362$

Variable	Adjusted RR[a]	*P* Value
During/after SUPPORT versus before SUPPORT[b]	0.76, 95% CI 0.59–0.96	.02
Positive pressure ventilation in the DR	3.61, 95% CI 2.02–6.45	<.001

For each categorical variable, the reference group is factor not present; for SUPPORT the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, cord pH, GA, gestational hypertension or preeclampsia, and *Z* score of BW for GA and gender.

[a] Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

[b] Primary analysis.

TABLE 4 Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Upper GA Group: $28^{0/7}$ to $34^{6/7}$ Weeks' Gestation, $n = 2742$

Variable	Adjusted RR[a]	*P* Value
During/after SUPPORT versus before SUPPORT[b]	0.57, 95% CI 0.46–0.70	<.001
Positive pressure ventilation in the DR	6.29, 95% CI 4.73–8.37	<.001
GA (per wk)	0.74, 95% CI 0.70–0.78	<.001
Gestational hypertension or preeclampsia	0.72, 95% CI 0.56–0.92	.009
Z score of BW for GA and gender	0.91, 95% CI 0.83–1.00	.046

For each categorical variable, the reference group is factor not present; for SUPPORT, the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, cord pH, GA, gestational hypertension or preeclampsia, and *Z* score of birth weight for GA and gender.

[a] Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

[b] Confirmatory analysis (positive controls).

.001). The proportion of surfactant administration decreased during SUPPORT ($P < .025$).

Most of the other outcomes except retinopathy of prematurity did not change during or after SUPPORT. The percentage of DR intubation did not change during baseline in either GA group (Fig 2). In the lower GA group, the proportion of DR intubation decreased within 15 months of SUPPORT, whereas in the upper GA group, it did not significantly change until later.

Comparison Between PMH and VON

We compared data from 576 neonates born at PMH with data from 85 118 contemporaneous neonates born in 1 of 396 North American VON centers (Table 7).

In the lower GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT at PMH (82% vs 60%; adjusted RR 0.74, 95% CI 0.64–0.86) and in VON (85% vs 84%; adjusted RR 0.98, 95% CI 0.98–0.99). The decrease was greater at PMH than in VON (adjusted ratio of RR 0.76, 95% CI 0.65–0.87). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in the VON data. The change over time was not significantly different between PMH and VON.

In the upper GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT both at PMH and in VON. The decrease was greater at PMH than in VON (adjusted ratio of RR 0.52, 95% CI 0.39–0.68). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in VON. The change over time was not significantly different between PMH and VON.

DISCUSSION

In the current study, a change in care process (proportion of DR intubation) was observed in eligible but nonenrolled patients and in noneligible more mature patients soon after SUPPORT initiation and persisted through 16 months of posttrial evaluation. This change in practice at PMH was much larger than in other comparable centers that did not participate in any trial involving random allocation to DR

TABLE 5 Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Lower GA Group: $24^{0/7}$ to $27^{6/7}$ Weeks' Gestation

Care Process or Outcome Variable[a]	Before SUPPORT, $n = 161$	During SUPPORT, $n = 132$	After SUPPORT, $n = 76$	*P* Value
Intubation in the DR, *n* (%)	136 (85)	81 (61)**	46 (61)**	<.001
Positive pressure ventilation in the DR, *n* (%)	140 (91)	106 (80)*	60 (79)*	.01
CPAP in DR, *n* (%)	48 (31)	74 (56)**	48 (63)**	<.001
Intubation in the NICU within the first 4 h after admission to the unit, *n* (%)	7 (4)[b]	14 (11)	10 (13)	.03
Intubation during the first 24 h of life, *n* (%)	141 (88)	95 (72)**	56 (73)*	.002
Surfactant, *n* (%)	121 (79)	78 (59)**	50 (66)	.001
Pneumothorax, *n* (%)	11 (7)	13 (10)	14 (18)*	.03
Death before discharge, *n* (%)	43 (27)	34 (26)	18 (24)	.91
Chronic lung disease, *n* (%)	83 (52)	61 (46)	43 (57)	.34
Total no. days intubated (endotracheal tube or tracheostomy) ($n = 338$); median (quartiles)[c]	10 (2–23)	5(1–14)	11 (2–29)	.05
Patent ductus arteriosus, *n* (%)	77 (48)	61 (46)	39 (51)	.78
Necrotizing enterocolitis, stage ≥2, *n* (%)	14 (9)	10 (8)	5 (7)	.91
Intraventricular hemorrhage, grade 3 or 4, *n* (%)	25 (16)	20 (15)	18 (24)	.25
Periventricular leukomalacia, *n* (%)	9 (6)	7 (5)	5 (7)	.92
Retinopathy of prematurity, stage ≥3, *n* (%)	30 (19)	12 (9)	14 (18)	.04

P values in the last column on the right are based on χ^2 analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined by using $P < .025$, and *P* values indicated as * $P < .025$, or ** $P < .001$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

[a] Complete data were available for patients.

[b] Two patients, initially intubated in the DR, were intubated again within 4 h after admission in the NICU after a trial on CPAP.

[c] Kruskal-Wallis tests.

TABLE 6 Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group. $28^{0/7}$ to $34^{6/7}$ Weeks' Gestation

Care Process or Outcome Variable[a]	Before SUPPORT, $n = 952$	During SUPPORT, $n = 1657$	After SUPPORT, $n = 549$	*P* Value
Intubation in the DR, *n* (%)	177 (19)	162 (10)**	47 (9)**	<.001
Positive pressure ventilation in the DR, *n* (%)	332 (36)	513 (31)*	150 (28)**	002
CPAP in the DR, *n* (%)	314 (34)	588 (36)	194 (36)	.74
Intubation in the NICU within the first 4 h after admission to the unit, *n* (%)	43 (5)	82 (5)	28 (5)	.84
Intubation during the first 24 h of life, *n* (%)	220 (23)	242 (15)**	75 (14)**	<.001
Surfactant, *n* (%)	105 (11)	131 (8)*	50 (9)	.01
Pneumothorax, *n* (%)	29 (3)	40 (2)	12 (2)	.51
Death before discharge, *n* (%)	17 (2)	19 (1)	8 (2)	.41
Chronic lung disease, *n* (%)	31 (3)	40 (2)	16 (3)	.44
Total no. days intubated (endotracheal tube or tracheostomy) ($n = 694$); median (quartiles)[b]	1 (1–3)	1 (0–4)	1 (1–6)	.097
Patent ductus arteriosus, *n* (%)	68 (7)	106 (6)	23 (4)	.07
Necrotizing enterocolitis, stage ≥2, *n* (%)	17 (2)	23 (1)	12 (2)	.42
Intraventricular hemorrhage, grade 3 or 4, *n* (%)	8 (0.8)	7 (0.4)	5 (0.9)	.22
Periventricular leukomalacia, *n* (%)	3 (0.3)	13 (0.8)	4 (0.7)	.323
Retinopathy of prematurity, stage ≥3, *n* (%)	3 (0.3)	0 (0)	3 (0.5)	.008

P values in the last column on the right are based on χ^2 analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using χ^2 tests, Fisher's exact tests, or Tukey tests, with significance determined by using $P < .025$, and *P* values indicated as * $P < .025$, or ** $P < .001$. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

[a] 95% of data were available; we used the total number available as denominator.

[b] Kruskal-Wallis tests.

intubation, suggesting that the trial participation itself influenced clinical practice well beyond the study participants.

PMH is a high-volume delivery unit with 12 000 to 15 000 deliveries per year. At PMH, the decision whether to intubate is made by resuscitation teams of practitioners who are trained in the neonatal resuscitation program. Teams for neonates with GA of 30 to 35 weeks include a nurse, a respiratory therapist, and a neonatal nurse practitioner or a senior pediatric resident. Teams for lower GA neonates also include a neonatal-perinatal fellow. Additional personnel are available for backup. The same teams provided care to all neonates, whether enrolled into SUPPORT or not. PMH did not have a policy about DR endotracheal intubation; decisions are left to team leaders according to national guidelines for neonatal resuscitation. At PMH before SUPPORT, most preterm neonates <28 weeks' GA were intubated in the DR. PMH did not participate in the NRN Feasibility Trial,[13] which preceded SUPPORT. At PMH, the only evident change in DR management was initiation of a resuscitation rotation for fellows in neonatal-perinatal medicine in 2005. The Neonatal Resuscitation Program mentioned the use of CPAP in the DR for preterm neonates in 2006, and included CPAP in the resuscitation algorithm in 2010[31,32]; however, immediate application of CPAP in the DR at PMH was not recommended for all preterm neonates <32 weeks until May 1, 2011.

The strengths of the current study include[33,34] large sample size; prospective validated databases thereby minimizing missing data, information bias, and loss to follow-up; stratified analysis yielding internal controls (upper GA group); and multivariate comparison with contemporaneous external controls (comparable VON

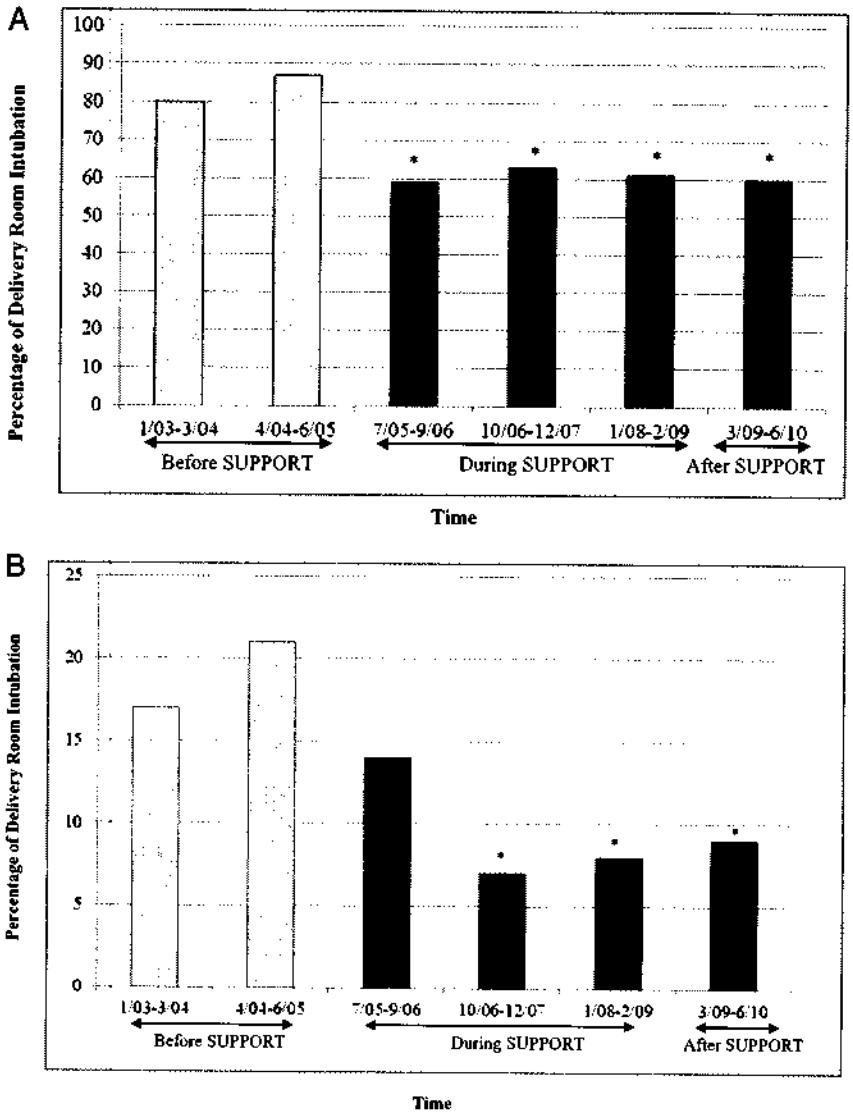

FIGURE 2

Analysis of temporal patterns in DR intubation rates by GA group at PMH. This analysis was performed using consecutive 15- to 16-month blocks. A, Lower GA group ($24^{0/7}$–$27^{6/7}$ weeks' GA infants): The percentages of DR intubation were not significantly different between blocks before SUPPORT ($P = .37$); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into the SUPPORT ($P < .001$). This change already occurred within the first 15 months of recruitment into SUPPORT. *Indicates significant (with Bonferroni adjustment, $P < .0125$) pairwise difference from baseline before starting the SUPPORT. B, Upper GA group ($28^{0/7}$–$34^{6/7}$ weeks' GA infants). The percentage of DR intubations was not significantly different between the 2 blocks before SUPPORT ($P = .10$); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into SUPPORT ($P < .001$); however, this change started to reach significance only after 15 months of recruitment into SUPPORT. *Indicates significant (with Bonferroni adjustment, $P < .0125$) pairwise difference from baseline before starting SUPPORT.

centers not participating in DR trials) with a similar baseline proportion of DR intubation. Secular trends are unlikely to explain the primary results because DR intubation at PMH decreased much more than in other comparable centers. It is unlikely that the current study affected the proportion of DR intubation because when the first data were obtained and presented at a national meeting, the change in practice had already taken place. We did not observe a regression to the mean but instead a sustained reduction in DR intubation at PMH during/after SUPPORT. A differential Hawthorne effect was ruled out because providers were not aware of an observational study of eligible, nonenrolled patients during SUPPORT.[7,8] This study was limited to a single institution rather than all NRN centers participating in SUPPORT because the generic database of the NRN includes only the most immature infants; patients in the upper GA group were important in this study as positive controls who were not eligible for SUPPORT and thus not subjected to selection bias. Selection bias at PMH in the lower GA group during SUPPORT is unlikely to explain the observed decrease in DR intubation in nonenrolled patients, because respiratory distress is associated with lower exposure to antenatal steroids,[35] and more frequent DR positive pressure ventilation (Appendix) would be expected to increase, rather than decrease, DR intubation. The lower percentage of antenatal steroids among nonenrolled patients could have resulted because of many reasons, including not enough time before delivery.[7] Rich and colleagues' study showed that a significantly larger proportion of eligible infants whose mothers were not approached for consent to SUPPORT had no prenatal steroid exposure.[7] The frequency of antenatal corticosteroid administration at PMH is low because preeclampsia and diabetes are considered contraindications.[36] Multivariate analyses showed that the RR of DR intubation decreased at PMH and decreased more at PMH than in VON, even taking into account antenatal corticosteroid administration. We were unable to analyze bronchopulmonary dysplasia, or other elements of care process examined in SUPPORT (ie, targeted ventilation strategy and oxygen saturation), which were not included in the PMH databases. In addition, target oxygen saturation values of 88% to 94%, a PMH NICU policy since May 2002,[37]

TABLE 7 Adjusted RR Estimates in Preterm Infants Born With GA 24 to $29^{6/7}$ Weeks at PMH and in Comparable North American Centers in the VON Before SUPPORT (2003–2004) and During/After SUPPORT (2006–2009)

Care Process	GA Group, wk	Location	Before SUPPORT	During/After SUPPORT	Adjusted RR[a] During/After Versus Before SUPPORT (95% CI)	Ratio of RRs PMH Versus VON (95% CI)	*P* Value
Intubated in DR	$24^{0/7}$–$27^{6/7}$	PMH	105/128 (82%)	99/164 (60%)	0.745 (0.644–0.861)	0.757 (0.654–0.875)	.0002
		VON	11 728/13726 (85.4%)	29 715/35 447 (83 8%)	0.984 (0.976–0.992)		
					n = 49 055		
	$28^{0/7}$–$29^{6/7}$	PMH	51/86 (59%)	57/198 (29.0%)	0.495 (0.375–0.652)	0.516 (0.391–0.681)	<.0001
		VON	5427/10 008 (54.2%)	13 457/25 928 (51.9%)	0.959 (0.939–0.979)		
					n = 35 851		
Received any invasive ventilation	$24^{0/7}$–$27^{6/7}$	PMH	119/128 (93.0%)	144/164 (88.0%)	0.952 (0.886–1.023)	0.965 (0.898–1.037)	.33
		VON	13 158/13 727 (95.9%)	33 469/35 453 (94.4%)	0.986 (0.982–0.991)		
					n = 49 068		
	$28^{0/7}$–$29^{6/7}$	PMH	63/86 (73.0%)	134/198 (68.0%)	0.939 (0.804–1.095)	0.988 (0.846–1.154)	.88
		VON	7599/10 008 (75.9%)	18 669/25 930 (72.0%)	0.950 (0.937–0.962)		
					n = 35 855		

[a] RR estimates are adjusted for infants' GA, gender, *z*-score for BW (computed within GA and gender), and exposure to antenatal corticosteroids by using robust Poisson regression generalized estimating equation models. Location (PMH and VON) and time period (during/after SUPPORT and before SUPPORT) were represented by a 4-level categorical variable. RRs and the ratio of RR estimates were computed based on the appropriate linear contrast of model parameters.

was used for nonenrolled patients. Because the study used databases, it was not possible to perform a propensity match, or a cluster analysis of DR team members or individual providers and to obtain their rationale for deciding whether to intubate the trachea. It is possible that the change in DR intubation was related to increased availability of T-piece devices for DR resuscitation, or to training and experience with these devices and DR CPAP.

CONCLUSIONS

A change in process of care was observed in nonenrolled patients during/after recruitment to an unblinded RCT, in the absence of changes in standard care, initiation of a protocol, or previously described trial effect. This suggests that care for patients who are not enrolled in RCTs should routinely be monitored and audited to identify changes in practice that may either be beneficial or detrimental without the evidence from a completed trial. Further studies are needed to investigate the determinants of changes in individual decisions about care process (eg, observations of short-term outcomes versus experience with novel processes of care). A trial design in which centers are randomized to participation in RCTs could further analyze the impact of changes in care process associated with unblinded RCTs.

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The first version of the PMH cohort was a poster presentation at the Pediatric Academy Society Meeting, Honolulu, HI, May 4, 2008: Brion LP, Wyckoff MH, Jaleel M, Sanchez PJ, Burchfield J, Christie L. Delivery room practice change following the initiation of the SUPPORT trial.

The final version of the PMH cohort was a platform presentation at the Pediatric Academy Society Meeting, Boston, MA, April 28, 2012: LeVan JM, Wyckoff MH, Jaleel MA, Sanchez PJ, Ahn C, Burchfield J, Christie L, Brion LP. Impact of initiating the NICHD Neonatal Research Network SUPPORT Trial on management and outcomes of gestational-age matched non-enrolled patients.

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(Continued from first page)

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APPENDIX Baseline Characteristics of Infants 24 to 27 $^{6/7}$ Weeks' Gestation Born at PMH During SUPPORT (July 2005–February 2009)

Characteristic	SUPPORT, n = 73, Excluded From the Current Study	NONSUPPORT, n = 132, Included in the Current Study	P Value
GA, wk, mean (SD)	25.3 (1.0)	25.9 (1.0)	<.001
BW, g, mean (SD)	876 (189)	907 (238)	.37
Size for age, n (%)			.03
Small for GA	1(1)	14 (11)	
Large for GA	19 (26)	25 (19)	
Female, n (%)	29 (40)	61 (46)	.23
Multiple birth, n (%)	12 (16)	19 (14)	.69
Use of antenatal steroids, n (%)	49 (67)	52 (39)	<.001
Abruptio placentae, n (%)	3 (4)	11 (8)	.39
Placenta previa, n (%)	1 (1)	1 (1)	1.000
Maternal diabetes, n (%)	6 (8)	10 (8)	1.000
Gestational hypertension or preeclampsia, n (%)	15 (21)	28 (21)	1.000
Clinic attendance, n (%)	63 (86)	113 (86)	1.000
Positive pressure ventilation in the DR, n (%)	42 (58)	106 (80)	.001

Significance based on Fisher's exact tests or Student's t tests.

Change in Care Among Nonenrolled Patients During and After a Randomized Trial

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in ~~to~~ a related trial.

Objective: To test the hypothesis that endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial ~~SUPPORT trial~~ within NICUs in NRN centers.

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the ~~NICHD Neonatal Research Network (NRN)~~ SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a Feasibility Trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: Proportion of DR ETI

Results: The proportion ~~rate~~ of DR ETI decreased significantly after SUPPORT, adjusted relative risk (RR) 0.89, 95% confidence interval (CI) 0.86-0.93. DR ETI decreased significantly in the group of infants from centers that had not participated in the

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Feasibility Trial (91% vs. 75%, adjusted RR 0.86, 95% CI 0.83-0.89, p <0.0001) but no in ~~did not decrease after SUPPORT in~~ the group of infants from the other centers ~~previously participating in the Feasibility Trial~~ (61% before vs. 58% after SUPPORT-, adjusted ~~relative risk~~ (RR) 0.96, 95% CI ~~confidence interval (CI)~~ 0.89-1.05, p=0.40)~~,~~ ~~but decreased significantly in the group of infants from the other centers (91% vs. 75%, adjusted RR 0.86, 95% CI 0.83-0.89, p <0.0001)~~.

Conclusions and Relevance: After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after release of the results of the SUPPORT trial to NRN centers had significantly lower percentages of DR ETI compared to infants born before the SUPPORT trial. This result was limited to the subgroup of infants from centers that did not participate ~~not included~~ in the Feasibility Trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of DR ETI and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN previously conducted a Feasibility Trial in 5 centers, to determine the feasibility of randomization to DR CPAP vs. DR ETI in the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the Feasibility Trial has shown that participation in the SUPPORT Trial affected clinical practice, specifically the proportion DR ETI among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the Feasibility Trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003-2012).

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical

estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trial, i.e.,

physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included an indicator for study

group (post vs. pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in rate of DR ETI varied across the subgroups of infants in centers who did and did not participate in the Feasibility Trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR intubation model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, a total of n=1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

The primary outcome, the proportion of DR ETI, decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. The adjusted risk of DR ETI significantly decreased after the SUPPORT trial, RR 0.89, 95% confidence interval 0.86-0.93 (Table 2). Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first

to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the Feasibility Trial.

The indicator for the subgroups of centers who did and did not participate in the Feasibility Trial, and its interaction with the pre vs. post-SUPPORT indicator, was significant, so results for DR intubation are presented within these subgroups (Table 2). The DR intubation rate did not decrease after SUPPORT in the subgroup of infants from centers that had participated in the feasibility trial (61.3% before vs. 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)).

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before initiation of the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the Feasibility Trial. Since we did not analyze serial changes in the proportion of DR ETI in this study, the data do not allow us to determine when DR ETI decreased in each center. However, in another study we have shown that the proportion of DR ETI in one of these centers that did not participate in the Feasibilty Trial ~~Study~~ decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[4] ~~The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).~~[4] In contrast, the proportion of DR ETI did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the Feasibility Trial (and thus already had experience with using T-piece resuscitators and CPAP in the DR). In one of these 3 centers, the proportion of ETI had decreased before the Feasibility Trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000.[17] The strengths of this study include the use of a prospective database and a large sample size of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion

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and exclusion criteria that were similar to those used in the SUPPORT trial, inclusion of centers with or without prior participation in a similar trial with randomization to DR CPAP vs. DR ETI, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); and lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends. Nevertheless, another study has shown that DR ETI decreased by 22% after SUPPORT in one NRN center, and only by 1.6% in a large comparable cohort of infants born in level IIIb or IIIc North American centers participating in the Vermont Oxford Network, excluding centers participating in SUPPORT or in the Network Delivery Room Management Trial, and neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies.[4] Additional limitations of the present study included: lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

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Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to

show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites.

This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial. This result was limited to the subgroup of infants from centers not included in the Feasibility Trial.

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Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

From: Luc Brion
To: Sanchez, Pablo; "Barbara Stoll"; Roy Heyne; "Wally Carlo, M.D."; "Gantz, Marie"; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"; Myra Wyckoff; Mambarambath Jaleel; (b)(6) @gmail.com"
Subject: RE: Updated files
Date: Sunday, January 12, 2014 10:33:37 AM
Attachments: Jackie LeVan Manuscript NRN 1-12-14 rev.docx

Here is another revision, in which I edited the discussion to show a comparison with secular trends in a comparable cohort in VON during a very similar period.
Luc

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Hi Luc---see attached—some errors in the reference numbers –minor comments—interesting—you were right about the participation in the feasibility trial .. pablo

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
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To: 'Barbara Stoll'; Roy Heyne; 'Wally Carlo, M.D.'; 'Gantz, Marie'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'nfiner@ucsd.edu'; Sanchez, Pablo; Myra Wyckoff; Mambarambath Jaleel; 'doctorlevan@gmail.com'; Luc Brion
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I did some minor changes in the text and in Table 2.
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Subject: RE: Updated files
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Attachments: Jackie LeVan Manuscript NRN 1-12-14.docx

Please ignore my email from last night.
I added the primary outcome for the whole set into the text of the results.
Luc

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Date: Sunday, January 12, 2014 12:27:17 AM
Attachments: Jackie LeVan Manuscript NRN 1-11-14-rev.docx

Thanks, Pablo, for all your comments.
Here is the revised version.
Best regards,
Luc

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Affiliations: [1]Department of Pediatrics, University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

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No reprints needed

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 3473 words
Article length: 2,8574 words
Revised 1/11/14

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation in to a related trial.

Objective: To test the hypothesis that endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial ~~SUPPORT trial~~ within NICUs in NRN centers.

Design: Retrospective cohort study using the prospective NRN generic database

Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the ~~NICHD Neonatal Research Network (NRN)~~ SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a Feasibility Trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: Proportion of DR ETI

Results: The proportion ~~rate~~ of DR ETI decreased significantly after SUPPORT, adjusted relative risk (RR) 0.89, 95% confidence interval (CI) 0.86-0.93. DR ETI decreased significantly in the group of infants from centers that had not participated in the

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Feasibility Trial (91% vs. 75%, adjusted RR 0.86, 95% CI 0.83-0.89, p <0.0001) but no in ~~did not decrease after SUPPORT in~~ the group of infants from the other centers ~~previously participating in the Feasibility Trial~~ (61% before vs. 58% after SUPPORT~~,~~ adjusted ~~relative risk~~ (RR) 0.96, 95% CI ~~confidence interval (CI)~~ 0.89-1.05, p=0.40)~~, but decreased significantly in the group of infants from the other centers (91% vs. 75%, adjusted RR 0.86, 95% CI 0.83-0.89, p <0.0001)~~.

Conclusions and Relevance: After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after release of the results of the SUPPORT trial to NRN centers had significantly lower percentages of DR ETI compared to infants born before the SUPPORT trial. This result was limited to the subgroup of infants from centers that did not participate ~~not included~~ in the Feasibility Trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of DR ETI and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN previously conducted a Feasibility Trial in 5 centers, to determine the feasibility of randomization to DR CPAP vs. DR ETI in the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center that had not participated in the Feasibility Trial has shown that participation in the SUPPORT Trial affected clinical practice, specifically the proportion DR ETI among non-enrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if the proportion of DR ETI decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the Feasibility Trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after release of the results of the SUPPORT trial to NRN centers. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003-2012).

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical

estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, and respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., DR ETI.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcomes of the SUPPORT trial, i.e.,

physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included an indicator for study

group (post vs. pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[6] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[7-16] To assess whether the change in rate of DR ETI varied across the subgroups of infants in centers who did and did not participate in the Feasibility Trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR intubation model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

Maternal and Neonatal Characteristics

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). Three of the 11 centers included in our study participated in the Feasibility Study, a total of n=1321 infants. The baseline maternal and neonatal characteristics of the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the Feasibility Trial.

The indicator for the subgroups of centers who did and did not participate in the Feasibility Trial, and its interaction with the pre vs. post-SUPPORT indicator, was significant, so results for DR intubation are presented within these subgroups (Table 2). The DR intubation rate did not decrease after SUPPORT in the subgroup of infants from centers that had participated in the feasibility trial (61.3% before vs. 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)).

Other outcomes

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 3). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before initiation of the SUPPORT trial. The proportion of DR ETI significantly decreased in the subgroup of infants from centers that had not participated in the Feasibility Trial. Since we did not analyze serial changes in the proportion of DR ETI in this study, the data do not allow us to determine when DR ETI decreased in each center. However, in another study we have shown that the proportion of DR ETI in one of these centers that did not participate in the Feasibility Trial ~~Study~~ decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[4] The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[4] In contrast, the proportion of DR ETI did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the Feasibility Trial (and thus already had experience with using T-piece resuscitators and CPAP in the DR). In one of these 3 centers, the proportion of ETI had decreased before the Feasibility Trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000.[17] The strengths of this study include the use of a prospective database and a large sample size of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in the SUPPORT trial, inclusion of centers with or without prior participation in a similar trial with randomization to DR

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CPAP vs. DR ETI, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after

the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial. This result was limited to the subgroup of infants from centers not included in the Feasibility Trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo J. Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study. The content of the publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and

accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

From:	Luc Brion
To:	"Barbara Stoll"; Roy Heyne; "Wally Carlo, M.D."; "Gantz, Marie"; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"; "Lisa Ann <wrage@rti.org>, "; Myra Wyckoff; Mambarambath Jaleel; "doctorlevan@gmail.com"; Luc Brion
Subject:	Updated files
Date:	Saturday, January 11, 2014 7:10:18 PM
Attachments:	Jackie LeVan Manuscript NRN 1-11-14.docx Table 2.docx

I did some minor changes in the text and in Table 2.
Luc

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Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[4]
All subjects	1313/1617 (81%)	1539/2232 (69%)	<0.0001	0.88 (0.85-0.91)	<0.0001
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviation: RR, relative risk

[1] results are shown for groups defined by combining subjects from centers who did or did not participate in the Feasibility Trial

[2] unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] adjusted p-values from robust Poisson model

From:	Luc Brion
To:	Barbara Stoll; Roy Heyne; "Wally Carlo, M.D."; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; " <nfiner@ucsd.edu>, " Wrage@ws-mr3.cc.emory.edu; Lisa Ann <wrage@rti.org>, ; Myra Wyckoff; Mambarambath Jaleel; doctorlevan@gmail.com; Luc Brion
Subject:	RE: Your Manuscript # 20131573R1 submitted to JPediatr
Date:	Saturday, January 11, 2014 1:19:21 AM
Attachments:	Jackie LeVan Manuscript NRN 1-10-14.docx Appendix.docx Table 3.docx Table 2_edlw10Jan14.docx Table 1.docx Figure 2.docx Figure 1.docx

Dear Colleagues:

Thanks a lot for all the comments and for allowing to conduct these additional analyses.

Here is a manuscript with these additional data, written for JAMA Pediatrics.

I submit that this new version is better than the previous one.

Please review and edit.

Thanks,

Luc

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From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Tuesday, January 07, 2014 12:34 PM
To: Roy Heyne
Cc: 'Wally Carlo, M.D.'; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; " <nfiner@ucsd.edu>, " Wrage@ws-mr3.cc.emory.edu; Lisa Ann <wrage@rti.org>, ; Myra Wyckoff; <mcw3@cwru.edu>, Abbot Laptook <Alaptook@wihri.org>, Luc Brion <Luc.Brion@utsouthwestern.edu>,
Subject: Re: Your Manuscript # 20131573R1 submitted to JPediatr

I am OK with doing the additional analysis if numbers are sufficient in the feasibility group to tell us something. BUT could also support simply submitting to another journal without additional work

BJS**Roy Heyne <Roy.Heyne@utsouthwestern.edu> writes:**

Agree with additional analysis assuming we have enough data, but unless it demonstrates the change Luc expects, not sure how much it will change publishability. OK to start with JAMA Peds.

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, January 07, 2014 9:41 AM
To: Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wrage, Lisa Ann; paulo.sanchez@nationwidechildrens.org; Myra Wyckoff; Roy Heyne; [SCRN] Stoll, Barbara; mcw3@cwru.edu; Abbot Laptook
Cc: Luc Brion; doctorlevan@gmail.com
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr

I also agree.

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, January 07, 2014 9:43 AM
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Wally Carlo, M.D.; Wrage, Lisa Ann; paulo.sanchez@nationwidechildrens.org; Myra.wyckoff@utsouthwestern.edu; Roy.Heyne@utsouthwestern.edu; [SCRN] Stoll, Barbara; mcw3@cwru.edu; Abbot Laptook
Cc: Luc.Brion@UTSouthwestern.edu; doctorlevan@gmail.com
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr

I am also alright with it, assuming we have enough data to break the analysis down that way.

Marie

Marie Gantz, Ph.D.
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-----Original Message-----
From: Das, Abhik
Sent: Tuesday, January 07, 2014 [redacted]52 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; [redacted]@ucsd.edu; Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez (pablo.sanchez@nationwidechildrens.org); Myra Wyckoff (Myra.Wyckoff@utsouthwestern.edu); Roy Heyne (Roy.Heyne@utsouthwestern.edu); [SCRN] Stoll, Barbara; Michele Walsh (mcw3@cwru.edu); Abbot Laptook
Cc: [redacted]Brion@UTSouthwestern.edu); doctorlevan@gmail.com
Subject: RE: Your Manuscript # [redacted]31573R[redacted]ubmitted to JPediatr

I am ok with this.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
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To: [redacted]@ucsd.edu; Wally Carlo, M.D.; Wrage, Lisa Ann; Das, Abhik; Gantz, Marie; Pablo Sanchez (pablo.sanchez@nationwidechildrens.org); Myra Wyckoff (Myra.Wyckoff@utsouthwestern.edu); Roy Heyne (Roy.Heyne@utsouthwestern.edu); [SCRN] Stoll, Barbara; Michele Walsh (mcw3@cwru.edu); Abbot Laptook
Cc: [redacted]Brion@UTSouthwestern.edu); doctorlevan@gmail.com
Subject: RE: Your Manuscript # [redacted]31573R[redacted]ubmitted to JPediatr

Hi
See the comments below -
Do folks favor performing the analysis that Luc has proposed??
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch, NIH
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-----Original Message-----
From: LUC Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 06, 2014 6:30 PM
To: doctorlevan@gmail.com; Wrage, Lisa Ann (Wrage@rti.org); Das, Abhik (adas@rti.org); Gantz, Marie[

([redacted]@rti.org; Myra Wyckoff; Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Manimarambath Jaleel; [redacted]@uthscsa.edu; Wally Carlo (Wcarlo@uab.edu); Barbara Stoll (Barbara.Stoll@bcm.edu); [redacted]; Rosemary (NIH/NICHD) [E]
Subject: FW: Your Manuscript #20131573R has been submitted to JPediatr

Happy New Year to everyone.

Sorry but the manuscript was not accepted by Journal of Pediatrics.

We have previously discussed at length whether to consider a survey of practices. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened many years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.

I suggest to submit a revised manuscript either to JAMA Pediatrics, Early Human Development or Journal of Perinatology (classified by impact factor) after the revisions listed below:

1. Attach a revised version in which we corrected the starting time of the second cohort from "after publication of SUPPORT" into "after release of the results of SUPPORT to Triad/NRN centers".

2. I suggest to add to the manuscript a comparison of the change in DR intubation in centers that participated in the Feasibility trial versus those that did not. I would hypothesize that the first group would have less change in DR practice after the release of the SUPPORT results than the second group. This would allow us to assess whether there was a difference in change in DR intubation after releasing SUPPORT results in centers that already had experience with using CPAP in the DR (those that participate in the Feasibility trial) versus centers that were more likely to have less experience with CPAP in the DR before SUPPORT (e.g., Parkland, in which DR intubation was routine when SUPPORT). Please let me know if you agree with conducting this additional analysis.

If you have any suggestion please let me know.
I will be glad to talk further with you at the NRN meeting next week.
Thanks for your collaboration and best regards,

Luc

-----Original Message-----
From: [redacted]
On Behalf Of Journal Office
Sent: Monday, January 06, 2014 11:44 AM
To: Luc Brion; luchrion@gmail.com
Subject: Your Manuscript # 20131573R has been submitted to JPediatr

Ref: Ms. No. 20131573R1
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Brion,

Thank you for revising and resubmitting your manuscript. The Editors appreciate your efforts to satisfy the concerns of the reviewers and the requirements of The Journal of Pediatrics. We are very sorry to inform you that we will not be able to publish your manuscript because the consensus of the Editors was that it did not attain high enough priority for publication in The Journal.

The Editors share the concerns of Reviewer #2 in concluding that the effect seen would not specifically be limited to publication of SUPPORT. This may be true, especially because almost 1/4 of the time allotted to enroll patients (post-SUPPORT: 2010-2012) came private publication of SUPPORT in May 2010. Additionally, the primary outcome assessed was intubation, and the significance of these findings - without linking them directly to policy change based on the publication of SUPPORT - suggests a change in clinical practice over time.

Because of space limitations, we are able to accept only a few of submitted manuscripts. When establishing a priority for each manuscript and in reaching an editorial decision, the Editors consider the quality of the manuscript, the novelty and importance of the observation, and appropriateness for our readership. Because we have many meritorious manuscripts and very strict page limitations from the publisher, we are forced to make some difficult decisions. We hope this process was helpful in improving your manuscript for submission to another journal. Further comments from the reviewers are appended below.

Again, thank you for this submission and your support of The Journal of Pediatrics. Our best wishes for your success in publishing your paper elsewhere.

Sincerely,

Clyde J Wright, MD
Guest Editor

/rw/

Reviewers' comments:

Reviewer #1: The authors have addressed most of the issues raised by this reviewer. The discussion section of the manuscript is much improved.

A remaining suggestion is that of including a summary of the pre-trial (and post-trial if possible) guidelines/policies for delivery room management and oxygen saturation targeting in the participating centers. It is hard to believe such information was not available to the investigators at the time of planning of the SUPPORT trial. Such information may be quite valuable in deciding to adopt some of the changes in practice following this and other similar trials.

Reviewer #2: On re-reviewing this revised manuscript, the authors were unable to respond to the prior criticism that the mechanism of the post- vs pre-SUPPORT reduction in delivery room endotracheal intubation (ETI) rate is not elucidated. The study does not provide evidence that the reduction in ETI is attributable to the uptake of the evidence supplied by SUPPORT. Nor is evidence provided that the reduction in adverse secondary clinical outcomes (e.g. severe retinopathy of prematurity (ROP), was attributable to the evidence supplied by SUPPORT. The authors were unable to examine whether the reduction in severe ROP was attributable to the adoption of the lower SpO2 target range because the NICHD Network Generic Database did not contain individual patient data on the oxygen target range that was used before and after SUPPORT.
The conclusion that there was a reduction in the delivery room ETI rate post- vs pre-SUPPORT, with no confidence concerning attribution, is of limited importance. Even this conclusion is subject to weaknesses in the design and conduct of the study that are acknowledged by the authors in Discussion, 3rd paragraph.

UT Southwestern Medical Center
The future of medicine, today.

Barbara J. Stoll, MD

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Appendix. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.0025
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.0028
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

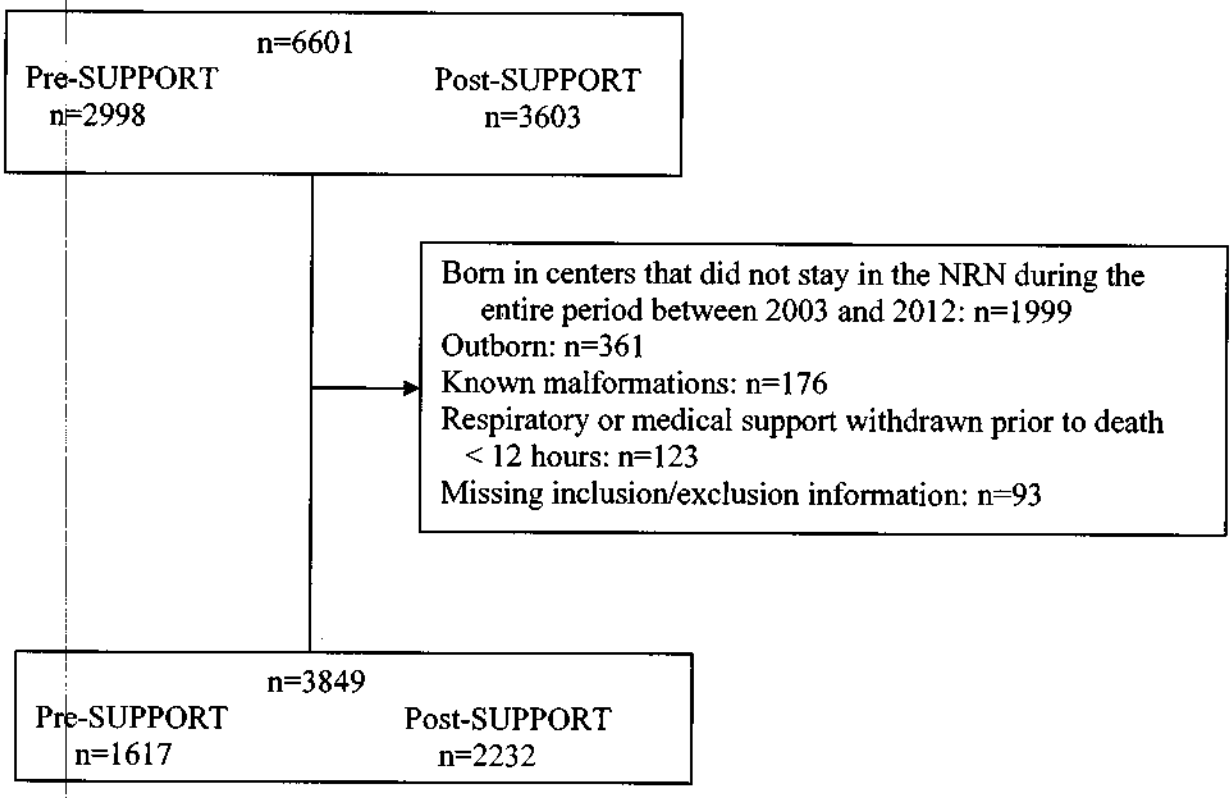
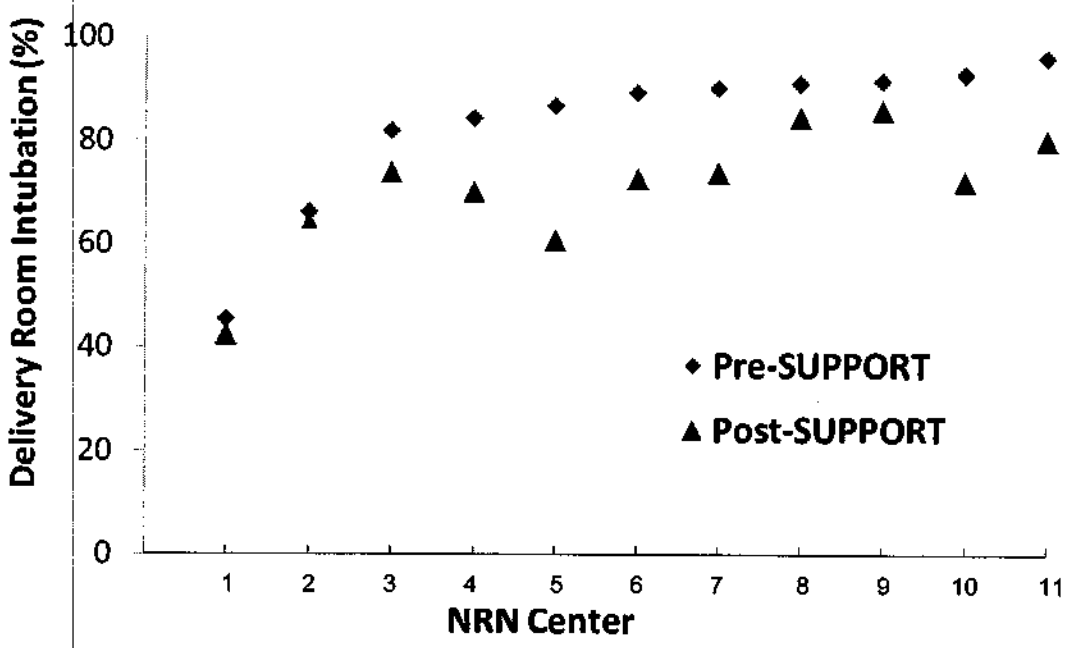

n=6601
Pre-SUPPORT
n=2998
Post-SUPPORT
n=3603
Born in centers that did not stay in the NRN during the entire period between 2003 and 2012: n=1999
Outborn: n=361
Known malformations: n=176
Respiratory or medical support withdrawn prior to death < 12 hours: n=123
Missing inclusion/exclusion information: n=93
n=3849
Pre-SUPPORT
n=1617
Post-SUPPORT
n=2232

Figure 2


Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

~~First draft: Dr. LeVan wrote the first draft of the manuscript.~~

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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~~Conflict of Interest Statement: There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.~~

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 339~~224~~ words
Article length: 2,839~~612~~ words
Revised 1~~2~~/10~~612~~/14~~3~~

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Importance: A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. It is not known whether changes in process of care associated with a randomized trial vary among centers depending on prior participation to a related trial.

~~Objective:~~

~~Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was T~~to test the hypothesis that ~~DR~~ endotracheal intubation in the delivery room (DR ETI) decreased after the NICHD Neonatal Research Network (NRN) SUPPORT trial SUPPORT trial within NICUs in NRN centers.

~~Study Design:~~

~~This was a R~~retrospective cohort study using the prospective NRN generic database ~~using the prospective NRN generic database.~~ Setting: Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) DR continuous positive airway pressure (CPAP) or DR ETI with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The NRN had previously conducted a Feasibility Trial to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.

Participants: Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care.

Main outcome measure: ~~The primary outcome was~~ Proportion of DR ETI~~intubation~~.

Results

The rate of DR ETI ~~intubation~~ did not decrease after SUPPORT in the group of infants from centers previously participating in the Feasibility Trial (61.3% before vs 57.5% after SUPPORT , adjusted RR 0.96 95% CI (0.89-1.05), p=0.39), but decreased significantly in the group of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 95% CI (0.83-0.89), p <0.0001).

~~DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, p < 0.0001. After adjustment for baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.89, 95% confidence interval 0.86-0.93) was significantly lower than one.~~

Conclusions and Relevance:

After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages

of DR ETI ~~intubation~~ compared to infants born before the SUPPORT trial. This result was limited to the subgroup of infants from centers not included in the Feasibility Trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were released to the NRN centers in December 2009 and published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of endotracheal intubation and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen

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saturation target groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The NRN ~~had~~ previously conducted a Feasibility Trial in 5 centers, to determine the feasibility of the SUPPORT Trial and the GA range that would be the most appropriate for the SUPPORT Trial.[3]

A previous study in one NRN center has shown that participation in the SUPPORT Trial affected a process of care, specifically the proportion of preterm inborn infants intubated in the DR (DR ETI), among nonenrolled patients during the trial and before release of its results.[4]

The objective of this study was to determine if clinical practice, specifically the proportion of ~~preterm inborn infants intubated in the DR~~DR ETI, decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in ~~ETI in the~~ DR ETI in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of ~~ETI in the DR~~DR ETI in each center after the SUPPORT trial would depend on the baseline proportion before the trial. We also speculated that the decrease in DR ETI after the SUPPORT Trial would be less in centers that had participated in the Feasibility Trial than in the other centers. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

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Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003--2012).

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers~~publication of the SUPPORT trial~~ (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical

estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ~~ETI in DR~~DR ETI.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of the SUPPORT trial, i.e.,

physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[23] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included an indicator for study

group (post vs. pre-SUPPORT) and pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[64] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[75-164] To assess whether the change in rate of DR intubation varied across the subgroups of infants in centers who did and did not participate in the Feasibility Trial we used stratified chi square tests and also included an indicator for these subgroups and its interaction with the pre vs post-SUPPORT indicator in the DR intubation model. Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used with aggregate center data to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period. We used stratified chi-square analysis and Robust Poisson regression models to compare the

~~change in proportion in ETI in centers that participated in the Feasibility trials with that in the other centers.~~

Results

Maternal and Neonatal Characteristics

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A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012.This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1). ~~).~~ Three of the 11 centers included in our study participated in the Feasibility Study, a total of n=1321 infants.

The baseline maternal and neonatal characteristics of ~~both~~ the pre and post-SUPPORT groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Primary outcome

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Using aggregate center data, Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in

proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the Feasibility Trial.

~~The primary outcome,~~ The indicator for the subgroups of centers who did and did not participate in the Feasibility Trial, and its interaction with the pre vs. post-SUPPORT indicator, was significant, so results for DR intubation are presented within these subgroups (Table 2). The DR intubation rate did not decrease after SUPPORT in the subgroup of infants from centers that had participated in the feasibility trial (61.3% before vs. 57.5% after SUPPORT, adjusted RR 0.96 (0.9-1.1), p=0.40) but decreased significantly in the subgroup of infants from the other centers (91.0% vs 75.2%, adjusted RR 0.86 (0.83-0.89)). ~~the proportion of DR ETI, decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, p < 0.0001 . The adjusted risk of DR ETI significantly decreased after the SUPPORT trial, RR 0.89, 95% confidence interval 0.86-0.93 (Table 2).~~

Other outcomes

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Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table ~~3~~2). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in the Appendix; ~~Table 3;~~ online only. Several differences were observed between the two periods. Post hoc

analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

~~Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18). The 3 centers with the lowest baseline proportion were those that had participated in the Feasibility Trial. The proportion of DR ETI did not decrease after SUPPORT in centers that had participated in the Feasibility Trial (61.3% before vs. 57.5% after SUPPORT, p=0.19) but decreased significantly in the other centers (91.0% vs. 75.2%, p <0.001). Stratified chi-square analysis showed that this reached statistical significance (chi-square = 39.7, p<0.001).~~

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born ~~after publication of the SUPPORT trial~~ in the 11 centers participating in the SUPPORT trial after release of the results of the trial to NRN centers had a lower proportion of DR ETI compared to those born before initiation of the SUPPORT trial. The proportion of DR ETI significantly decreased ~~only in centers~~in the subgroup of infants from centers that had not participated in the Feasibility Trial. Since we did not analyze serial changes in the proportion of DR ETI in this study, the data do not allow us to determine when DR ETI decreased in each center. However, in another study we have shown that the proportion of DR ETI in one of these centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs

during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[4] The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[4] In contrast, the proportion of DR ETI did not significantly decrease after SUPPORT in the subgroup of infants from the 3 centers that had participated in the Feasibility Trial (and thus already had experience with using T-piece resuscitators and CPAP in the DR). In one of these 3 centers, the proportion of ETI had decreased before the Feasibility Trial, when neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000~~We evaluated changes in ETI for all patients in the cohorts. Since we did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, In another center that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[176] Five of the 11 centers participated in a feasibility study prior to initiation of the SUPPORT trial.[17] It is possible that ETI decreased in these 5 centers because of experience with use of T-piece resuscitators and increased use of CPAP in the DR during the feasibility study limiting further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial. data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in the SUPPORT trial. The proportion of ETI in one of the participating centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs~~

~~during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[15] The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a feasibility study prior to initiation of the SUPPORT trial.[12] It is possible that ETI decreased in these 5 centers because of experience with use of T-piece resuscitators and increased use of CPAP in the DR during the feasibility study limiting further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial.~~

The strengths of this study include the use of a prospective database and a large sample size of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in the SUPPORT trial, inclusion of centers with or without prior participation in a similar trial with randomization to DR CPAP vs. DR ETI, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the -two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

~~Lack of correlation between the change in the proportion in ETI after the SUPPORT trial and baseline ETI proportion may have resulted from the limited number of centers in this~~

~~study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.~~

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice

guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$+$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial. This result was limited to the subgroup of infants from centers not included in the Feasibility Trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study. The content of the publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the

NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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~~4.~~

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcome

Outcome Intubated in delivery room[1]	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Subjects from centers in Feasibility Trial	326/532 (61%)	454/789 (58%)	0.18	0.96 (0.89-1.05)	0.40
Subjects from centers not in Feasibility Trial	987/1085 (91%)	1086/1443 (75%)	<0.0001	0.86 (0.83-0.89)	<0.0001

Abbreviation: RR, relative risk

[1] results are shown for groups defined by combining subjects from centers who did or did not participate in the Feasibility Trial

[2] unadjusted results presented as n/N (%), p-value from Chi-Square tests

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

From: Juliann DiFiore
To: Pickett, James
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele; Auman, Jeanette O.; Gantz, Marie; Zaterka-Baxter, Kristin
Subject: Re: IH and mortality data
Date: Thursday, January 09, 2014 5:10:28 PM

Sounds good.

Regards,

Julie

On 1/9/2014 5:08 PM, Pickett, James wrote:
> Hi Julie,
> Thanks, I hope your year is off to a glowing start.
> I will be happy to review your data and see what additional details I can provide. I won't be able to review immediately as I am currently on deadline to complete activities for the INS3 trial that will be launching shortly. I am putting this on my schedule to review on Monday (1/13) and respond asap with results.
>
> J
>
> James Pickett - Res. Programmer / Analyst - Clinical Research Informatics * (919) 541-1253 * Haynes 399L * japickett@rti.org
> RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research Triangle Park, NC 27709-2194
>
>
> -----Original Message-----
> From: Juliann DiFiore [mailto:jmd3@case.edu]
> Sent: Thursday, January 09, 2014 1:51 PM
> To: Pickett, James
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele; Auman, Jeanette O.; Gantz, Marie; Zaterka-Baxter, Kristin
> Subject: Re: IH and mortality data
>
> Hi James,
>
> Happy New Year!
>
> I am following up on the missing infant data that we discussed before the holidays. I have attached a spreadsheet which shows the specific infants that were not on the DVD. This list was extrapolated from the zipped raw waveform files on the DVD and the Excel file ihdatarequest_forJulie.xlsx. In summary, there are a total of 63 infants missing with the following criteria:
> 1. 24 died.
> a. 18 of the infants died within 1-5 days of life. Not expecting any data from those.
> b. 6 of the infants who died had >1wk of data (8-20 days). I was hoping we could find those infants as they would be useable for this analysis.
> 2. 39 infants survived with all infants having 50+ days of data (52-291 days). Can you please look this list over and verify that you do not have these infants?
>
> Lastly, in the Excel files, ihdatarequest20140107.xlsx and ihdatarequest_forJulie.xlsx infant (b)(6) is missing. (This infant is included in the raw waveform files on the DVD) Would you please send me the information for that infant?
>
> Thanks!
>

> Julie
>
>
> with the the On 12/23/2013 3:23 PM, Pickett, James wrote:
>> Hello Juliann,
>> No, there were no additional discs to send. You have all the data that is available. With regards to infant count vs. recording availability, not all infants will have recordings. For example, there are 28 infants on that subject listing that met status (death) at day of life 1 that we are unlikely to have any oximeter data for -- I have verified that is the case for 3 via spot check. That one example covers approximately 50% of your missing data. I will be more than happy to work with you after the holidays to assist you with the remaining subjects in question.
>>
>> Regards,
>>
>> J
>>
>> James Pickett - Res. Programmer / Analyst - Clinical Research Informatics * (919) 541-1253 * Haynes 399L * japickett@rti.org
>> RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research
>> Triangle Park, NC 27709-2194
>>
>>
>> -----Original Message-----
>> From: Juliann DiFiore [mailto:jmd3@case.edu]
>> Sent: Monday, December 23, 2013 2:47 PM
>> To: Pickett, James
>> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele
>> Subject: IH and mortality data
>>
>> Hello James,
>>
>> I have been working through the data sent on the DVD for the IH and mortality secondary study. I noticed that there are infants missing in the zipped files. There are 1316 infants listed in the IHdatarequest.xlsx spreadsheet but only 1255 zipped files are enclosed on the DVD. The missing infants seem to be random by site. (ie missing per site: 4-site J, 8-site I, 1- site M, 5-site F...). Was there a 2nd DVD that was not enclosed in the envelope you sent in september?
>>
>> Regards,
>>
>> Julie
>>
>> --
>> 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
>> ----------

the specific written consent of the person to whome it pertains, or as otherwise permitted.
>>
>>
>
> --
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>

--
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disclosure of this information without the specific written consent of the person to whome it pertains, or as otherwise permitted.

From: Juliann DiFiore
To: Gantz, Marie; Pickett, James
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele; Auman, Jeanette O.; Zaterka-Baxter, Kristin
Subject: Re: IH and mortality data
Date: Thursday, January 09, 2014 4:40:38 PM

Could A-23702 be A-23701 since the first day of monitoring matches with A-23701 which is not on the DVD? However, the spreadsheet states there were only 2 days of monitoring for that infant and A-23702 has 10 days recorded. Do you want to verify that A-23701 only had 2 days of monitoring and not 10 or should I go ahead and delete A-23702?

On 1/9/2014 3:22 PM, Gantz, Marie wrote:
> Julie,
>
> The Excel spreadsheets include all 1316 infants included in the SUPPORT
> analysis. I'm not sure why oximetry data are there for the additional
> infant, but please ignore them.
>
> Marie
>
> Marie Gantz, Ph.D.
> Senior Research Statistician
> RTI International
> mgantz@rti.org
> 919-597-5110
>
>
> -----Original Message-----
> From: Juliann DiFiore [mailto:jmd3@case.edu]
> Sent: Thursday, January 09, 2014 1:51 PM
> To: Pickett, James
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele;
> Auman, Jeanette O.; Gantz, Marie; Zaterka-Baxter, Kristin
> Subject: Re: IH and mortality data
>
> Hi James,
>
> Happy New Year!
>
> I am following up on the missing infant data that we discussed before
> the holidays. I have attached a spreadsheet which shows the specific
> infants that were not on the DVD. This list was extrapolated from the
> zipped raw waveform files on the DVD and the Excel file
> ihdatarequest_forJulie.xlsx. In summary, there are a total of 63 infants
> missing with the following criteria:
> 1. 24 died.
> a. 18 of the infants died within 1-5 days of life. Not expecting
> any data from those.
> b. 6 of the infants who died had >1wk of data (8-20 days). I was
> hoping we could find those infants as they would be useable for this
> analysis.
> 2. 39 infants survived with all infants having 50+ days of data (52-291
> days). Can you please look this list over and verify that you do not

> have these infants?
>
> Lastly, in the Excel files, ihdatarequest20140107.xlsx and
> ihdatarequest_forJulie.xlsx infant A-23702 is missing. (This infant is
> included in the raw waveform files on the DVD) Would you please send me
> the information for that infant?
>
> Thanks!
>
> Julie
>
>
> with the the On 12/23/2013 3:23 PM, Pickett, James wrote:
>> Hello Juliann,
>> No, there were no additional discs to send. You have all the data
> that is available. With regards to infant count vs. recording
> availability, not all infants will have recordings. For example, there
> are 28 infants on that subject listing that met status (death) at day of
> life 1 that we are unlikely to have any oximeter data for -- I have
> verified that is the case for 3 via spot check. That one example covers
> approximately 50% of your missing data. I will be more than happy to
> work with you after the holidays to assist you with the remaining
> subjects in question.
>> Regards,
>>
>> J
>>
>> James Pickett - Res. Programmer / Analyst - Clinical Research
> Informatics * (919) 541-1253 * Haynes 399L *
> japickett@rti.org
>> RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research
>> Triangle Park, NC 27709-2194
>>
>>
>> -----Original Message-----
>> From: Juliann DiFiore [mailto:jmd3@case.edu]
>> Sent: Monday, December 23, 2013 2:47 PM
>> To: Pickett, James
>> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele
>> Subject: IH and mortality data
>>
>> Hello James,
>>
>> I have been working through the data sent on the DVD for the IH and
> mortality secondary study. I noticed that there are infants missing in
> the zipped files. There are 1316 infants listed in the
> IHdatarequest.xlsx spreadsheet but only 1255 zipped files are enclosed
> on the DVD. The missing infants seem to be random by site. (ie missing
> per site: 4-site J, 8-site I, 1- site M, 5-site F...). Was there a 2nd
> DVD that was not enclosed in the envelope you sent in september?
>> Regards,
>>
>> Julie
>>
>> --
>> 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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>
> --
> Juliann Di Fiore
> Research Engineer
> Case Western Reserve University
> Rainbow Babies & Children's Hospital
> Division of Neonatology, Room 3100
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Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
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11100 Euclid Ave
Cleveland, OH 44106
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From: Juliann DiFiore
To: Pickett, James
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele; joa@rti.org; mgantz@rti.org; kzaterka@rti.org
Subject: Re: IH and mortality data
Date: Thursday, January 09, 2014 1:50:41 PM
Attachments: infants not on the DVD from RTI.xlsx

Hi James,

Happy New Year!

I am following up on the missing infant data that we discussed before the holidays. I have attached a spreadsheet which shows the specific infants that were not on the DVD. This list was extrapolated from the zipped raw waveform files on the DVD and the Excel file ihdatarequest_forJulie.xlsx. In summary, there are a total of 63 infants missing with the following criteria:
1. 24 died.
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Lastly, in the Excel files, ihdatarequest20140107.xlsx and ihdatarequest_forJulie.xlsx infant A-23702 is missing. (This infant is included in the raw waveform files on the DVD) Would you please send me the information for that infant?

Thanks!

Julie

with the the On 12/23/2013 3:23 PM, Pickett, James wrote:
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> J
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> James Pickett - Res. Programmer / Analyst - Clinical Research Informatics * (919) 541-1253 * Haynes 399L * japickett@rti.org
> RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research Triangle Park, NC 27709-2194
>
>
> -----Original Message-----

> From: Juliann DiFiore [mailto:jmd3@case.edu]
> Sent: Monday, December 23, 2013 2:47 PM
> To: Pickett, James
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Walsh, Michele
> Subject: IH and mortality data
>
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>
> I have been working through the data sent on the DVD for the IH and mortality secondary study. I noticed that there are infants missing in the zipped files. There are 1316 infants listed in the IHdatarequest.xlsx spreadsheet but only 1255 zipped files are enclosed on the DVD. The missing infants seem to be random by site. (ie missing per site: 4-site J, 8-site I, 1- site M, 5-site F...). Was there a 2nd DVD that was not enclosed in the envelope you sent in september?
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> Regards,
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> Julie
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> --
> Juliann Di Fiore
> Research Engineer
> Case Western Reserve University
> Rainbow Babies & Children's Hospital
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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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INFANTS THAT WERE NOT INCLUDED ON THE DVD

Center ID	Network number	(b)(6)	Death at any time v	Day of life of final status
A			1	2
B			1	1
B			1	1
B			1	10
B			1	8
E			1	20
E			1	1
E			1	1
F			1	1
F			1	1
F			1	5
I			1	1
I			1	1
J			1	1
J			1	18
K			1	1
K			1	3
K			1	4
K			1	1
P			1	1
P			1	3
P			1	11
Q			1	1
Q			1	18
A			2	114
A			2	80
A			2	96
A			2	95
B			2	52
C			2	103
E			2	105
E			2	97

These are infants who died. Some have more than a week of data.

These are survivors with many days of data that were not on the DVI

E	(b)(6)	2	108
E		2	67
E		2	108
E		2	73
E		2	57
F		2	231
F		2	65
H		2	108
H		2	88
H		2	130
H		2	131
H		2	127
H		2	97
H		2	76
I		2	108
I		2	158
I		2	119
I		2	72
I		2	139
I		2	114
I		2	90
I		2	64
J		2	89
J		2	291
K		2	188
K		2	86
L		2	100
M		2	58
N		2	104
Q		2	95
Q		2	94

Blansfield, Earl (NIH/NICHD) [E]

From: Raju, Tonse (NIH/NICHD) [E]
Sent: Tuesday, January 07, 2014 11:05 AM
To: Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Subject: RE: Final Decision made for 13-551-R

I concur with Bob.

Tonse N.K. Raju, MD, DCH
Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health
Phone: 301-402-1872, Fax: 301-496-3790
rajut@mail.nih.gov

-----Original Message-----
From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, January 07, 2014 10:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Final Decision made for 13-551-R

I'm trying to understand the newsworthiness of the findings. My first impression is that (b)(5)
(b)(5) e:

"Our contemporary data support the 2013 AAP screening guidelines for ROP for infants 24 0/7 to 27 6/7 weeks gestational age.1 Some infants do not meet treatment criteria until after discharge home. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment."

So, in other words, (b)(5)
(b)(5)

Please let me know whether you think that assessment is accurate.

Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 07, 2014 9:53 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: FW: Final Decision made for 13-551-R

Hi

As we have previously discussed, here is a heads up on another upcoming SUPPORT publication.

This manuscript was just accepted for publication in Journal of Perinatology. This is a secondary analysis of the NRN's SUPPORT data looking at Retinopathy Of Prematurity (ROP) over time in the NICU and post discharge. From a scientific point of view, these (b)(5)

(b)(5)

Happy to discuss if you feel we need to do something. This will likely come out sometime in the next few months, but I don't have a date yet.

Thanks for your help

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

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301-435-7909

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, January 07, 2014 9:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Final Decision made for 13-551-R

Here's the final one.

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: Monday, January 06, 2014 2:59 PM
To: Kennedy, Kathleen A
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Final Decision made for 13-551-R

Congratulations –

Can you send us a final copy of the accepted version?
Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

From: jperinatol@us.nature.com [mailto:jperinatol@us.nature.com]
Sent: Monday, January 06, 2014 3:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Final Decision made for 13-551-R

Dear Dr Higgins:

Here is a copy of the decision letter for manuscript "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" by Kathleen Kennedy, Lisa Wrage, Rosemary Higgins, Neil Finer, Waldemar Carlo, Michele Walsh, Abbot Laptook, Roger Faix, Bradley Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, and Dale Phelps [Paper #13-551-R], which you were a Contributing Author.

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Sincerely,

Edward E. Lawson, M.D.

Editor-in-Chief
the Journal of Perinatology
Johns Hopkins Medicine
600 N. Wolfe St
Baltimore, MD 21287

Subject: Manuscript #13-551-R Decision

2nd Jan 2014

Dear Dr. Kennedy:

Manuscript #: 13-551-R
Title: Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants Corresponding Author: Dr Kennedy

I am happy to inform you that your manuscript is accepted for publication. This is a very nice manuscript that we are very pleased to have in The Journal. Your changes are most appropriate and I believe have improved the readability, though the manuscript remains long for the message, which is very complete.

Galley proofs will be sent to you directly from the publisher. Minor corrections may be made to the text by the publisher's copy editors or myself.

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APC form <https://urldefense.proofpoint.com/v1/url?u=http://www.nature.com/licenceforms/jp/jp-apc-form.pdf&k=yYSsEqip9%2FcIjLHUhVwIqA%3D%3D%0A&r=YEG%2BqmVpD%2FUoTjwyQ8cuzLFb3ea3iN2G2nc0uX80cko%3D%0A&m=n2Bd9dpFI6JaXLu1dJTTa37eYJvUVdqruNMGBdXv7%2FI%3D%0A&s=adb45fb2f686489db5ad211c28eac9bba3bbf3318c8ebf0fed53deacf1ba0db1>

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Thank you for supporting the Journal of Perinatology. I encourage you to continue considering the Journal for your future scholarly works.

Sincerely,

Edward E. Lawson, M.D.
Editor-in-Chief
the Journal of Perinatology
Johns Hopkins Medicine
600 N. Wolfe St
Baltimore, MD 21287

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Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 07, 2014 10:28 AM
To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Final Decision made for 13-551-R

Yes, accurate.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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: Tuesday, January 07, 2014 10:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
Cc: Raju, Tonse (NIH/NICHD) [E]
Subject: RE: Final Decision made for 13-551-R

I'm trying to understand the newsworthiness of the findings. My first impression is that (b)(5)
(b)(5)

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(b)(5)

Please let me know whether you think that assessment is accurate.

Thanks.

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To: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]
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This manuscript was just accepted for publication in Journal of Perinatology. This is a secondary analysis of the NRN's SUPPORT data looking at Retinopathy Of Prematurity (ROP) over time in the NICU and post discharge. From a scientific point of view, (b)(5)

(b)(5)

Happy to discuss if you feel we need to do something. This will likely come out sometime in the next few months, but I don't have a date yet.

Thanks for your help

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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 [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, January 07, 2014 9:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Final Decision made for 13-551-R

Here's the final one.

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: Monday, January 06, 2014 2:59 PM
To: Kennedy, Kathleen A
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Final Decision made for 13-551-R

Congratulations –

Can you send us a final copy of the accepted version?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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: jperinatol@us.nature.com [mailto:jperinatol@us.nature.com]
Sent: Monday, January 06, 2014 3:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Final Decision made for 13-551-R

Dear Dr Higgins:

Here is a copy of the decision letter for manuscript "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants" by Kathleen Kennedy, Lisa Wrage, Rosemary Higgins, Neil Finer, Waldemar Carlo, Michele Walsh, Abbot Laptook, Roger Faix, Bradley Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, and Dale Phelps [Paper #13-551-R], which you were a Contributing Author.

You can now use a single sign-on for all your accounts, view the status of all your manuscript submissions and reviews, access usage statistics for your published articles and download a record of your refereeing activity for the Nature journals.

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Sincerely,

Edward E. Lawson, M.D.
Editor-in-Chief
the Journal of Perinatology
Johns Hopkins Medicine
600 N. Wolfe St
Baltimore, MD 21287

Subject: Manuscript #13-551-R Decision

2nd Jan 2014

Dear Dr. Kennedy:

Manuscript #: 13-551-R
Title: Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants
Corresponding Author: Dr Kennedy

I am happy to inform you that your manuscript is accepted for publication. This is a very nice manuscript that we are very pleased to have in The Journal. Your changes are most appropriate and I believe have improved the readability, though the manuscript remains long for the message, which is very complete.

Galley proofs will be sent to you directly from the publisher. Minor corrections may be made to the text by the publisher's copy editors or myself.

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Thank you for supporting the Journal of Perinatology. I encourage you to continue considering the Journal for your future scholarly works.

Sincerely,

Edward E. Lawson, M.D.

Editor-in-Chief
the Journal of Perinatology
Johns Hopkins Medicine
600 N. Wolfe St
Baltimore, MD 21287

Attachment: jper_copyright.pdf - 1st Mar 04 22:39:42

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; (b)(6) gmail.com; Das, Abhik (adas@rti.org); Wrage, Lisa Ann (wrage@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)
Subject: FW: Your Manuscript # 20131573R1 submitted to JPediatr
Date: Tuesday, January 07, 2014 9:10:59 AM

Here are the first responses

Luc

From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Monday, January 06, 2014 6:57 PM
To: Sanchez, Pablo
Cc: Luc Brion; " (b)(6) @gmail.com>, " Wrage@ndb-mr3.cc.emory.edu; Lisa.Ann@ndb-mr3.cc.emory.edu
Subject: Re: Your Manuscript # 20131573R1 submitted to JPediatr

Too bad

I agree with Pablo

BUT would try JAMA Pediatrics first

BJS"**Sanchez, Pablo" <Pablo.Sanchez@nationwidechildrens.org> writes:**

Hi Luc--I am sorry--very surprised that they rejected it after wanting a revision... I have heard of it happening, but unusual --always think that it is a done deal --personally I would not do any more analyses (except the correction - #1) but would go ahead and submit--no analyses will answer the question conclusively, so would not spend more time on it. Have you thought of Archives Diseases of Childhood-Fetal and Neonatal? Higher impact factor--and by the way, this month's lead article is by [illegible] on the Support trial .. .. but any that you mention is fine -- doubt that JAMA Pediatrics will take it but they send it back quickly--my thoughts--pablo

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 06, 2014 6:30 PM
[illegible]@gmail.com; Wrage, Lisa Ann ([illegible].org); Das, Abhik (adas@rti.org); 'Gantz, Marie' (mgantz@rti.org); Myra Wyckoff; Sanchez, Pablo; Roy Heyne; Mambarambath Jaleel; nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@[illegible]); Rosemary Higgins (higginsr@mail.nih.gov)
Subject: FW: Your Manuscript # 20131573R1 submitted to JPediatr

Happy New Year to everyone.

Sorry but the manuscript was not accepted by Journal of Pediatrics.

We have previously discussed in length whether to conduct a survey of practices. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.

I suggest to submit a revised manuscript either to JAMA Pediatrics, Early Human Development or Journal of Perinatology (classified by impact factor) after the revisions listed below.

1. I attach a revised version in which we corrected the starting time of the second cohort from "after publication of SUPPORT" into "after release of the results of SUPPORT Trial to NRN centers".

2. I suggest to add to the manuscript a comparison of the change in DR intubation in centers that participated in the Feasibility trial versus those that did not. I would hypothesize that the first group would have less change in DR practice after the release of the SUPPORT results that the second group. This would allow us to assess whether there was a difference in change in DR intubation after releasing SUPPORT results in centers that already had experience with using CPAP in the DR (those that participate in the Feasibility Trial) versus in centers that were more likely to have less experience with CPAP in the DR before SUPPORT (e.g., Parkland, in which DR intubation was routine when SUPPORT). Please let me know if you agree with conducting this additional analysis.

If you have any suggestion please let me know.
I will be glad to talk further with you at the NRN meeting next week.
Thanks for your collaboration and best regards,

Luc

-----Original Message-----
From:
ees.jpeds.0.26696f3b760f00@eesmail.elsevier.com [mailto:ees.jpeds.0.26696f3b760f00@eesmail.elsevier.com]
On Behalf Of Journal Office
Sent: Monday, January 06, 2014 11:44 AM
To: Luc Brion; lucbrion@gmail.com
Subject: Your Manuscript #20131573R1 Submitted to JPediatr

Ref.: Ms. No. 20131573R1
Change in Practice after The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Brion,

Thank you for revising and resubmitting your manuscript. The Editors appreciate your efforts to satisfy the concerns of the reviewers and the requirements of the Journal of Pediatrics. We are very sorry to inform you that we will not be able to publish your manuscript because the consensus of the Editors was that it did not attain high enough priority for publication in The Journal.

The Editors share the concerns of Reviewer #2 in concluding that the effect seen could not specifically be linked to publication of SUPPORT. This may be true, especially because almost 1/4 of the time allotted to enroll patients "post-SUPPORT" (2010-2012) came prior to publication of SUPPORT in May 2010. Additionally, the primary outcome assessed was intubation, and the significance of these findings - without linking them directly to policy change based on the publication of SUPPORT - suggests a change in clinical practice over time.

Because of space limitations, we are able to accept <20% of submitted manuscripts. When establishing a priority for each manuscript and in reaching an editorial decision, the Editors consider the quality of the manuscript, the novelty and importance of the observation, and appropriateness for our readership. Because we have many meritorious manuscripts and very strict page limitations from the publisher, we are forced to make some difficult decisions. We hope this process was helpful in improving your manuscript for submission to another journal. Further comments from the reviewers are appended below.

Again, thank you for this submission and your support of The Journal of Pediatrics. Our best wishes for your success in publishing your paper elsewhere.

Sincerely,

Clyde J Wright, MD
Guest Editor

[redacted]

Reviewers' comments:

Reviewer #1: The authors have addressed most of the issues raised by this reviewer. The discussion section of the manuscript is much improved.

A remaining suggestion is that of including a summary of the previous (and post-trial if possible) guidelines/policies for delivery room management and oxygen saturation targeting in participating centers. It is hard to believe such information was not available to the investigators at the time of planning of the SUPPORT trial. Such information may be quite valuable in deciding to adopt some of the changes in practice following this and other similar trials.

Reviewer #2: On re-reviewing this revised manuscript, the authors were unable to respond to the major criticism that the mechanism of the post-versus pre-SUPPORT reduction in delivery room endotracheal intubation (ETI) rate is not elucidated. The study does not provide evidence that the reduction in ETI is attributable to the uptake of the evidence supplied by SUPPORT, nor is evidence provided that the reduction in adverse secondary clinical outcomes, eg severe retinopathy of prematurity (ROP), was attributable to the evidence supplied by SUPPORT. The authors were unable to examine whether the reduction in severe ROP was attributable to the adoption of the lower SpO2 target range because the NICHD Network Genetic Database did not contain individual patient data on the oxygen target ranges that were used before and after SUPPORT.
The conclusion that there was a reduction in the delivery room ETI rate post- vs pre-SUPPORT, with no evidence confirming attribution, is of limited importance. Even that conclusion is subject to weaknesses in the design and conduct of the study I referred to and acknowledged by the authors in Discussion, 3rd paragraph.

[redacted]

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
Director, The Pediatric Center of Emory and Children's Healthcare of Atlanta
President, Emory-Children's Center
1760 Haygood Drive
Atlanta, GA 30322
Office: 404-727-2456 Fax: 404-727-5737
bstoll@emory.edu

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr
Date: Tuesday, January 07, 2014 9:04:00 AM

Thanks, Rose
Looking forward to seeing you next week.
Best regards,
Luc

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 07, 2014 7:26 AM
To: nfiner@ucsd.edu; 'Wally Carlo, M.D.'; Lisa Wrage (wrage@rti.org); Abhik Das (adas@rti.org); mgantz@rti.org; Pablo Sánchez (pablo.sanchez@nationwidechildrens.org); Myra Wyckoff; Roy Heyne; barbara_stoll@oz.ped.emory.edu; Michele Walsh (mcw3@cwru.edu); Abbot Laptook
Cc: Luc Brion; doctorlevan@gmail.com
Subject: FW: Your Manuscript # 20131573R1 submitted to JPediatr

Hi
See the comments below -
Do folks favor performing the analysis that Luc has prposed??
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch 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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Thanks for your collaboration and best regards,

Luc

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From: ees.jpeds.0.26696f.3b760f00@eesmail.elsevier.com
[mailto:ees.jpeds.0.26696f.3b760f00@eesmail.elsevier.com] On Behalf Of Journal Office
Sent: Monday, January 06, 2014 11:44 AM
To: Luc Brion; lucbrion@gmail.com
Subject: Your Manuscript # 20131573R1 submitted to JPediatr

Ref.: Ms. No. 20131573R1
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

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Sincerely,

Clyde J Wright, MD

Guest Editor

/rwl

Reviewers' comments:

(b)(4),(b)(6)

From: Luc Brion
To: (b)(6) gmail.com; Wrage, Lisa Ann (wrage@rti.org); Das, Abhik (adas@rti.org); "Gantz, Marie" (mgantz@rti.org); Myra Wyckoff; Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Mambarambath Jaleel; nfiner@ucsd.edu; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Your Manuscript # 20131573R1 submitted to JPediatr
Date: Monday, January 06, 2014 6:30:01 PM
Attachments: Jackie LeVan Manuscript NRN 1-6-14.docx

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Sent: Monday, January 06, 2014 11:44 AM
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Subject: Your Manuscript # 20131573R1 submitted to JPediatr

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

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The Editors share the concerns of (b)(4),(b)(6)

(b)(4),(b)(6)

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Again, thank you for this submission and your support of The Journal of Pediatrics. Our best wishes for your success in publishing your paper elsewhere.

Sincerely,

Clyde J Wright, MD
Guest Editor

/rwl

Reviewers' comments:

(b)(4),(b)(6)

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa A. Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD, [1] Pablo J. Sánchez, MD, [1,4] Roy Heyne, MD, [1] Mambarambath Jaleel, [1] MD, Neil N. Finer, MD,[5] Waldemar A. Carlo, MD, [6] Abhik Das, PhD,[3] Barbara J. Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern, Dallas, TX; [2]Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu
No reprints needed

First draft: Dr. LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Statement: No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Conflict of Interest Statement: There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 224 words
Article length: 2,612 words
Revised 12/612/143

List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.89, 95% confidence interval 0.86-0.93) was significantly lower than one.

Conclusions:

After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of endotracheal intubation and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the

risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of ETI in the DR in each center after the SUPPORT trial would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional

data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003--2012).

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after release of the results of SUPPORT Trial to NRN centers~~publication of the SUPPORT trial~~ (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of the SUPPORT trial, i.e., physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature

within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[3] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[4] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth

as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-14] Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012.This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1).

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

The primary outcome, the proportion of DR ETI, decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. The adjusted risk of DR ETI significantly decreased after the SUPPORT trial, RR 0.89, 95% confidence interval 0.86-0.93 (Table 2).

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 2). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ($P<0.001$).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, $p=0.18$).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of the SUPPORT trial in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those born before initiation of the SUPPORT trial. We evaluated changes in ETI for all patients in the cohorts. Since we did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise

information on the timing of changes in ETI practices at a subset of the 11 centers that participated in the SUPPORT trial. The proportion of ETI in one of the participating centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[15] The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a feasibility study prior to initiation of the SUPPORT trial.[17] It is possible that ETI decreased in these 5 centers because of experience with use of T-piece resuscitators and increased use of CPAP in the DR during the feasibility study limiting further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial.

The strengths of this study include the use of a prospective database and a large sample size of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in the SUPPORT trial, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Lack of correlation between the change in the proportion in ETI after the SUPPORT trial and baseline ETI

proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers. Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice

guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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12.

Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

From: Luc Brion
To: Wrage, Lisa Ann; Das, Abhik; (b)(6) @gmail.com
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr
Date: Monday, January 06, 2014 5:24:43 PM

Correct, these data are already collected for the manuscript.
I will write to all authors this evening to find out if they agree.
Luc

From: Wrage, Lisa Ann [wrage@rti.org]
Sent: Monday, January 06, 2014 3:28 PM
To: Luc Brion; Das, Abhik; doctorlevan@gmail.com
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr

So it is data we already have and are using in this study already, correct? It is fine with me if we do it, do you think that checking in with other co-authors to see what they think (in terms of what it adds to the paper or how it might strengthen the paper) is a good idea?
Thanks.
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 06, 2014 4:18 PM
To: Das, Abhik; Wrage, Lisa Ann; doctorlevan@gmail.com
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr

Lisa and Abhik:
Thanks a lot for your response.
#1 & 3: I will change the text accordingly
#2: This would assess whether there was a difference in change in DR intubation after releasing SUPPORT results in centers that already had experience with using CPAP in the DR (those that participate in the Feasibility Trial) versus in centers that had not participated in the Feasibility trial, some of which may have had very little experience with CPAP in the DR before SUPPORT (e.g., Parkland, in which intubation was routine when SUPPORT) Luc

---

From: Das, Abhik [adas@rti.org]
Sent: Monday, January 06, 2014 3:10 PM
To: Wrage, Lisa Ann; Luc Brion; (b)(6) @gmail.com
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr

If #2 is based on NRN data and doesn't involve any additional data collection, then we can perhaps do it if the other co-authors are willing?

Thanks

Abhik

-----Original Message-----
From: Wrage, Lisa Ann
Sent: Monday, January 06, 2014 4:06 PM
To: Luc Brion; (b)(6) @gmail.com
Cc: Das, Abhik
Subject: RE: Your Manuscript # 20131573R1 submitted to JPediatr

Hi Luc and Jackie,
I am sorry that the paper was not accepted.

I think that #1 is fine.

As to #2, I believe that Abhik has said that this would require an additional proposal and subcommittee or other approval first. Could you remind me of the specifics of why you wanted to add this in?

Re: #3, the post-SUPPORT cohort was specified as 1/2010 to 12/31-2012, and this was based on presentation of the results of SUPPORT to the NRN Steering committee in Nov 2009 (from one version of the protocol) or from another version: Study Design: "...a second cohort of patients starting after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012). ".
So, to me what needs to be clarified in the paper is this (specifically that it was based on the results released within the NRN), rather than redoing the whole analysis removing the several months included before the publication came out to the wider audience.

Happy New Year!
Lisa

-----Original Message-----
From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 06, 2014 2:00 PM
To: (b)(6) @gmail.com; Wrage, Lisa Ann
Subject: FW: Your Manuscript # 20131573R1 submitted to JPediatr

Jackie and Lisa;
Sorry but J Pediatrics did not accept the revised manuscript.
Please review the email and let me know what you think should be the best approach.
Here are my first thoughts
1. We could submit the manuscript with minor changes or as is to another journal with lower impact.
2. We could include a comparison of the change in DR intubation between centers that participated in the Feasibility trial versus those that did not.
3. Lisa; could you please verify the exact timing of the post-SUPPORT epoch for this manuscript; are we missing the months in the inclusion criteria, or do we need to revise the analysis to include only the months after the publication (e.g., June 2010- December 2012) .
Best regards,
Luc

From: ees.jpeds.0.26696f.3b760f00@eesmail.elsevier.com [ees.jpeds.0.26696f.3b760f00@eesmail.elsevier.com] on behalf of Journal Office [journal.pediatrics@cchmc.org]
Sent: Monday, January 06, 2014 11:43 AM
To: Luc Brion; (b)(6) @gmail.com
Subject: Your Manuscript # 20131573R1 submitted to JPediatr

Ref.: Ms. No. 20131573R1
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Brion,

Thank you for revising and resubmitting your manuscript. The Editors appreciate your efforts to satisfy the concerns of the reviewers and the requirements of The Journal of Pediatrics. We are very sorry to inform you that we will not be able to publish your manuscript because the consensus of the Editors was that it did not attain high enough priority for publication in The Journal.

The Editors share the concerns of (b)(4),(b)(6)

(b)(4),(b)(6)

Because of space limitations, we are able to accept <20% of submitted manuscripts. When establishing a priority for each manuscript and in reaching an editorial decision, the Editors consider the quality of the manuscript, the novelty and importance of the observation, and appropriateness for our readership. Because we have many meritorious manuscripts and very strict page limitations from the publisher, we are forced to make some difficult decisions. We hope this process was helpful in improving your manuscript for submission to another journal. Further comments from the reviewers are appended below.

Again, thank you for this submission and your support of The Journal of Pediatrics. Our best wishes for your success in publishing your paper elsewhere.

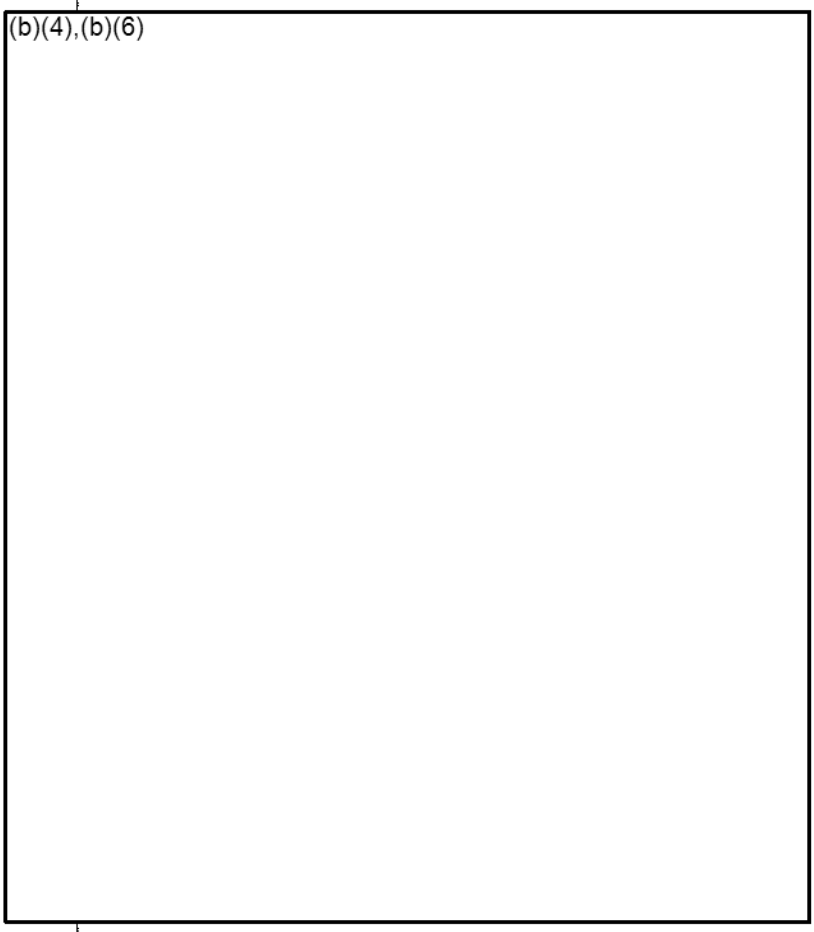
Sincerely,

Clyde J Wright, MD
Guest Editor

/rwl

Reviewers' comments:

(b)(4),(b)(6)



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From: Namasivayam Ambalavanan
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Final uploaded draft and Submission pdf - plan submission on Jan 8, 2014
Date: Sunday, January 05, 2014 1:59:00 PM
Attachments: SubmitPDF_PCO2_SUPPORT_Jan5_2014.pdf
PCO2_SUPPORT_Jan5_2014_Main Document_Word972003.doc
PCO2_SUPPORT_Jan5_2014_Supplementalfile_Word972003.doc

Dear All,
Attached is the final draft of the manuscript that has been uploaded to the Pediatrics journal website, and the pdf of the submission for your records. I will look over it and then click "submit" in a couple of days (Wednesday Jan 8, 2014 am), if no one has any major comments.
Thanks,
Ambal

From: Namasivayam Ambalavanan
Sent: Sunday, December 29, 2013 2:23 PM
Subject: RE: PaCO2 manuscript : Final draft (Dec 29, 2013) before submission on Jan 8, 2014

Dear All,
Attached is the most recent draft of our manuscript on PaCO2 in relation to outcome in SUPPORT. I have made some changes following NICHD clearance, Publication Subcommittee reviews, and comments by co-authors on the previous draft. One change is to emphasize that PaCO2 is a marker of illness severity and that there is for the most part no interaction between SUPPORT treatment group allocation and PaCO2. I will submit on Jan 8th (Wednesday; about 10 days from now) to Pediatrics if there are no further comments/suggestions.
Thank you,
Ambal

Title:

$PaCO_2$ and outcomes in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Authors:

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Short Title: $PaCO_2$ and Outcomes

Abbreviations: BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe 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; Intracranial hemorrhage; Blood Gas Analysis

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RR70, M01 RR80, M01 RR125, M01 RR633, M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 TR93, UL1 TR142, UL1 TR442, UL1 TR454).

Conflicts of interest: The authors have no conflicts of interest relevant to this article to disclose.

Word count: abstract: 250; text of manuscript: 2972 (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 and greater fluctuations in PaCO2 were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment or death. Correlation of $PaCO_2$ with FiO_2 and ventilation days support maximum $PaCO_2$ as a marker of illness severity in extremely premature infants.

ABSTRACT:

Objective: To determine the association of $PaCO_2$ with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18-22 months in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO_2 target 85-89% vs 91-95%) and ventilation strategies. Five $PaCO_2$ variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max $PaCO_2$], hypocapnic [lowest quartile of Min $PaCO_2$], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min $PaCO_2$]). Adjusted and unadjusted analyses compared $PaCO_2$ variables for infants with and without sIVH, BPD, and NDI (+/- death). **Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max $PaCO_2$ with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all $p < 0.0001$). No interaction was found between $PaCO_2$ category and SpO_2 treatment group for sIVH/death, NDI/death, or death. Fluctuators were at higher risk for BPD/death in higher SpO_2 target group. Max $PaCO_2$ was positively correlated with maximum FiO_2 ($r_s 0.55$, $p<0.0001$) & ventilator days ($r_s 0.61$, $p<0.0001$). **Conclusions:** Higher $PaCO_2$ was associated with sIVH, BPD, and NDI (+/- death). Correlation of $PaCO_2$ with FiO_2 and ventilator days supports higher Max $PaCO_2$ as a marker of illness severity.

(Abstract Word Count = 250)

MANUSCRIPT TEXT

INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ($PaCO_2$) are associated with and may possibly contribute to outcomes of prematurity such as intraventricular hemorrhage (IVH)[1], periventricular leukomalacia (PVL)[2, 3], bronchopulmonary dysplasia (BPD)[4], and neurodevelopmental impairment (NDI).[5] We have previously shown that both high and low $PaCO_2$ levels and wide fluctuations in $PaCO_2$ are associated with severe IVH (sIVH; IVH Grades III or IV).[1] Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.[2, 3, 6]

Increased $PaCO_2$ increases cerebral blood flow,[7-9] while decreased $PaCO_2$ reduces cerebral blood flow.[10] Cerebral blood flow decreases with increased oxygenation[9] but interactions between $PaCO_2$ and oxygenation have not been assessed in preterm infants. Lung injury maybe reduced by tolerance of a higher $PaCO_2$[4, 11, 12] as well as lower oxygen saturation (SpO_2) targets.[13] The combination of a higher $PaCO_2$ (permissive hypercapnia) as well as a lower PaO_2 (targeting lower SpO_2) might reduce BPD more than with either permissive hypercapnia or a lower SpO_2 target 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 SpO_2 targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy ($PaCO_2$>65 mm Hg permitted intubation, while a $PaCO_2$<65 mm Hg with a pH>7.20 was an extubation criterion) or intubation and surfactant within 1 hour after birth ($PaCO_2$<50 mm Hg with a pH>7.30 was an extubation criterion).[13, 14] Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although infants in the CPAP group less frequently required surfactant, intubation, postnatal steroids, and received fewer days of

mechanical ventilation. In the lower SpO_2 target group, death occurred more frequently (19.9 vs. 16.2%; p= 0.04) while severe retinopathy among survivors occurred less often (8.6 vs. 17.9%; p<0.001), without significant differences in other outcomes.[13] However, no significant differences in the composite outcome of death or NDI were noted among infants in any of the treatment groups.[15]

Clinical outcomes that are not significantly different by SpO_2 target groups might be different when the combination of $PaCO_2$ and SpO_2 (actual or target group) is analyzed. We hypothesized that both extremes of $PaCO_2$ would be associated with severe IVH, and that effect modification by SpO_2 will be observed, with hypercapnia associated with sIVH in the low but not high SpO_2 group (due to greater cerebral blood flow at lower SpO_2). We also hypothesized that BPD would be lower in infants with hypercapnia in the low SpO_2 group (due to less mechanical ventilation), and that higher $PaCO_2$ will be associated with a higher risk of NDI (due to an increased risk of sIVH).

PATIENTS AND METHODS

Patient characteristics:

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.[13, 14] The characteristics of this population[13] and of the follow-up cohort[15] have been previously reported.

$PaCO_2$ variables

Five $PaCO_2$ variables were defined for this observational study, using routine blood gas (arterial or capillary) measurements not governed by study protocol. For postnatal days 1-14, the $PaCO_2$ from blood gases collected closest to 8 am, 4 pm, and midnight was recorded. From these

data, the minimum level, maximum level (Max $PaCO_2$), standard deviation, and time-weighted $PaCO_2$ were derived. Time-weighted $PaCO_2$ was calculated[1]: the sum of all $PaCO_2$ values multiplied by the time interval from previous blood gas was divided by the overall time period. Time between blood gases was capped at 24 hours (~5% of all measurements) so any one blood gas represents no more than a 24 hour period. The median (mean; 5^{th}-95^{th} centiles) number of blood gases per infant was 2 (2, 1-3) on study day 1, 3 (2.4, 1-3) on day 3, 2 (2.1, 1-3) on day 7, and 2 (2, 1-3) on day 14. Infants were categorized into 4 groups (hypercapnic, hypocapnic, fluctuators, and normocapnic) by first separately ranking the maximum and minimum $PaCO_2$ over days 1-14 into quartiles. Infants with minimum $PaCO_2$ in the lowest quartile who were not also in the highest quartile of maximum $PaCO_2$ were categorized as 'hypocapnic'. Infants with maximum $PaCO_2$ in the highest quartile who were not also in the lowest quartile of minimum $PaCO_2$ were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum $PaCO_2$ and the highest quartile of maximum $PaCO_2$ were categorized as 'fluctuators', and the remaining infants, those whose minimum $PaCO_2$ level were in quartiles 2-4 and maximum $PaCO_2$ in quartiles 1-3 were categorized as 'normocapnic'.

Other variables

Maternal hypertension was defined as pregnancy induced hypertension (PIH). 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 and on days 3, 7, and 14, and severe illness was defined *a priori* as FiO_2 >0.4 and mechanical ventilation for 8+ hours in the 1^{st} 14 days. Severe IVH was defined as IVH grade 3-4 (most severe grade identified in 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: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition of less than 70, a modified Gross Motor Function Classification System 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 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the $PaCO_2$ and other variables for infants with the specified outcome were compared to those without 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 exploratory goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the maximum $PaCO_2$, the 4 level $PaCO_2$ categorical variable, as well as time-weighted $PaCO_2$ were obtained using generalized estimating equation models for binary outcomes taking into account correlations within multiple-birth clusters, thus accounting for multiple births randomized to the same treatment arm in SUPPORT. Variables included in models along with the $PaCO_2$ variable were: birth weight, GA group, gender, race, prenatal steroids, PIH, premature rupture of membranes, and center. SUPPORT treatment group variables (High/Low SpO2; CPAP/ventilator) were included in models that contained maximum $PaCO_2$ and the 4 level $PaCO_2$ variable. Interactions of these $PaCO_2$ and treatment group variables were included to assess if the effect of $PaCO_2$ varied by SUPPORT treatment group. A variable for actual median SpO_2 in the first 14 days was included in the model containing time-weighted $PaCO_2$, and interaction of these two variables was included to determine if the effect of time-

weighted $PaCO_2$ varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

As higher maximum $PaCO_2$ may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher maximum FiO_2, days of mechanical ventilation, and severe illness), correlations of maximum $PaCO_2$ with maximum FiO_2 and days of ventilation, and its relationship with severe illness (as previously defined) were calculated.

RESULTS

Adjusted analysis for Severe IVH/Death (**Table 1**):

Maximum $PaCO_2$ was associated with higher odds of sIVH/death (OR 1.39 [95% CI 1.27-1.53] for an increase in maximum $PaCO_2$ of 10 mmHg, p <0 .0001). Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (reference group) or hypocapnic infants. No interaction was found between $PaCO_2$ category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (Higher or Lower SpO_2). The interaction term for time-weighted $PaCO_2$ and actual median SpO_2 in the first 14 days was significant ($p<0.05$), with a higher OR for $PaCO_2$ associated with a lower median SpO_2 (OR of 1.6 [1.17-2.17] for median SpO_2 of 91, vs. 1.18 [0.85-1.62] for SpO_2 of 94) indicating that higher average $PaCO_2$ was associated with severe IVH/death only if the SpO_2 was lower. Other variables associated ($p<0.05$) with sIVH/death included: lower birth weight and gestational age, male gender, no PIH, and center.

Adjusted analysis for BPD/Death (**Table 2**):

Maximum $PaCO_2$ (OR 1.57 [1.41-1.75] per increase of 10 mmHg, $p < 0.0001$) and time-weighted $PaCO_2$ (OR 2.41 [1.89-3.09] per increase of 10 mmHg, $p < 0.0001$) were associated with higher odds of BPD/death. The interaction term between $PaCO_2$ category and treatment group (Higher or Lower SpO_2) was significant for fluctuators ($p=0.006$), with the OR for fluctuators in the higher SpO_2 group being 7.4 [2.6-21], as compared to 1.18 [0.51-2.70] for the low SpO_2 group. Other variables associated ($p<0.05$) with BPD/death were lower birth weight, male gender, and center.

Adjusted analysis for NDI/Death (**Table 3**):

Maximum $PaCO_2$ (OR 1.38 [1.25-1.52] per increase of 10 mmHg, $p<.0001$) and time-weighted $PaCO_2$ (OR 1.44 [1.09-1.90] per increase of 10 mmHg, $p < 0.0001$) were associated with higher odds of NDI/death. No interactions were noted between $PaCO_2$ category and SpO_2 treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic or hypocapnic infants. Other variables associated ($p<0.05$) with NDI/death were lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for Death before discharge (**Table 4**):

Maximum $PaCO_2$ (OR 1.36 [1.22-1.51] per increase of 10 mmHg, $p<.0001$) was associated with higher odds of death before discharge. No interactions were noted between $PaCO_2$ category and SpO_2 treatment group.Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic or hypocapnic infants. Other variables associated ($p<0.05$) with death before discharge were lower birth weight, male gender, absence of PIH, and center.

Maximum $PaCO_2$ was positively correlated with both maximum FiO_2 (Spearman correlation coefficient [r_s] = 0.55, $p<0.0001$) and days of ventilation ($r_s = 0.61$, $p<0.0001$). There

was also a significant difference in $PaCO_2$ in infants having severe illness (median maximum $PaCO_2$=78) vs. infants without severe illness (median maximum $PaCO_2$=61), p <0.0001.

Unadjusted Results (**Supplemental Tables 1-4**):

Infants who developed sIVH had a lower minimum, higher maximum and greater variation in $PaCO_2$ compared to those without sIVH. Maximum $PaCO_2$ demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median maximum $PaCO_2$ between infants with sIVH and those without sIVH. The magnitude of separation in minimum, standard deviation, and time-weighted $PaCO_2$ were statistically highly significant (p<0.0001) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted $PaCO_2$ compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to results for severe IVH and severe IVH or death.

DISCUSSION

We found that extremes of $PaCO_2$ were associated with worse outcome (sIVH, BPD, NDI, either alone or in combination with death) in extremely preterm infants. A higher maximum $PaCO_2$ in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO_2, days of ventilation, and severe illness). A higher average $PaCO_2$ was associated with sIVH/death only if the actual SpO_2 was lower. Our results suggest that a higher level and greater fluctuation in $PaCO_2$ are indicators of illness severity.

Our study has the limitation that data on ventilator settings and oxygenation index were not available. Other limitations include variation in frequency and method (arterial or capillary)

of blood gas sampling that were based on usual clinical practice, and the use of a dichotomous outcome variables, which do not provide information regarding magnitude of outcome (E.g. severe vs. moderate BPD). However, this study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, specific criteria for intubation and extubation were used, and trained research coordinators collected data. Eighteen to 22 month follow-up was achieved in almost 94% of infants by certified trained personnel. An additional strength of our study is that we evaluated both interaction with actual saturation and treatment group (higher or lower SpO_2 target), to distinguish illness severity and effects of treatment group allocation (e.g. higher average $PaCO_2$ was associated with sIVH/death only if the actual SpO_2 was lower, but there was no interaction with treatment group).

Previously, we have shown in a single-center retrospective analysis that both high and low $PaCO_2$ levels and wide fluctuations in $PaCO_2$ are associated with increased sIVH.[1] The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. As maximum $PaCO_2$ was correlated with longer duration of mechanical ventilation and higher magnitude of oxygen supplementation, it is likely that infants with higher maximum $PaCO_2$ had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average $PaCO_2$ in combination with a lower SpO_2 being associated with sIVH/death, suggesting that these infants were sicker with greater gas exchange difficulty. No interaction was observed between maximum $PaCO_2$ and SpO_2 groups for sIVH, probably because randomization in this trial likely led to a similar range of $PaCO_2$ in both SpO_2 groups.

In this cohort, the average (time-weighted) $PaCO_2$ even in infants without severe IVH was $\geq$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.[12] Our data indicate clinical practices in academic centers have evolved to maintain $PaCO_2$ in the permissive hypercapnia range. However, as the maximum $PaCO_2$ exceeded this range even in infants without sIVH, it is apparent that tight control of $PaCO_2$ within this narrow range is difficult.

A higher maximum and time-weighted $PaCO_2$ and a greater magnitude of fluctuation in $PaCO_2$ 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 $PaCO_2$ rather than because of rapid weaning and physician intent. Although we show 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 CO_2 elimination for a given minute ventilation, due to a higher alveolar CO_2 (P_ACO_2). Also, hypercapnia also stimulates respiratory drive, which may help in ventilator weaning. An interesting finding in the present study was that greater fluctuation in $PaCO_2$ was associated with BPD/death only in the higher SpO_2 but not in the low SpO_2 group. It is speculated that greater oxygen exposure in the higher SpO_2 group may interact with volutrauma/atelectrauma associated with fluctuating $PaCO_2$ possibly increasing the risk for BPD/death.

Maximum $PaCO_2$ was significantly associated with higher NDI/death, confirming our previous single-center study.[5] This association may be secondary to maximum $PaCO_2$ being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.[19] Alterations in $PaCO_2$ may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in $PaCO_2$[7-9] may result in sIVH[1] and contribute to NDI. A reduction in cerebral blood flow due to decreased $PaCO_2$[10] may

lower white matter perfusion and result in periventricular leukomalacia (PVL).[2, 3, 6] Brain injury associated with extremes of $PaCO_2$ may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.[20, 21]

In conclusion, our work demonstrates that maximum $PaCO_2$ is a marker of illness severity and an independent predictor of worse outcome in ELBW infants. Therefore, similar to oxygenation index or PaO_2, maximum $PaCO_2$ 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 $PaCO_2$ at later time points with outcomes needs to be determined.

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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 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.

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:

Specific contributions of authors:

Namasivayam Ambalavanan, MD: Conception, design, data analysis & interpretation, drafting and revision of manuscript

Waldemar A. Carlo, MD: Conception, design, drafting and revision of manuscript

Michele C. Walsh, MD MS: Conception, design, drafting and revision of manuscript

Lisa Wrage MPH: Design, data analysis & interpretation

Abhik Das, PhD: Design, data analysis & interpretation,

Matthew Laughon MD MPH: Drafting and revision of manuscript

C. Michael Cotten MD: Drafting and revision of manuscript

Kathleen Kennedy MD: Drafting and revision of manuscript

Abbot Laptook MD: Drafting and revision of manuscript

Seetha Shankaran, MD: Drafting and revision of manuscript

Rosemary D. Higgins, MD: Conception, design, drafting and revision of manuscript

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 participated in this study:
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Table 1: Adjusted results for $PaCO_2$ variables in relation to outcome of severe IVH/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.39 (1.27-1.53)	<0.0001
$PaCO_2$ Category:		
Hypocapnic	1.11 (0.73-1.67)	0.63
Hypercapnic	2.60 (1.77-3.82)	<0.0001
Fluctuator	2.81 (1.68-4.72)	<0.0001
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)**		
Median SpO_2=91	1.60 (1.17-2.17)	0.003
Median SpO_2=92	1.44 (1.09-1.91)	0.01
Median SpO_2=93	1.30 (0.98-1.73)	0.07
Median SpO_2=94	1.18 (0.85-1.62)	0.32

** interaction term for time-weighted $PaCO_2$ x Median SpO_2 in the first 14 days was significant (p=0.048) indicating that the effect of time-weighted $PaCO_2$ depended on level of Median SpO_2.

Table 2: Adjusted results for $PaCO_2$ variables in relation to outcome of BPD/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.57 (1.41-1.75)	<0.0001
$PaCO_2$ Category:	**Higher SpO_2 Target**	
Hypocapnic	0.73 (0.46-1.16)	0.18
Hypercapnic	2.54 (1.41-4.60)	0.002
Fluctuator	7.4 (2.6-21.0)	0.0002
Normocapnic	REFERENCE	-
	Lower SpO_2 Target	
Hypocapnic	1.01 (0.63-1.63)	0.96
Hypercapnic	3.38 (1.93-5.93)	<0.0001
Fluctuator	1.18 (0.51-2.70)	0.70
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	2.41 (1.89-3.09)	<0.0001

** interaction term for $PaCO_2$ category x treatment group (Higher or Lower SpO_2) was significant for Fluctuators

Table 3: Adjusted results for $PaCO_2$ variables in relation to outcome of NDI/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.38 (1.25-1.52)	<0.0001
$PaCO_2$ Category:		
Hypocapnic	1.03 (0.69-1.53)	0.90
Hypercapnic	2.69 (1.82-3.96)	<0.0001
Fluctuator	3.07 (1.84-5.12)	<0.0001
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	1.44 (1.09-1.90)	0.009

Table 4: Adjusted results for $PaCO_2$ variables in relation to outcome of death before discharge

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.36 (1.22-1.51)	<0.0001
$PaCO_2$ Category:		
Hypocapnic	0.90 (0.54-1.50)	0. 07
Hypercapnic	2.47 (1.61-3.77)	<0.0001
Fluctuator	1.88 (1.03-3.43)	0.04
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	1.28 (0.94-1.74)	0.12

Supplemental 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]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
$PaCO_2$, minimum level	#	163	1098		325	971	
	Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
	Median, IQR	32 (27-37)	34 (29-38)	0.005	33 (28-38)	34 (30-38)	0.69
$PaCO_2$, maximum level	#	163	1098		325	971	
	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)	<0.0001	76 (65-88)	64 (54-74)	<0.0001
$PaCO_2$, standard deviation	#	163	1077		314	951	
	Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<0.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<0.0001
$PaCO_2$, time-weighted	#	163	1098		325	971	
	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)	0.009	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<0.0001
$PaCO_2$ category:	#	163	1098		325	971	
	# (%)			<0.0001			<0.0001
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)	655 (59.7)		130 (40.0)	603 (62.1)	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value[1]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	0.13	166 (49.6)	496 (50.7)	0.73
Treatment: SpO_2 group, Higher or Lower O_2	#	164	1106		335	979	
	High O2, # (%)	81 (49.4)	559 (50.5)	0.78	156 (46.6)	505 (51.6)	0.11
Median SpO2 DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<0.0001
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)	0.03	750 (640-881)	850 (710-990)	<0.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	0.08	197 (58.8)	514 (52.5)	0.046
Race: NH Black NH White Hispanic Other	# (%)	 55 (33.5) 55 (33.5) 44 (26.8) 10 (6.1)	 421 (38.1) 442 (40.0) 208 (18.8) 35 (3.2)	0.016	 112 (33.4) 133 (39.7) 72 (21.5) 18 (5.4)	 376 (38.4) 387 (39.5) 187 (19.1) 29 (3.0)	0.09
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	0.26	112 (33.4)	376 (38.4)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	0.12	133 (39.7)	387 (39.5)	0.96

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value[1]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	0.03	21 (6.6)	110 (12.0)	0.008
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	0.006	97 (30.4)	336 (34.9)	0.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	0.84	325 (97.3)	938 (95.8)	0.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	0.022	120 (35.9)	200 (20.4)	<0.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	0.04	29 (8.7)	29 (3.0)	<0.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	0.47	117 (37.9)	384 (39.2)	0.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	0.69	108 (32.2)	325 (33.2)	0.74

[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]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
$PaCO_2$, 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)	0.015	33 (29-38)	34 (30-38)	0.25
$PaCO_2$, 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)	<0.0001	73 (65-85)	60 (50-69)	<0.0001
$PaCO_2$, 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)	<0.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<0.0001
$PaCO_2$, 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)	<0.0001	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<0.0001
$PaCO_2$ category:	#	441	659		639	659	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	78 (17.7) 101 (22.9) 48 (10.9) 214 (46.5)	138 (20.9) 59 (9.0) 24 (3.6) 438 (66.5)	<0.0001	100 (15.7) 170 (26.6) 74 (11.6) 295 (46.2)	138 (20.9) 59 (9) 24 (3.6) 438 (66.5)	<0.0001
Treatment: CPAP or Surfactant group	#	442	666		650	666	
	CPAP, # (%)	223 (50.4)	346 (52)	0.62	317 (48.8)	346 (52.0)	0.25

Characteristic		BPD (N=442)	No BPD (N=666)	p-value[1]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
Treatment: SpO_2 group, Higher or Lower O_2	#	442	666		650	666	
	High O2, # (%)	237 (53.6)	331 (49.7)	0.20	331 (50.9)	331 (49.7)	0.66
Median SpO2 DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<0.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<0.0001
Birth Weight (g)	#	666	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650-870)	900 (770-1020)	<0.0001	740 (643-870)	900 (770-1020)	<0.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	0.04	375 (57.7)	337 (50.6)	0.01
Race NH Black NH White Hispanic Other	# (%) 157 (35.5) 200 (45.3) 73 (16.5) 12 (2.7)	 268 (40.2) 237 (35.6) 137 (20.6) 24 (3.6)	0.013	 221 (34) 284 (43.7) 122 (18.8) 23 (3.5)	 268 (40.2) 237 (35.6) 137 (20.6) 24 (3.6)	0.02
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	0.11	221 (34)	268 (40.2)	0.02
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	0.001	284 (43.7)	237 (35.6)	0.003
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	0.18	68 (11.1)	63 (10.1)	0.58
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)	0.22
Prenatal steroids	#	442	666		649	666	

Characteristic		BPD (N=442)	No BPD (N=666)	p-value[1]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
	Yes, # (%)	427 (96.6)	636 (95.5)	0.36	629 (96.9)	636 (95.5)	0.18
1 minute Apgar < 3	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<0.0001	207 (31.9)	114 (17.1)	<0.0001
5 minute Apgar < 3	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	0.11	41 (6.3)	17 (2.6)	0.001
Prophylactic indomethacin	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	0.75	240 (38.5)	261 (39.2)	0.79
Vaginal delivery	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240(36.0)	0.004	193 (29.7)	240 (36.0)	0.01

[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]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
$PaCO_2$, 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)	0.001	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)	<0.0001	76 (66-88)	64 (54-74)	<0.0001
$PaCO_2$, 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)	<0.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<0.0001
$PaCO_2$, 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)	0.0014	51.7 (47.1-56)	48 (42.8-52.3)	<0.0001
$PaCO_2$ category:	#	98	872		346	872	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	22 (22.5) 25 (25.5) 17 (17.4) 34 (34.7)	171 (19.6) 111 (12.7) 44 (5.1) 546 (62.6)	<0.0001	51 (14.7) 111 (32.1) 49 (14.2) 135 (39.0)	171 (19.6) 111 (12.7) 44 (5.1) 546 (62.6)	<0.0001
Treatment: CPAP or Surfactant group	#	98	878		356	878	

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value[1]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44
Treatment: SpO_2 group, Higher or Lower O_2	#	98	878		356	878	
	High O2, # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Median SpO2 DOL 1-14	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92-94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<0.0001
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643-914)	850 (710-995)	<0.0001	734 (621-870)	850 (710-995)	<0.0001
Gender	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	0.01
Race: NH Black NH White Hispanic Other	# (%)	 37 (37.8) 37 (37.8) 21 (21.4) 3 (3.1)	 333 (37.9) 354 (40.3) 161 (18.3) 30 (3.4)	0.89	 125 (35.1) 139 (39) 78 (21.9) 14 (3.9)	 333 (37.9) 354 (40.3) 161 (18.3) 30 (3.4)	0.47
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
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	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	97	863		341	863	

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value[1]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
	Yes, # (%)	26 (26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16
Prenatal steroids	#	98	878		355	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	98	877		355	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	0.0003	130 (36.6)	181 (20.6)	<0.0001
5 minute Apgar < 3	#	98	878		356	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	0.04	29 (8.2)	27 (3.1)	0.0001
Prophylactic indomethacin	#	98	878		330	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	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 Bivariate analyses for Death

Characteristic		**Death (N=237)**	**No Death (N=997)**	**p-value[1]**
$PaCO_2$, minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	0.026
$PaCO_2$, maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<0.0001
$PaCO_2$, standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<0.0001
$PaCO_2$, time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<0.0001
$PaCO_2$ category:	#	227	991	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	26 (11.5) 82 (36.1) 29 (12.8) 90 (39.7)	196 (19.8) 140 (14.1) 64 (6.5) 591 (59.6)	<0.0001
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO_2 group, Higher or Lower O_2	#	237	997	
	High O2, # (%)	107 (45.2)	515 (51.7)	0.07
Median SpO2 DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<0.0001

Characteristic		Death (N=237)	No Death (N=997)	p-value[1]
Gender	#	237	997	
	Male, # (%)	144 (60.8)	526 (52.8)	0.026
Race: NH Black NH White Hispanic Other	# (%)	 77(32.5) 96 (40.5) 53 (22.4) 11 (4.6)	 381 (38.2) 397 (39.8) 186 (18.7) 33 (3.3)	0.26
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
HTN, pregnancy induced	#	226	938	
	Yes, # (%)	16 (7.1)	111 (11.8)	0.04
Rupture of membranes > 24 hours prior to birth	#	224	980	
	Yes, # (%)	72 (32.1)	332 (33.9)	0.62
Prenatal steroids	#	236	997	
	No, # (%)	7 (3)	41 (4.1)	0.41
1 minute Apgar < 3	#	236	996	
	Yes, # (%)	90 (38.1)	221 (22.2)	<0.0001
5 minute Apgar < 3	#	237	997	
	Yes, # (%)	22 (9.3)	34 (3.4)	<0.0001
Prophylactic indomethacin	#	211	997	
	Yes, # (%)	83 (39.3)	384 (38.5)	0.82
Vaginal delivery	#	237	997	
	Yes, # (%)	77 (32.5)	326 (32.7)	0.95

[1] p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

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From: Rowe, Mona (NIH/NICHD) [E]
To: Carr, Sarah (NIH/OD) [E]
Cc: Hirschfeld, Steven (NIH/NICHD) [E]; Zajicek, Anne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Mofenson, Lynne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Hazra, Rohan (NIH/NICHD) [E]; Eisenberg, Esther (NIH/NICHD) [C]; De Paolo, Louis (NIH/NICHD) [E]; Hayunga, Eugene G. (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Signore, Caroline (NIH/NICHD) [E]
Subject: RE: Quick Turnaround Review and Comment: CONFIDENTIAL Revised Draft Common Rule NPRM
Date: Friday, January 03, 2014 4:28:56 PM
Attachments: NICHD Comments - OHRP Proposed Common Rule.docx
Sensitivity: Confidential

Sarah—please note NICHD's comments –thanks to *all staff* who took the time to look at these over the holidays and for Steve's insightful assessment of the many themes we received in the emails. We believe that the overall comments are important, even though we may not always have line by line notes for all of them. However, special thanks to Rose Higgins who made some individual notes, by line, available. Have a good weekend.

Mona

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From: Carr, Sarah (NIH/OD) [E]
Sent: Friday, December 20, 2013 9:24 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Paltoo, Dina (NIH/OD) [E]; Fomous, Cathy (NIH\OD) [C]; Paine, Taunton (NIH/OD) [C]; Scheiderer, Cary (NIH/OD) [E]; Milner, Lauren (NIH/OD) [E]; Moore, Jerry (NIH/OD) [E]; Mullins, Angelee (NIH/OD) [E]; Brewer, Ann (NIH/OD) [E]; Goodrich-Doctor, Adrienne (NIH/NIAID) [E]
Subject: Quick Turnaround Review and Comment: CONFIDENTIAL Revised Draft Common Rule NPRM
Importance: High
Sensitivity: Confidential

Dear Colleagues:

Please find attached for your review and comment a copy of the fourth revised draft Common Rule NPRM. The document consists of:

- a preamble (pp. 1-117);
- an appendix with a table comparing the proposed exemptions to the current exemptions (pp.

118-124);

- a regulatory impact analysis (pp. 125-185); and
- the revised draft regulatory text (pp. 186-211).

Copied below, in case it's helpful, are the 16 major changes proposed in the NPRM (these appear on pp. 5-6 of the preamble). The two other attachments are a track changes version of the current Common Rule showing the proposed changes (pp. 1-28) and a mark-up of the third version of the NPRM, which we reviewed in June 2013, showing the changes that appear in the revised draft. Please remember that all of these documents are confidential and cannot be shared beyond NIH.

We would welcome both general and specific narrative comments on any part of the NPRM. Please provide them in a separate word document (do not embed your comments in any of the NPRM documents). When making a specific comment, please be sure to cite both the page and line number of the text on which you are commenting.

Unfortunately, because the HHS deadline for comments is extremely compressed, we must ask you to submit your IC's comments by **COB Friday, January 3, 2014.**

If you have any questions about the documents or this request, please let me know.

Thank you for your attention to this important matter.

Happy Holidays,

Sarah

Major Proposed Revisions

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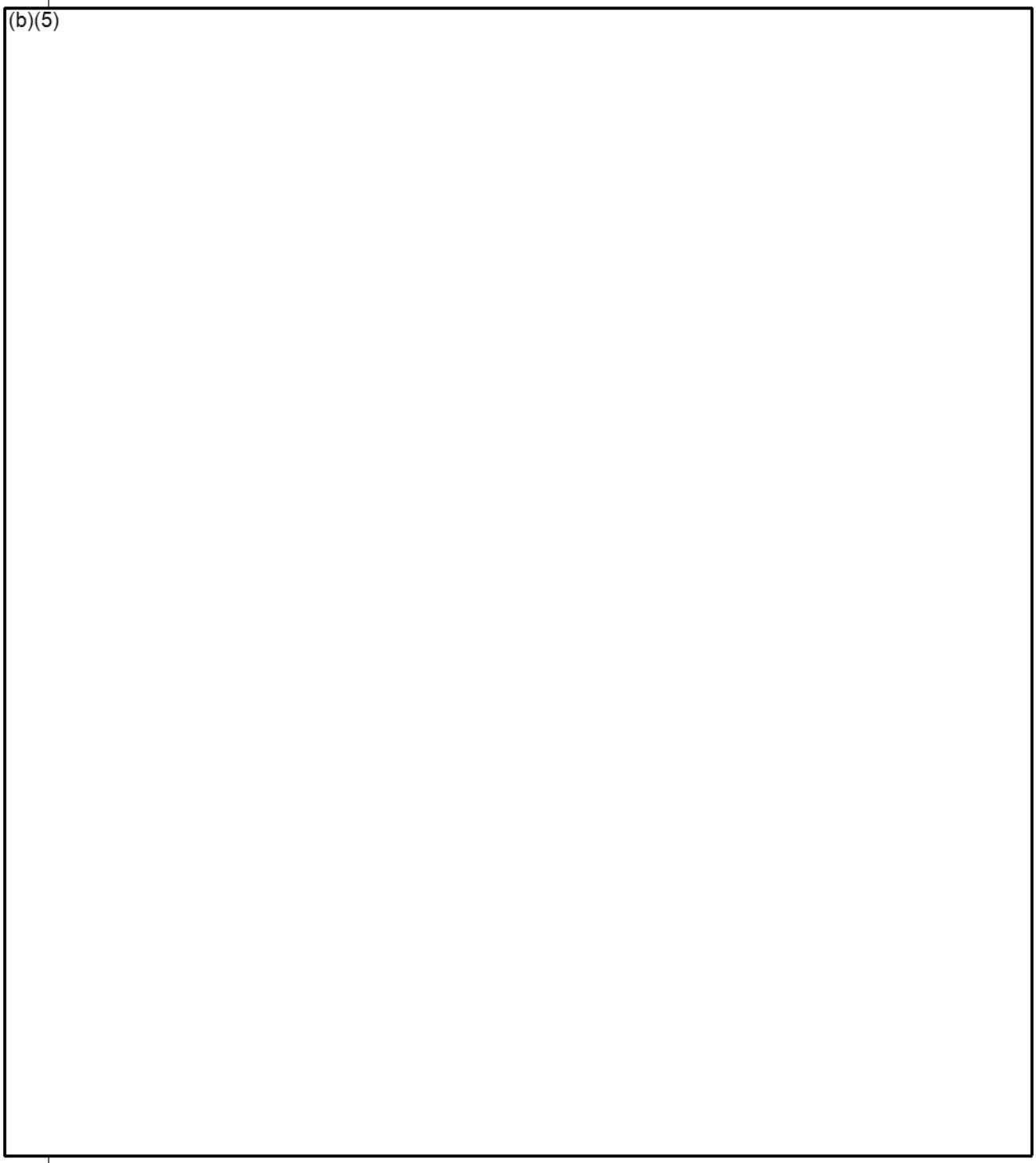
(b)(5)



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From: Carr, Sarah (NIH/OD) [E]
Sent: Monday, December 09, 2013 8:00 PM
To: TNBC
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Moore, Jerry (NIH/OD) [E]; Brewer, Ann (NIH/OD) [E]
Subject: CONFIDENTIAL Heads Up -- Revised Draft Common Rule NPRM Coming
Importance: High

Dear Colleagues:

We have good news regarding the Common Rule NPRM. OHRP is very close to completing the revised draft of the proposed reforms. We've been notified that HHS agencies will receive the revised package (i.e., the revised draft preamble, including the Regulatory Impact Assessment, and draft regulatory text) for review and comment on **Monday, December 23, 2013**. Unfortunately, however, particularly given the season, we will have to complete the review in very short order, which means that we will send the package to you as soon as it arrives and ask for your IC's comments and feedback by **Friday, January 3, 2014**.

We hope this heads up is helpful in terms of planning and preparation. If you have any questions at this point, please let us know.

Sarah

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From:	Namasivayam Ambalavanan
To:	Shankaran, Seetha; Kennedy, Kathleen A; 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; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan
Subject:	RE: PaCO2 manuscript : Final draft (Dec 29, 2013) before submission on Jan 8, 2014
Date:	Sunday, December 29, 2013 3:23:46 PM
Attachments:	PCO2_SUPPORT_Dec29_2013.docx

Dear All,

Attached is the most recent draft of our manuscript on PaCO2 in relation to outcome in SUPPORT. I have made some changes following NICHD clearance, Publication Subcommittee reviews, and comments by co-authors on the previous draft. One change is to emphasize that PaCO2 is a marker of illness severity and that there is for the most part no interaction between SUPPORT treatment group allocation and PaCO2. I will submit on Jan 8th (Wednesday; about 10 days from now) to Pediatrics if there are no further comments/suggestions.

Thank you,

Ambal

From: Namasivayam Ambalavanan
Sent: Thursday, August 01, 2013 1:52 PM
To: Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Namasivayam Ambalavanan
Subject: RE: PaCO2 manuscript : Fifth draft of August 1, 2013 + Authorship Acknowledgement
Importance: High

Dear All,

Thank you for your comments on the previous drafts. Attached is the fifth draft of our manuscript evaluating PCO2 in SUPPORT. There are minor changes since the previous draft. The paper has been formatted for PEDIATRICS. The word count is a bit high (3075 rather than 3000), so will need a little trimming. Also attached is the Authorship Agreement – please complete and email (click the button on form to automatically email it to me) or print and fax (205-934-3100) to me. Once I hear back from anyone, if there are no further major comments, I will send to the Publications subcommittee, and then make changes in response to Publication Subcomm Reviewer comments, and then finally send for NICHD Clearance before submission.

Sincerely,

Ambal

From: Namasivayam Ambalavanan [NAmbalavanan@peds.uab.edu]
Sent: Friday, July 05, 2013 11:35 AM
To: Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Shankaran, Seetha; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Fourth draft of July 5, 2013

Dear All,

Here is the much-awaited fourth draft of our manuscript examining PCO2 in SUPPORT. The main changes in this draft are:

1) Thanks to much work by Lisa Wrage, the main results are now the adjusted results, and the unadjusted results have been moved to Supplemental Tables
2) Some clarifications of methods and explanations in Discussion.
3) A few novel results. Eg. an interaction between PCO2 and SpO2 for severe IVH, again suggesting that sicker kids are more likely to have worse outcomes. Again, this is what we'd expect, but I suppose we should not always hope for unexpected findings.

Thanks,
Ambal

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
University of Alabama at Birmingham
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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

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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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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 practtioners allow co2 to be hoigh on min settings,,,,and those kids are probably way different than kids pn high sttings 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 $PaCO_2$, minimal $PaCO_2$, time-weighted $PaCO_2$, and SD of $PaCO_2$ as independent continuous variables with actual time-weighted PaO_2 (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, PPROM, 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 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 C02 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 PC02),* ***>> 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 PC02,>> ***Yes. As above, I think we should have***

hypocapnia only, not fluctuators.
Fluctuators (in both upper quartile of max PCC02 lower quartile of min PC02)>> ***Yes.***
Normocapnic (in middle two quartiles of max PC02 ***AND*** *min PCC02)*

To define Max PC02 and Min PC02 do you simply want me to use the maximum and minimum value of all values of PC02 for each infant using PC02 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 C02 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]
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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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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. You 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 $PaCO_2$ with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Authors:

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Short Title: $PaCO_2$ and IVH

Abbreviations: BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe 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; Intracranial hemorrhage; Blood Gas Analysis

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RR70, M01 RR80, M01 RR125, M01 RR633, M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 TR93, UL1 TR142, UL1 TR442, UL1 TR454).

Conflicts of interest: The authors have no conflicts of interest relevant to this article to disclose.

Word count: abstract: 250; text of manuscript: 2973 (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 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 in extremely premature infants

ABSTRACT:

Objective: To determine the association of $PaCO_2$ with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18-22 months in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO_2 target 85-89% vs 91-95%) and ventilation strategies. Five $PaCO_2$ variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max $PaCO_2$], hypocapnic [lowest quartile of Min $PaCO_2$], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min $PaCO_2$]). Adjusted and unadjusted analyses compared $PaCO_2$ variables for infants with and without sIVH, BPD, and NDI (+/- death). **Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max $PaCO_2$ with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all $p < 0.0001$). No interaction was found between $PaCO_2$ category and SpO_2 treatment group for sIVH/death, NDI/death, or death. Fluctuators were at higher risk for BPD/death in higher SpO_2 target group. Max $PaCO_2$ was positively correlated with maximum FiO_2 ($r_s 0.55$, $p<0.0001$) & ventilator days ($r_s 0.61$, $p<0.0001$). **Conclusions:** Higher $PaCO_2$ was associated with sIVH, BPD, and NDI (+/- death). Correlation of $PaCO_2$ with FiO_2 and ventilator days supports higher Max $PaCO_2$ as a marker of illness severity.

(Abstract Word Count = 250)

MANUSCRIPT TEXT

INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ($PaCO_2$) are associated with and may possibly contribute to outcomes of prematurity such as intraventricular hemorrhage (IVH)[1], periventricular leukomalacia (PVL)[2, 3], bronchopulmonary dysplasia (BPD)[4], and neurodevelopmental impairment (NDI).[5] We have previously shown that both high and low $PaCO_2$ levels and wide fluctuations in $PaCO_2$ are associated with severe IVH (sIVH; IVH Grades III or IV).[1] Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.[2, 3, 6]

Increased $PaCO_2$ increases cerebral blood flow,[7-9] while decreased $PaCO_2$ reduces cerebral blood flow.[10] Cerebral blood flow decreases with increased oxygenation[9] but interactions between $PaCO_2$ and oxygenation have not been assessed in preterm infants. Lung injury maybe reduced by tolerance of a higher $PaCO_2$[4, 11, 12] as well as lower oxygen saturation (SpO_2) targets.[13] The combination of a higher $PaCO_2$ (permissive hypercapnia) as well as a lower PaO_2 (targeting lower SpO_2) might reduce BPD more than with either permissive hypercapnia or a lower SpO_2 target 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 SpO_2 targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy ($PaCO_2$>65 mm Hg permitted intubation, while a $PaCO_2$<65 mm Hg with a pH>7.20 was an extubation criterion) or intubation and surfactant within 1 hour after birth ($PaCO_2$<50 mm Hg with a pH>7.30 was an extubation criterion).[13, 14] Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although infants in the CPAP group less frequently required surfactant, intubation, postnatal steroids, and fewer days of mechanical

ventilation. In the lower SpO_2 target group, death occurred more frequently (19.9 vs. 16.2%; p= 0.04) while severe retinopathy among survivors occurred less often (8.6 vs. 17.9%; p<0.001), without significant differences in other outcomes.[13] However, no significant differences in the composite outcome of death or NDI were noted 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 (actual or target group) is analyzed. 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 sIVH in the low but not high SpO_2 group (due to greater cerebral blood flow at lower SpO_2). We also hypothesized that BPD would be lower in infants with hypercapnia in the low SpO_2 group (due to less mechanical ventilation), and that higher $PaCO_2$ will be associated with a higher risk of NDI (due to an increased risk of sIVH).

PATIENTS AND METHODS

Patient characteristics:

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.[13, 14] The characteristics of this population[13] and of the follow-up cohort[15] have been previously reported.

$PaCO_2$ variables

Five $PaCO_2$ variables were defined for this observational study, using routine blood gas (arterial or capillary) measurements not governed by study protocol. For postnatal days 1-14, the $PaCO_2$ from blood gases collected closest to 8 am, 4 pm, and midnight was recorded. From these data, the minimum level, maximum level (Max $PaCO_2$), standard deviation, and time-weighted

$PaCO_2$ were derived. Time-weighted $PaCO_2$ was calculated[1]: the sum of all $PaCO_2$ values multiplied by the time interval from previous blood gas was divided by the overall time period. Time between blood gases was capped at 24 hours (~5% of all measurements) so any one blood gas represents no more than a 24 hour period. The median (mean; 5^{th}-95^{th} centiles) number of blood gases per infant was 2 (2, 1-3) on study day 1, 3 (2.4, 1-3) on day 3, 2 (2.1, 1-3) on day 7, and 2 (2, 1-3) on day 14. Infants were categorized into 4 groups (hypercapnic, hypocapnic, fluctuators, and normocapnic) by first separately ranking the maximum and minimum $PaCO_2$ over days 1-14 into quartiles. Infants with minimum $PaCO_2$ in the lowest quartile who were not also in the highest quartile of maximum $PaCO_2$ were categorized as 'hypocapnic'. Infants with maximum $PaCO_2$ in the highest quartile who were not also in the lowest quartile of minimum $PaCO_2$ were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum $PaCO_2$ and the highest quartile of maximum $PaCO_2$ were categorized as 'fluctuators', and the remaining infants, those whose minimum $PaCO_2$ level were in quartiles 2-4 and maximum $PaCO_2$ in quartiles 1-3 were categorized as 'normocapnic'.

Other variables

Maternal hypertension was defined as pregnancy induced hypertension (PIH). 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 and on days 3, 7, and 14, and severe illness was defined *a priori* as FiO_2 >0.4 and mechanical ventilation for 8+ hours in the 1^{st} 14 days. Severe IVH was defined as IVH grade 3-4 (most severe grade identified in 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: a cognitive composite score on the Bayley Scales of Infant and Toddler Development,

third edition of less than 70, a modified Gross Motor Function Classification System 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 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the $PaCO_2$ and other variables for infants with the specified outcome were compared to those without 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 exploratory goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the maximum $PaCO_2$, the 4 level $PaCO_2$ categorical variable, as well as time-weighted $PaCO_2$ were obtained using generalized estimating equation models for binary outcomes taking into account correlations within multiple-birth clusters, thus accounting for multiple births randomized to the same treatment arm in SUPPORT. Variables included in models along with the $PaCO_2$ variable were: birth weight, GA group, gender, race, prenatal steroids, PIH, premature rupture of membranes, and center. SUPPORT treatment group variables (High/Low SpO2; CPAP/ventilator) were included in models that contained maximum $PaCO_2$ and the 4 level $PaCO_2$ variable. Interactions of these $PaCO_2$ and treatment group variables were included to assess if the effect of $PaCO_2$ varied by SUPPORT treatment group. A variable for actual median SpO_2 in the first 14 days was included in the model containing time-weighted $PaCO_2$, and interaction of these two variables was included to determine if the effect of time-

weighted $PaCO_2$ varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

As higher maximum $PaCO_2$ may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher maximum FiO_2, days of mechanical ventilation, and severe illness), correlations of maximum $PaCO_2$ with maximum FiO_2 and days of ventilation, and its relationship with severe illness (as previously defined) were calculated.

RESULTS

Adjusted analysis for Severe IVH/Death (**Table 1**):

Maximum $PaCO_2$ was associated with higher odds of sIVH/death (OR 1.39 [95% CI 1.27-1.53] for an increase in maximum $PaCO_2$ of 10 mmHg, $p < 0.0001$). Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (reference group) or hypocapnic infants. No interaction was found between $PaCO_2$ category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (Higher or Lower SpO_2). The interaction term for time-weighted $PaCO_2$ and actual median SpO_2 in the first 14 days was significant ($p<0.05$), with a higher OR for $PaCO_2$ associated with a lower median SpO_2 (OR of 1.6 [1.17-2.17] for median SpO_2 of 91, vs. 1.18 [0.85-1.62] for SpO_2 of 94) indicating that higher average $PaCO_2$ was associated with severe IVH/death only if the SpO_2 was lower. Other variables associated ($p<0.05$) with sIVH/death included: lower birth weight and gestational age, male gender, no PIH, and center.

Adjusted analysis for BPD/Death (**Table 2**):

Maximum $PaCO_2$ (OR 1.57 [1.41-1.75] per increase of 10 mmHg, $p < 0.0001$) and time-weighted $PaCO_2$ (OR 2.41 [1.89-3.09] per increase of 10 mmHg, $p < 0.0001$) were associated with higher odds of BPD/death. The interaction term between $PaCO_2$ category and treatment group (Higher or Lower SpO_2) was significant for fluctuators ($p=0.006$), with the OR for fluctuators in the higher SpO_2 group being 7.4 [2.6-21], as compared to 1.18 [0.51-2.70] for the low SpO_2 group. Other variables associated ($p<0.05$) with BPD/death were lower birth weight, male gender, and center.

Adjusted analysis for NDI/Death (**Table 3**):

Maximum $PaCO_2$ (OR 1.38 [1.25-1.52] per increase of 10 mmHg, $p<.0001$) and time-weighted $PaCO_2$ (OR 1.44 [1.09-1.90] per increase of 10 mmHg, $p < 0.0001$) were associated with higher odds of NDI/death. No interactions were noted between $PaCO_2$ category and SpO_2 treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic or hypocapnic infants. Other variables associated ($p<0.05$) with NDI/death were lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for Death before discharge (**Table 4**):

Maximum $PaCO_2$ (OR 1.36 [1.22-1.51] per increase of 10 mmHg, $p<.0001$) was associated with higher odds of death before discharge. No interactions were noted between $PaCO_2$ category and SpO_2 treatment group.Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic or hypocapnic infants. Other variables associated ($p<0.05$) with death before discharge were lower birth weight, male gender, absence of PIH, and center.

Maximum $PaCO_2$ was positively correlated with both maximum FiO_2 (Spearman correlation coefficient [r_s] = 0.55, $p<0.0001$) and days of ventilation ($r_s = 0.61$, $p<0.0001$). There

was also a significant difference in $PaCO_2$ in infants having severe illness (median maximum $PaCO_2$=78) vs. infants without severe illness (median maximum $PaCO_2$=61), p <0.0001.

Unadjusted Results (**Supplemental Tables 1-4**):

Infants who developed sIVH had a lower minimum, higher maximum and greater variation in $PaCO_2$ compared to those without sIVH. Maximum $PaCO_2$ demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median maximum $PaCO_2$ between infants with sIVH and those without sIVH. The magnitude of separation in minimum, standard deviation, and time-weighted $PaCO_2$ were statistically highly significant (p<0.0001) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted $PaCO_2$ compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to results for severe IVH and severe IVH or death.

DISCUSSION

We found that extremes of $PaCO_2$ were associated with worse outcome (sIVH, BPD, NDI, either alone or in combination with death) in extremely preterm infants. A higher maximum $PaCO_2$ in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO_2, days of ventilation, and severe illness). A higher average $PaCO_2$ was associated with sIVH/death only if the actual SpO_2 was lower. Our results suggest that a higher level and greater fluctuation in $PaCO_2$ are indicators of illness severity.

Our study has the limitation that data on ventilator settings and oxygenation index were not available. Other limitations include variation in frequency and method (arterial or capillary)

of blood gas sampling that were based on usual clinical practice, and the use of a dichotomous outcome variables, which do not provide information regarding magnitude of outcome (E.g. severe vs. moderate BPD). However, this study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, specific criteria for intubation and extubation were used, and trained research coordinators collected data. Eighteen to 22 month follow-up was achieved in almost 94% of infants by certified trained personnel. An additional strength of our study is that we evaluated both interaction with actual saturation and treatment group (higher or lower SpO_2 target), to distinguish illness severity and effects of treatment group allocation (e.g. higher average $PaCO_2$ was associated with sIVH/death only if the actual SpO_2 was lower, but there was no interaction with treatment group).

Previously, we have shown in a single-center retrospective analysis that both high and low $PaCO_2$ levels and wide fluctuations in $PaCO_2$ are associated with increased sIVH.[1] The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. As maximum $PaCO_2$ was correlated with longer duration of mechanical ventilation and higher magnitude of oxygen supplementation, it is likely that infants with higher maximum $PaCO_2$ had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average $PaCO_2$ in combination with a lower SpO_2 being associated with sIVH/death, suggesting that these infants were sicker with greater gas exchange difficulty. No interaction was observed between maximum $PaCO_2$ and SpO_2 groups for sIVH, probably because randomization in this trial likely led to a similar range of $PaCO_2$ in both SpO_2 groups.

In this cohort, the average (time-weighted) $PaCO_2$ even in infants without severe IVH was $\geq$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.[12] Our data indicate clinical practices in academic centers have evolved to maintain $PaCO_2$ in the permissive hypercapnia range. However, as the maximum $PaCO_2$ exceeded this range even in infants without sIVH, it is apparent that tight control of $PaCO_2$ within this narrow range is difficult.

A higher maximum and time-weighted $PaCO_2$ and a greater magnitude of fluctuation in $PaCO_2$ 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 $PaCO_2$ rather than because of rapid weaning and physician intent. Although we show 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 CO_2 elimination for a given minute ventilation, due to a higher alveolar CO_2 (P_ACO_2). Also, hypercapnia also stimulates respiratory drive, which may help in ventilator weaning. An interesting finding in the present study was that greater fluctuation in $PaCO_2$ was associated with BPD/death only in the higher SpO_2 but not in the low SpO_2 group. It is speculated that greater oxygen exposure in the higher SpO_2 group may interact with volutrauma/atelectrauma associated with fluctuating $PaCO_2$ possibly increasing the risk for BPD/death.

Maximum $PaCO_2$ was significantly associated with higher NDI/death, confirming our previous single-center study.[5] This association may be secondary to maximum $PaCO_2$ being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.[19] Alterations in $PaCO_2$ may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in $PaCO_2$[7-9] may result in sIVH[1] and contribute to NDI. A reduction in cerebral blood flow due to decreased $PaCO_2$[10] may

lower white matter perfusion and result in periventricular leukomalacia (PVL).[2, 3, 6] Brain injury associated with extremes of $PaCO_2$ may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.[20, 21]

In conclusion, our work demonstrates that maximum $PaCO_2$ is a marker of illness severity and an independent predictor of worse outcome in ELBW infants. Therefore, similar to oxygenation index or PaO_2, maximum $PaCO_2$ 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 $PaCO_2$ at later time points with outcomes needs to be determined.

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 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.

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:

Specific contributions of authors:

Namasivayam Ambalavanan, MD: Conception, design, data analysis & interpretation, drafting and revision of manuscript

Waldemar A. Carlo, MD: Conception, design, drafting and revision of manuscript

Michele C. Walsh, MD MS: Conception, design, drafting and revision of manuscript

Lisa Wrage MPH: Design, data analysis & interpretation

Abhik Das, PhD: Design, data analysis & interpretation,

Matthew Laughon MD MPH: Drafting and revision of manuscript

C. Michael Cotten MD: Drafting and revision of manuscript

Kathleen Kennedy MD: Drafting and revision of manuscript

Abbot Laptook MD: Drafting and revision of manuscript

Seetha Shankaran, MD: Drafting and revision of manuscript

Rosemary D. Higgins, MD: Conception, design, drafting and revision of manuscript

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 participated in this study:
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Table 1: Adjusted results for $PaCO_2$ variables in relation to outcome of severe IVH/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.39 (1.27-1.53)	<0.0001
$PaCO_2$ Category:		
Hypocapnic	1.11 (0.73-1.67)	0.63
Hypercapnic	2.60 (1.77-3.82)	<0.0001
Fluctuator	2.81 (1.68-4.72)	<0.0001
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)**		
Median SpO_2=91	1.60 (1.17-2.17)	0.003
Median SpO_2=92	1.44 (1.09-1.91)	0.01
Median SpO_2=93	1.30 (0.98-1.73)	0.07
Median SpO_2=94	1.18 (0.85-1.62)	0.32

** interaction term for time-weighted $PaCO_2$ x Median SpO_2 in the first 14 days was significant (p=0.048) indicating that the effect of time-weighted $PaCO_2$ depended on level of Median SpO_2.

Table 2: Adjusted results for $PaCO_2$ variables in relation to outcome of BPD/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.57 (1.41-1.75)	<0.0001
$PaCO_2$ Category:	**Higher SpO_2 Target**	
Hypocapnic	0.73 (0.46-1.16)	0.18
Hypercapnic	2.54 (1.41-4.60)	0.002
Fluctuator	7.4 (2.6-21.0)	0.0002
Normocapnic	REFERENCE	-
	Lower SpO_2 Target	
Hypocapnic	1.01 (0.63-1.63)	0.96
Hypercapnic	3.38 (1.93-5.93)	<0.0001
Fluctuator	1.18 (0.51-2.70)	0.70
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	2.41 (1.89-3.09)	<0.0001

** interaction term for $PaCO_2$ category x treatment group (Higher or Lower SpO_2) was significant for Fluctuators

Table 3: Adjusted results for $PaCO_2$ variables in relation to outcome of NDI/death

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.38 (1.25-1.52)	<0.0001
$PaCO_2$ Category:		
Hypocapnic	1.03 (0.69-1.53)	0.90
Hypercapnic	2.69 (1.82-3.96)	<0.0001
Fluctuator	3.07 (1.84-5.12)	<0.0001
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	1.44 (1.09-1.90)	0.009

Table 4: Adjusted results for $PaCO_2$ variables in relation to outcome of death before discharge

$PaCO_2$ Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.36 (1.22-1.51)	<0.0001
$PaCO_2$ Category:		
Hypocapnic	0.90 (0.54-1.50)	0. 07
Hypercapnic	2.47 (1.61-3.77)	<0.0001
Fluctuator	1.88 (1.03-3.43)	0.04
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	1.28 (0.94-1.74)	0.12

Supplemental 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]**	**Death or Severe IVH (N=335)**	**No Death or Severe IVH (N=979)**	**p-value[1]**
$PaCO_2$, minimum level	#	163	1098		325	971	
	Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
	Median, IQR	32 (27-37)	34 (29-38)	0.005	33 (28-38)	34 (30-38)	0.69
$PaCO_2$, maximum level	#	163	1098		325	971	
	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)	<0.0001	76 (65-88)	64 (54-74)	<0.0001
$PaCO_2$, standard deviation	#	163	1077		314	951	
	Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<0.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<0.0001
$PaCO_2$, time-weighted	#	163	1098		325	971	
	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)	0.009	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<0.0001
$PaCO_2$ category:	#	163	1098		325	971	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value[1]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
	# (%)			<0.0001			<0.0001
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)	655 (59.7)		130 (40.0)	603 (62.1)	
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	0.13	166 (49.6)	496 (50.7)	0.73
Treatment: SpO_2 group, Higher or Lower O_2	#	164	1106		335	979	
	High O2, # (%)	81 (49.4)	559 (50.5)	0.78	156 (46.6)	505 (51.6)	0.11
Median SpO2 DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<0.0001
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)	0.03	750 (640-881)	850 (710-990)	<0.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	0.08	197 (58.8)	514 (52.5)	0.046
Race:	# (%)						
NH Black		55 (33.5)	421 (38.1)	0.016	112 (33.4)	376 (38.4)	0.09
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)	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value[1]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	0.26	112 (33.4)	376 (38.4)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	0.12	133 (39.7)	387 (39.5)	0.96
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	0.03	21 (6.6)	110 (12.0)	0.008
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	0.006	97 (30.4)	336 (34.9)	0.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	0.84	325 (97.3)	938 (95.8)	0.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	0.022	120 (35.9)	200 (20.4)	<0.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	0.04	29 (8.7)	29 (3.0)	<0.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	0.47	117 (37.9)	384 (39.2)	0.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	0.69	108 (32.2)	325 (33.2)	0.74

[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]**	**Death or BPD (N=650)**	**No Death or BPD (N=666)**	**p-value[1]**
$PaCO_2$, 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)	0.015	33 (29-38)	34 (30-38)	0.25
$PaCO_2$, 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)	<0.0001	73 (65-85)	60 (50-69)	<0.0001
$PaCO_2$, 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)	<0.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<0.0001
$PaCO_2$, 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)	<0.0001	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<0.0001
$PaCO_2$ category:	#	441	659		639	659	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	78 (17.7) 101 (22.9) 48 (10.9) 214 (46.5)	138 (20.9) 59 (9.0) 24 (3.6) 438 (66.5)	<0.0001	100 (15.7) 170 (26.6) 74 (11.6) 295 (46.2)	138 (20.9) 59 (9) 24 (3.6) 438 (66.5)	<0.0001
Treatment: CPAP or Surfactant group	#	442	666		650	666	
	CPAP, # (%)	223 (50.4)	346 (52)	0.62	317 (48.8)	346 (52.0)	0.25

Characteristic		BPD (N=442)	No BPD (N=666)	p-value[1]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
Treatment: SpO_2 group, Higher or Lower O_2	#	442	666		650	666	
	High O2, # (%)	237 (53.6)	331 (49.7)	0.20	331 (50.9)	331 (49.7)	0.66
Median SpO2 DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<0.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<0.0001
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)	<0.0001	740 (643-870)	900 (770-1020)	<0.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	0.04	375 (57.7)	337 (50.6)	0.01
Race: NH Black NH White Hispanic Other	# (%)	 157 (35.5) 200 (45.3) 73 (16.5) 12 (2.7)	 268 (40.2) 237 (35.6) 137 (20.6) 24 (3.6)	0.013	 221 (34) 284 (43.7) 122 (18.8) 23 (3.5)	 268 (40.2) 237 (35.6) 137 (20.6) 24 (3.6)	0.02
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	0.11	221 (34)	268 (40.2)	0.02
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	0.001	284 (43.7)	237 (35.6)	0.003
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	0.18	68 (11.1)	63 (10.1)	0.58
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)	0.22
Prenatal steroids	#	442	666		649	666	

Characteristic		BPD (N=442)	No BPD (N=666)	p-value[1]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
	Yes, # (%)	427 (96.6)	636 (95.5)	0.36	629 (96.9)	636 (95.5)	0.18
1 minute Apgar < 3	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<0.0001	207 (31.9)	114 (17.1)	<0.0001
5 minute Apgar < 3	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	0.11	41 (6.3)	17 (2.6)	0.001
Prophylactic indomethacin	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	0.75	240 (38.5)	261 (39.2)	0.79
Vaginal delivery	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240(36.0)	0.004	193 (29.7)	240 (36.0)	0.01

[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]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
$PaCO_2$, 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)	0.001	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)	<0.0001	76 (66-88)	64 (54-74)	<0.0001
$PaCO_2$, 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)	<0.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<0.0001
$PaCO_2$, 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)	0.0014	51.7 (47.1-56)	48 (42.8-52.3)	<0.0001
$PaCO_2$ category:	#	98	872		346	872	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	22 (22.5) 25 (25.5) 17 (17.4) 34 (34.7)	171 (19.6) 111 (12.7) 44 (5.1) 546 (62.6)	<0.0001	51 (14.7) 111 (32.1) 49 (14.2) 135 (39.0)	171 (19.6) 111 (12.7) 44 (5.1) 546 (62.6)	<0.0001
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

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value[1]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
Treatment: SpO_2 group, Higher or Lower O_2	#	98	878		356	878	
	High O2, # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Median SpO2 DOL 1-14	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92-94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<0.0001
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643-914)	850 (710-995)	<0.0001	734 (621-870)	850 (710-995)	<0.0001
Gender	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	0.01
Race: NH Black NH White Hispanic Other	# (%) 37 (37.8) 37 (37.8) 21 (21.4) 3 (3.1)	 333 (37.9) 354 (40.3) 161 (18.3) 30 (3.4)	0.89	 125 (35.1) 139 (39) 78 (21.9) 14 (3.9)	 333 (37.9) 354 (40.3) 161 (18.3) 30 (3.4)	0.47
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
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	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	97	863		341	863	
	Yes, # (%)	26 (26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value[1]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
Prenatal steroids	#	98	878		355	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	98	877		355	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	0.0003	130 (36.6)	181 (20.6)	<0.0001
5 minute Apgar < 3	#	98	878		356	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	0.04	29 (8.2)	27 (3.1)	0.0001
Prophylactic indomethacin	#	98	878		330	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	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 Bivariate analyses for Death

Characteristic		**Death (N=237)**	**No Death (N=997)**	**p-value[1]**
$PaCO_2$, minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	0.026
$PaCO_2$, maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<0.0001
$PaCO_2$, standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<0.0001
$PaCO_2$, time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<0.0001
$PaCO_2$ category:	#	227	991	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	26 (11.5) 82 (36.1) 29 (12.8) 90 (39.7)	196 (19.8) 140 (14.1) 64 (6.5) 591 (59.6)	<0.0001
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO_2 group, Higher or Lower O_2	#	237	997	
	High O2, # (%)	107 (45.2)	515 (51.7)	0.07
Median SpO2 DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<0.0001

Characteristic		Death (N=237)	No Death (N=997)	p-value[1]
Gender	#	237	997	
	Male, # (%)	144 (60.8)	526 (52.8)	0.026
Race: NH Black NH White Hispanic Other	# (%)	 77(32.5) 96 (40.5) 53 (22.4) 11 (4.6)	 381 (38.2) 397 (39.8) 186 (18.7) 33 (3.3)	0.26
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
HTN, pregnancy induced	#	226	938	
	Yes, # (%)	16 (7.1)	111 (11.8)	0.04
Rupture of membranes > 24 hours prior to birth	#	224	980	
	Yes, # (%)	72 (32.1)	332 (33.9)	0.62
Prenatal steroids	#	236	997	
	No, # (%)	7 (3)	41 (4.1)	0.41
1 minute Apgar < 3	#	236	996	
	Yes, # (%)	90 (38.1)	221 (22.2)	<0.0001
5 minute Apgar < 3	#	237	997	
	Yes, # (%)	22 (9.3)	34 (3.4)	<0.0001
Prophylactic indomethacin	#	211	997	
	Yes, # (%)	83 (39.3)	384 (38.5)	0.82
Vaginal delivery	#	237	997	
	Yes, # (%)	77 (32.5)	326 (32.7)	0.95

[1] p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

From: Vaucher, Yvonne
To: Stevens, Timothy
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
Subject: Re: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments
Date: Saturday, December 21, 2013 10:03:45 PM

Tim,

The paper reads very clearly and you addressed the comments of the reviewers well. The results confirm the very high rate of respiratory morbidity in the ELGAN group and raises the question (not the point of this paper) of the relative contribution of modifiable familial and environmental contributors to respiratory morbidity given the 40+% exposure to household smoke, lack of any breast milk intake in 2/3, failure of 25+% to receive RSV prophylaxis, and failure of ~20% to receive flu immunization.I doubt we are going to make much further progress in limiting oxygen exposure to a degree that will substantially decrease toxicity, especially since for the ELGAN group RA may actually be hyperoxic at a local cellular level so it may be worth looking at the relative contributions of these and other modifiable factors in he risk of wheezing cough, hospitalization in another paper.

My only editorial comment: On page 17, last results para before discussion, the second sentence "While the incidence…. " has "was different"repeated twice.

Yvonne Vaucher
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Subject: RE: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments

Tim:

Great job.

Enclosed are minor comments. I agree with Marie that it is better to say composite outcome that competing outcome.

However, a more global/important comment is that there is a bias for reporting positive results. I have included Table 4 here to make the point. There are 16 measures of pulmonary morbidity (with death as a composite outcome in this table). Even though only three are significantly different, we conclude that there is an "overall increase in the risk of death or respiratory morbidity".

I am sorry I did not notice this the previous time when I sent my comments.

Wally

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Subject: RE: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments

Nice job, Tim. Minor comments are in the attached. Happy holidays, everyone!

Marie

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Cc: Stevens, Timothy; higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments

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Dr. Tim Stevens has responded to the reviewer comments (attached). He would like to submit the revised manuscript (also attached) to J Peds by the end of the month so please review and indicate whether you have any questions or comments by Friday, December 20. He can reached at Timothy_Stevens@URMC.Rochester.edu<mailto:Timothy_Stevens@URMC.Rochester.edu>

Thanks, Jamie

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Saturday, December 14, 2013 8:12 PM
To: higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Newman, Jamie
Subject: revised manuscript

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I want to submit it by the end of the month, so will need comments by then.

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Tim

From: Wally Carlo, M.D.
To: Susan Hintz; Pat Barnes; DBULAS@childrensnational.org; Tom Slovis; Neil Finer; wrage@rti.org; Abhik Das; Jon Tyson; David Stevenson; Michele.Walsh@UHhospitals.org; Abbott Laptook; Bradley.yoder@hsc.utah.edu (Bradley.yoder@hsc.utah.edu); Krisa Van Meurs; Roger.Faix@hsc.utah.edu (Roger.Faix@hsc.utah.edu); wrich@ucsd.edu; nxs5@case.edu; hcheng@rti.org; Roy.Heyne@utsouthwestern.edu Heyne; Betty Vohr; Michael.Acarregui@providence.org Acarregui; Yvonne Vaucher; Dr. Athina Pappas; Myriam Peralta, M.D.; Dee Wilson; (b)(6) @gmail.com Evans; ricki.goldstein@duke.edu; gary_myers@urmc.rochester.edu; bpoindex@iupui.edu Poindexter; emcgowan@tuftsmedicalcenter.org McGowan; Ira Adams-Chapman; JaFuller@salud.unm.edu edu (JaFuller@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]; (b)(6) @aol.com
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: New England Journal of Medicine 13-15067
Date: Saturday, December 21, 2013 4:41:45 PM

Susan:

Pretty minor comments. Agree to try JAMA.

Wally

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From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Saturday, December 21, 2013 3:29 PM
To: Pat Barnes; DBULAS@childrensnational.org; Tom Slovis; Neil Finer; wrage@rti.org; Abhik Das; Jon Tyson; David Stevenson; Wally Carlo, M.D.; Michele.Walsh@UHhospitals.org; Abbott Laptook; Bradley.yoder@hsc.utah.edu (Bradley.yoder@hsc.utah.edu); Krisa Van Meurs; Roger.Faix@hsc.utah.edu (Roger.Faix@hsc.utah.edu); wrich@ucsd.edu; nxs5@case.edu; hcheng@rti.org; Roy.Heyne@utsouthwestern.edu Heyne; Betty Vohr; Michael.Acarregui@providence.org Acarregui; Yvonne Vaucher; Dr. Athina Pappas; Myriam Peralta, M.D.; Dee Wilson; (b)(6) @gmail.com Evans; ricki.goldstein@duke.edu; gary_myers@urmc.rochester.edu; bpoindex@iupui.edu Poindexter; emcgowan@tuftsmedicalcenter.org McGowan; Ira Adams-Chapman; JaFuller@salud.unm.edu edu (JaFuller@salud.unm.edu); Rosemary Higgins; (b)(6) @aol.com
Cc: Stephanie Archer
Subject: Re: New England Journal of Medicine 13-15067

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Thanks again for your efforts and dedicated work on this project.

Susan

Susan R. Hintz, M.D., M.S. Epi
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From: editorial@nejm.org
Date: December 20, 2013 at 6:18:00 AM PST
To: srhintz@stanford.edu
Subject: New England Journal of Medicine 13-15067

Dear Dr. Hintz,

Your manuscript, "Neonatal Neuroimaging and Neurodevelopmental Outcomes at 18-22 Months Corrected Age in Extremely Preterm Infants: The NEURO Study," was evaluated by external reviewers and was discussed among the editors. Although it is interesting, I am sorry to say it was not accepted for publication. This was an editorial decision and reflects an assessment of the merits of your manuscript as compared with the many others we receive. Unfortunately, many manuscripts must be declined for lack of space.

Thank you very much for the opportunity to review this manuscript.

Sincerely,

Caren G. Solomon, M.D.
Deputy Editor

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Reviewer: 1

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

Page 1650 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

From:	Krisa Van Meurs
To:	Susan Hintz
Cc:	Pat Barnes; DBULAS@childrensnational.org; Tom Slovis; Neil Finer; wrage@rti.org; Abhik Das; Jon Tyson; David Stevenson; Wally Carlo, M.D.; Michele.Walsh@UHhospitals.org; Abbott Laptook; Bradley.yoder@hsc.utah.edu (Bradley.yoder@hsc.utah.edu); Roger.Faix@hsc.utah.edu (Roger.Faix@hsc.utah.edu); wrich@ucsd.edu; nxs5@case.edu; hcheng@rti.org; Roy.Heyne@utsouthwestern.edu Heyne; Betty Vohr; Michael.Acarregui@providence.org Acarregui; Yvonne Vaucher; Dr. Athina Pappas; mperalta@peds.uab.edu Peralta M.D.; Dee Wilson (b)(6) @gmail.com Evans; ricki.goldstein@duke.edu; gary_myers@urmc.rochester.edu; bpoindex@iupui.edu Poindexter; emcgowan@tuftsmedicalcenter.org McGowan; Ira Adams-Chapman; JaFuller@salud.unm.edu edu (JaFuller@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E] (b)(6) @aol.com; Archer, Stephanie (NIH/NICHD) [E]
Subject:	Re: New England Journal of Medicine 13-15067
Date:	Saturday, December 21, 2013 8:03:34 PM

I also agree with submitting to JAMA.

Krisa

Sent from my iPhone

On Dec 21, 2013, at 1:29 PM, Susan Hintz <srhintz@stanford.edu> wrote:

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>
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Thank you very much for the opportunity to review this manuscript.
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Deputy Editor
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Boston, MA 02115
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Fax: (617) 739-9864
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Reviewer: 1

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer: 2

Comments for the Author

(b)(4),(b)(6)

Page 1654 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 1655 of 2000

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From:	Wally Carlo, M.D.
To:	Gantz, Marie; Newman, Jamie; Neil Finer; Phelps, Dale; mcw3@cwru.edu; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; Das, Abhik; Do, Barbara; kurt.schibler@cchmc.org; Wade RIch; nxs5@cwru.edu; richard.ehrenkranz@yale.edu; Myriam Peralta, M.D.; bvohr@wihri.org; (b)(6) @aol.com; Kimberly.Yolton@cchmc.org; Roy.Heyne@utsouthwestern.edu; Yvonne Vaucher; ira_adams-chapman@oz.ped.emory.edu; emcgowan@tuftsmedicalcenter.org; Athina Pappas; srhintz@stanford.edu; Michael.Acarregui@providence.org; JaFuller@salud.unm.edu; Ricki Goldstein, M.D.; moshea@wakehealth.edu; cbauer@peds.med.miami.edu; Gary Meyers; (b)(6) @gmail.com; Anna Bodnar
Cc:	Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject:	RE: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments
Date:	Friday, December 20, 2013 6:21:49 PM
Attachments:	Manuscript - Nov-13_MGwc.doc Table 4 Outcomes with Death.docx

Tim:

Great job.

Enclosed are minor comments. I agree with Marie that it is better to say composite outcome that competing outcome.

However, a more global/important comment is that there is a bias for reporting positive results. I have included Table 4 here to make the point. There are 16 measures of pulmonary morbidity (with death as a composite outcome in this table). Even though only three are significantly different, we conclude that there is an "overall increase in the risk of death or respiratory morbidity".

I am sorry I did not notice this the previous time when I sent my comments.

Wally

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, December 20, 2013 4:40 PM
To: Newman, Jamie; Neil Finer; Wally Carlo, M.D.; Phelps, Dale; mcw3@cwru.edu; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; Das, Abhik; Do, Barbara; kurt.schibler@cchmc.org; Wade RIch; nxs5@cwru.edu; richard.ehrenkranz@yale.edu; Myriam Peralta, M.D.; bvohr@wihri.org; (b)(6) @aol.com; Kimberly.Yolton@cchmc.org; Roy.Heyne@utsouthwestern.edu; Yvonne Vaucher; ira_adams-chapman@oz.ped.emory.edu; emcgowan@tuftsmedicalcenter.org; Athina Pappas; srhintz@stanford.edu; Michael.Acarregui@providence.org; JaFuller@salud.unm.edu; Ricki Goldstein, M.D.; moshea@wakehealth.edu; cbauer@peds.med.miami.edu; Gary Meyers; (b)(6) @gmail.com; Anna Bodnar

Cc: Stevens, Timothy; higginsr@mail.nih.gov; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments

Nice job, Tim. Minor comments are in the attached. Happy holidays, everyone!

Marie

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

From: Newman, Jamie
Sent: Monday, December 16, 2013 10:46 AM
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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Saturday, December 14, 2013 8:12 PM
To: higginsr@mail.nih.gov; Newman, Jamie
Subject: revised manuscript

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I want to submit it by the end of the month, so will need comments by then.

Thanks

Tim

Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT)

Timothy P. Stevens, MD MPH[1]; Neil N. Finer, MD[2]; Waldemar A. Carlo, MD[3]; Peter G. Szilagyi, MD[1]; Dale L. Phelps, MD[1]; Michele C. Walsh, MD MS[4]; Marie G. Gantz, PhD[5]; Abbot R. Laptook, MD[6]; Bradley A. Yoder, MD[7]; Roger G. Faix, MD[7]; Jamie E. Newman, PhD, MPH[5]; Abhik Das, PhD[8]; Barbara T. Do, MSPH[5]; Kurt Schibler, MD[9]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Richard A. Ehrenkranz, MD[10]; Myriam Peralta-Carcelen, MD MPH[3]; Betty R. Vohr, MD[6]; Deanne E. Wilson-Costello, MD[4]; Kimberly Yolton, PhD[9]; Roy J. Heyne, MD[11]; Anna M. Dusick, MD FAAP[12]; Patricia W. Evans, MD[13]; Yvonne E. Vaucher, MD MPH[2]; Ira Adams-Chapman, MD[14]; Elisabeth C. McGowan, MD[15]; Anna Bodnar, MD[7]; Athina Pappas, MD[16]; Susan R. Hintz, MD MS Epi[17]; Michael J. Acarregui, MD[18]; Janell Fuller, MD[19]; Ricki F. Goldstein, MD[20]; Charles R. Bauer, MD[21]; T. Michael O'Shea, MD MPH[22]; Gary J. Myers, MD[1]; Rosemary D. Higgins, MD[23] 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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[13] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
[14] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
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[21] University of Miami Miller School of Medicine, Miami, FL
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[23] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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Short Title: Respiratory Outcomes of the SUPPORT Study

Abbreviations:

BPD – Bronchopulmonary Dysplasia

CA - Corrected Age

CPAP – Continuous Positive Airway Pressure

NICHD - National Institute of Child Health and Human Development

NRN – NICHD Neonatal Research Network

PMA – Postmenstrual Age

ROP – Retinopathy of Prematurity

SUPPORT - Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial

Key Words: 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, endotracheal

Pulmonary surfactants/therapeutic use

Oxygen inhalation therapy/methods

Oxygen administration & dosage

Follow-up studies

Funding Sources: 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 (Recruitment 2004-2009; Follow-up 2006-2011). In addition to the grants listed in the acknowledgements section below, NICHD also provided grant support for the SUPPORT Breathing Outcomes Secondary Protocol to Dr. Stevens (K23 HD50646)

Financial Disclosure Statement: The authors gratefully recognize the generous support of NICHD and NHLBI as identified in the acknowledgements section below. The authors have no other financial relationships relevant to this article to disclose.

Conflict of Interest Statements: The authors have no conflicts of interest to disclose.

Clinical Trial Registry Name: Surfactant Positive Airway Pressure and Pulse Oximetry Trial (Support); ClinicalTrials.gov number, NCT00233324.

ABSTRACT

OBJECTIVE:

The NICHD SUPPORT Trial, using a factorial design that randomized extremely preterm infants to low versus high oxygen saturation targets and delivery room CPAP versus intubation and surfactant, found no significant difference in the primary composite outcome of death or BPD. We explored the early childhood pulmonary outcomes of these infants.

STUDY DESIGN:

The Breathing Outcomes Study, a prospective secondary to SUPPORT, assessed respiratory morbidity at 6 month intervals from hospital discharge to 18-22 months corrected age (CA). Two pre-specified primary outcomes, wheezing more than twice per week during the worst 2 week period and cough lasting more than 3 days without a cold were compared between each randomized intervention.

RESULTS:

One or more interviews were completed for 918 of 922 (99.6%) eligible infants. The incidence of wheezing and cough were 47.9% and 31.0%, respectively, and did not differ between study arms of either randomized intervention. Infants randomized to low versus high oxygen saturation targets had greater risk of death or respiratory morbidity (croup, treatment with oxygen or diuretics at home). Infants randomized to CPAP versus intubation/surfactant had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p<0.05$), respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p<0.05$) and physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p<0.05$) through 18-22 months CA.

CONCLUSION:

Treatment with low versus high oxygen saturation targets is associated a higher incidence of death or respiratory morbidity. Early CPAP rather than intubation/surfactant results in less respiratory morbidity by 18-22 months CA.

Abstract Word Count: 250

INTRODUCTION

Extremely preterm infants are at greater risk of respiratory morbidity 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) Lung injury, which may result from mechanical ventilation and supplemental oxygen exposure in the early neonatal period, has been identified as a risk factor for development of Bronchopulmonary Dysplasia (BPD) and pulmonary morbidity in infancy, childhood and beyond.(1, 2, 9, 10) Though infants with 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 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) 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 (intubation/surfactant). Our Network previously reported results of SUPPORT demonstrating no significant differences in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants randomized to either of the two respiratory interventions.(12-14) It is important to note that although the composite incidence of death or BPD was similar, infants randomized to lower rather than higher oxygen saturation targets had significantly lower incidences of retinopathy of prematurity but significantly greater mortality.

We now report on The Breathing Outcomes Study, a sub study to the SUPPORT Trial, which compared respiratory morbidities among extremely preterm infants treated with the SUPPORT interventions as neonates. It was hypothesized that infants randomized to lower rather than higher oxygen saturation targets and CPAP rather than intubation/surfactant would have a lower incidence of wheezing more than twice per week during their worst 2 week period, a lower incidence of cough lasting more than 3 days without a cold, and as a secondary outcome, less need for outpatient pulmonary care at 18-22 months' corrected age (CA, age in months following the expected date of full term delivery).

METHODS

Infants eligible for The Breathing Outcomes Study were 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 and seen in follow-up between 2006 and 2011. As a sub study to SUPPORT, Breathing Outcomes gained approval and began recruitment after SUPPORT began enrollment. As a result not all SUPPORT patients were successfully recruited into Breathing Outcomes. Written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT or separately for those patients already enrolled in SUPPORT but not yet discharged from the hospital. 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 prior to delivery to receive CPAP after birth, followed by a limited ventilation strategy if intubation was needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age (intubation/surfactant). Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with either an oxygen saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported.(13) The primary outcome of SUPPORT was the incidence of death or meeting criteria for the physiologic definition of BPD. (15) Traditional BPD, defined by the receipt of any supplemental oxygen at 36 weeks PMA, was also reported.

Comment [MG1]: Actually, we did not designate death/physiologic BPD as the primary outcome in SUPPORT because it was not clear from the protocol whether the primary should have used physiologic or traditional BPD. Both versions were presented as primary outcomes.

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 telephone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at or near 6, 12 and 18-22 months CA. 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 review the manual of operations (MOP) which included a written interview script. Interview trainees then interviewed a standardized patient simulated by the project trainers. With the aid of the MOP, 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, four interviews were conducted at approximately 6 month intervals beginning at the time of hospital discharge.(16) 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, parents 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 was designed to provide a complete respiratory history over the first 18-22 months' CA. In addition to reporting interview responses during the first 18-22 months CA (defined as the combined responses to the 6, 12, 18-22 month interviews and listed as 18-22 months in table 3), 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.(17)

Respiratory Questionnaires:

Questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study were used to elicit the frequency and characteristics of respiratory signs, including wheezing and cough; incidence of physician-diagnosed asthma or allergy, presence of pets in home, siblings, reactive airway disease; 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.(18, 19)

Outcomes

Primary Outcomes: Because preterm infants with or without BPD are at risk for altered airway function and greater risk of wheezing in infancy and later childhood (20-24), we chose to assess respiratory symptoms as a measure of pulmonary morbidity in infancy. Some authors have used incidence of recurrent wheezing as a primary measure of pulmonary morbidity (8, 23, 25) while others have used a combined outcome of either recurrent wheezing or chronic cough as a measure of occult wheezing in preterm infants. (1, 2, 26) To best capture overt and occult wheezing, two primary outcomes were assessed by parental report: the incidence of wheezing more than twice per week during the worst 2 week period and incidence of cough lasting more than 3 days without a cold.

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?". (18) The outcome for wheezing more than twice per week during the worst 2 week period was considered positive if the parent selected "More than two times a week"

in response to the question, "during the worst 2 week period, how often has your child's chest sounded wheezy or whistling". The incidence of cough lasting more than 3 days without a cold was ascertained using the Tucson question, "Has your child had a cough for 3 days or more when he/she did not have a cold?".(18)

Secondary outcomes and covariates: Secondary outcomes included incidence of any wheezing and incidence of the combined outcome, wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold. Also assessed were parental report of respiratory signs, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. To assure that follow up cohorts were comparable, questions not validated prior to this study were added to the Tucson questionnaires to more fully elicit use of preventive therapies including palivizumab and influenza immunization; attendance at daycare, frequency of BPD exacerbation or flare-up and impact on the family including whether the parent or caregiver needed to change their plans due their child's breathing: parental report of at least some breast milk intake on any of the 6, 12 or 18-22 month questionnaires; family history of inhaled allergies, food allergies, asthma, COPD or emphysema, other chronic respiratory illness; environmental exposure to tobacco smoke, daycare, children under 12 years old and pets; 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

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 the primary outcome of wheezing more than twice per week between groups with 90% power and alpha of 0.05 assuming an 80% minimum

follow-up rate and baseline incidence of wheezing more than twice per week of 29%.(24) 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.

The two primary analyses used the number of patients with either wheezing more than twice per week during their worst 2 week period or cough lasting more than 3 days without a cold as the numerator and the number of infants for whom that outcome was known as the denominator. Secondary responses were tabulated similarly. To assess the robustness of our findings, we calculated respiratory outcomes as a ~~competing~~ composite outcome with death and also calculated respiratory outcomes for patients with and without BPD. Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. 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.

Comment [MG2]: Maybe clearer since not everyone understands the concept of competing outcomes (as illustrated in some of the public conversations stemming from recent SUPPORT publicity)?

Given the 2x2 factorial design of our randomized trial, we considered the potential for interactions between primary outcomes of one ~~randomization~~ arm on the ~~opposite~~

Comment [MG3]: Suggested this edit because as written it might have led the reader to think that there were two actual randomizations (instead of one randomization to the 4 groups).

~~randomization~~other (CPAP vs. surfactant and lower vs higher saturation targets). Analysis by robust Poisson regression implemented in Generalized Estimating Equation (GEE) models conducted for the primary outcomes of the main trial did not identify significant interactions between the two treatment arms (p-value for interaction terms all > 0.05). For this reason, only marginal (main) effects of each randomization are reported. 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. The 918 subjects with at least one completed questionnaire were considered the study cohort (Figure 1). Follow up rates at each time point are listed in Figure 1.

Characteristics of the follow-up cohort

Among the follow up cohort, the group randomized to lower compared with higher oxygen saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with BPD defined using the traditional criteria of supplemental oxygen use at 36 weeks' PMA. The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to intubation/surfactant (Table 1). Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and intubation/surfactant groups (Table 2). Subjects with responses to all four questionnaires were similar in demographic characteristics, neonatal outcomes and home environmental exposures with the exception that those with less than four responses were more apt to have been discharged on respiratory medications (online data only).

Overall in the Breathing Outcomes cohort during the first 18-22 months CA, wheezing more than twice per week during the worst 2 week period was reported in 47.9% of patients, cough lasting more than 3 days without a cold in 31.0% and either wheezing more than twice per week or cough more than 3 days without a cold in 68.2%. Among cohort subjects, use of inhaled (26.3%) and/or systemic steroids (9.4%) was common. Cohort subjects also had high use of physician visits (63.8%), emergency room visits (46.6%) and hospitalizations for wheezing or breathing problems (31.0%).

Primary Outcomes

There was no difference in incidence of the two primary outcomes, wheezing more than twice per week during the worst 2 week period and cough lasting more than 3 days without a cold, between infants randomized to lower compared with higher oxygen saturation targets nor between infants randomized to treatment with CPAP rather than intubation/surfactant (Table 3). Analyzed as a combined outcome, the incidence of death or cough more than 3 days without a cold trended ($p=0.05$) lower among patients in the CPAP compared with intubation/surfactant study arms. The combined outcome of episodes of wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold for the overall cohort was 64.6% and did not differ significantly between infants randomized to lower rather than higher oxygen saturation target or CPAP rather than intubation/surfactant (Table 3) when analyzed alone or as a combined outcome with death.

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months CA, infants randomized to lower compared with higher oxygen saturation targets had a lower incidence of wheezing and in use of nebulized medications since NICU discharge

(Table 3). Over the first 18-22 months CA, infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (Table 3). When analyzed as compositeeting outcomes, the lower compared with higher saturation group had a higher incidence of death or respiratory morbidity (croup diagnosed by a doctor or to have been treated with a diuretic or oxygen at home) (Table 4).

Early CPAP Intervention

At 6 months CA, infants randomized to treatment with CPAP and a limited ventilation strategy rather than intubation/surfactant were reported to have fewer asthma, reactive airway disease or BPD exacerbation or flare-up episodes diagnosed by a doctor since NICU discharge and a trend toward fewer hospitalizations for wheezing or breathing problems. Perhaps related to these differences, parents or primary caregivers of infants randomized to CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (Table 3).

During the first 18-22 months CA, infants randomized to early CPAP versus intubation/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 exacerbation or flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, p=0.02), or wheezing or breathing problems that prompted a physician or emergency room visit (68.0% vs. 72.9%, p<0.05). Compared with those of infants in the intubation/surfactant group, parents or guardians of infants in the CPAP group were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, p<0.05). When outcomes were analyzed as compositeeting with death, similar

findings were observed with additional differences noted in incidence of treatment with oxygen or diuretics at home and a trend towards lower incidence of overnight hospitalization for breathing problems.

As expected, our study questionnaires were able to detect significant differences in respiratory outcomes for infants with versus without BPD (Table 5). While the incidence of wheezing more than twice per week was different between infants with and without BPD ~~was different~~, there was no difference in incidence of cough lasting more than 3 days as an indicator of occult wheezing. Taken together, the combined incidence of either overt (wheezing more than twice per week) or potential occult (cough lasting more than 3 days) wheezing was significantly different between infants with BPD and those without. (Table 5).

DISCUSSION

We report results of the Breathing Outcomes Study, a sub study to SUPPORT, which sought to quantify respiratory morbidity by 18-22 months corrected age for extremely premature children born 24-27 weeks gestation. We found no significant differences at 18-22 months CA in the incidence of either of the two primary outcomes, wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold, between patients randomized to lower versus higher oxygen saturation targets or randomized to CPAP versus intubation/surfactant.

In secondary analyses, although extremely preterm infants randomized to low compared with high oxygen saturation targets were less likely to have wheezing or use a home nebulizer at 6 months CA and to have wheezing apart from a cold between discharge and 18-22 months CA,

these differences were not seen when respiratory outcomes were analyzed as ~~competing~~ composite outcomes with death. In fact, analyzed this way, the incidence of death or adverse respiratory outcome for some measures of morbidity were worse for patients in the low saturation group. 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, 27-29) Though patients treated with lower compared with higher saturation targets in SUPPORT had a shorter duration of oxygen exposure, they had greater mortality, similar incidence of BPD, and based on results of the Breathing Outcomes Study, survivors had a similar use of outpatient services for respiratory care and only minor differences in the incidence of respiratory signs. Based on these findings, if oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant lung injury other than targeting lower oxygen saturations will be needed. (24, 30)

Comment [WC4]: I like composite better also

Comment [MG5]: Might be clearer?

Comment [MG6]: Because of the difference in death?

Though the primary outcomes were similar, patients in the first 18-22 months CA who were randomized to CPAP and limited ventilation rather than intubation followed by surfactant administration within 1 hour had a lower incidence of several important respiratory morbidities including respiratory illnesses diagnosed by a doctor, treatment with oxygen or diuretics at home and a trend towards lower incidence of overnight hospitalization for breathing problems. Likely related to these findings was a significant reduction in the proportion of parents reporting that they needed to change their daily plans due to their child's breathing difficulties. These differences persisted whether the outcome was analyzed among survivors only or as compositeeting outcomes with death.

Respiratory benefits of CPAP and a limited ventilation strategy were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic

criteria(15), was similar between CPAP and intubation/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 age among a 39 patient single-center sub cohort of study infants randomized to CPAP. (31, 32) These observations suggest that treatment of infants 25-27 6/7 weeks gestation at risk for RDS with a limited ventilation strategy is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone. As confirmed in our analysis of respiratory morbidity, BPD has proven to be useful surrogate to identify infants at highest risk of later morbidity. However, based upon the high incidence of respiratory morbidity among infants without BPD, it is likely, though not proven in this study, that the prevalence of respiratory morbidity in former preterm infants may be under recognized. Given the potential for respiratory therapies to improve pulmonary outcomes for infants with and without BPD, 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 signs and use of health care are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months CA. Over two-thirds of subjects in the Breathing Outcomes Study cohort reported wheezing more than twice per week during their worst 2 week period or a cough lasting more than 3 days without a cold. Treatment of these respiratory signs was not only associated with frequent use of both inhaled and systemic steroids, medications that have potential long term effects on growth and development, (33, 34)

but also with frequent physician and emergency room visits and hospitalizations, health services which contribute greatly to health care costs.(8)

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. (16, 35)

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.(16) 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 more common use of antenatal steroids than the entire eligible cohort. (36)

In summary, we found no significant differences in the incidence of wheezing more than twice per week during the worst 2 week period or cough lasting more than 3 days without a cold at 18-22 months CA between extremely preterm survivors who were randomized at delivery to either lower versus higher oxygen saturation targets or early CPAP and a limited ventilation strategy versus intubation/surfactant. In secondary analyses, we found minor reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months CA, but an overall increase in the risk of death or respiratory morbidity (croup, treatment with oxygen or diuretics at home) for infants randomized to lower vs. higher oxygen saturation targets. Also in secondary analyses, we report less respiratory morbidity among survivors and lower incidence or respiratory morbidity or death among infants randomized to CPAP rather than intubation/surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over intubation/surfactant.(12-14) 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 surfactant within 1 hour is safe and may result in less respiratory morbidity during the first 18-22 months CA. Lastly, our findings demonstrate a high risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation that not only require close medical monitoring but also pose potential burdens to families as well as to society by increasing health care costs.

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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.

Figure 1. Consort diagram including follow up rates.

Table 1. Demographic and neonatal characteristics of follow-up cohorts.

Table 2. Family and environmental exposure history of follow-up cohorts.

Table 3. Respiratory outcomes for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts at the 6 month interview and for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Table 4. Combined outcomes of death or respiratory morbidity for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Table 5. Respiratory outcomes for infants with oxygen requirement at 36 weeks post-menstrual age (traditional BPD) for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

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Table 4. Combined outcomes of death or respiratory morbidity for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Outcomes with Death	Low Sat N=586	High Sat N=569	ARR (95% CI)	p-value	CPAP N=583	Intubation/ Surfactant N=572	ARR (95% CI)	p-value
Primary Outcomes								
Has your child's chest sounded wheezy or whistling more than twice in one week?	337 (59.5)	344 (59.0)	1.06 (0.83, 1.37)	0.62	337 (58.0)	344 (60.6)	0.86 (0.67, 1.11)	0.26
Has your child had a cough for more than 3 days without a cold	262 (47.9)	254 (45.0)	1.18 (0.91, 1.51)	0.21	240 (42.9)	276 (49.9)	0.78 (0.60, 1.00)	0.05
Secondary Outcomes								
Wheezing/whistling more than twice in one week or cough more than 3 days	410 (75.0)	425 (75.2)	0.99 (0.74, 1.32)	0.96	414(74.1)	421 (76.1)	0.92 (0.69, 1.23)	0.56
Has your child's chest sounded wheezy or whistling?	379 (69.3)	395 (69.9)	0.98 (0.75, 1.29)	0.9	380 (68.0)	394 (71.2)	0.84 (0.64, 1.10)	0.21
Has your baby's chest sounded wheezy or whistling apart from colds?	252 (46.1)	275 (48.7)	0.91 (0.71, 1.17)	0.48	241 (43.1)	286 (51.7)	0.70 (0.54, 0.90)	<0.01*
Has your child had asthma, reactive airway disease or BPD exacerbation or flare-up diagnosed by a doctor?	274 (50.1)	270 (47.9)	1.17 (0.91, 1.50)	0.23	256 (45.8)	288 (52.2)	0.76 (0.59, 0.98)	0.03*
Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?	295 (53.9)	295 (52.3)	1.12 (0.87, 1.44)	0.39	279 (49.9)	311 (56.3)	0.78 (0.60, 1.00)	0.05
Any of asthma, reactive airway disease, BPD exacerbation or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor	339 (62.0)	351 (62.2)	1.05 (0.81, 1.36)	0.71	326 (58.3)	364 (65.9)	0.71 (0.54, 0.92)	<0.01*
Has your child had croup diagnosed by a doctor?	180 (32.9)	153 (27.1)	1.35 (1.03, 1.77)	0.03*	154 (27.5)	179 (32.4)	0.78 (0.60, 1.03)	0.08
Has your child ever had to visit the doctor or Emergency Room for breathing or wheezing problems?	427 (78.1)	430 (76.1)	1.11 (0.82, 1.50)	0.49	417 (74.6)	440 (79.6)	0.73 (0.54, 0.99)	<0.05*
Has your child had to stay in a hospital overnight?	303 (55.5)	310 (54.9)	1.06 (0.82, 1.37)	0.64	294 (52.6)	319 (57.8)	0.84 (0.65, 1.08)	0.17
Has your child had to stay in a hospital overnight for wheezing/breathing problems?	263 (48.2)	252 (44.6)	1.20 (0.93, 1.54)	0.17	242 (43.3)	273 (49.5)	0.78 (0.61, 1.01)	0.06
Treated with a diuretic medication?	165 (29.0)	137 (23.4)	1.42 (1.07, 1.88)	0.02*	137 (23.5)	165 (28.8)	0.74 (0.56, 0.98)	0.04*
Treated with an inhaled steroid medication?	246 (43.2)	240 (41.0)	1.15 (0.89, 1.47)	0.29	241 (41.3)	245 (42.8)	0.96 (0.75, 1.24)	0.76
Treated with a nebulized medication?	16 3(28.6)	155 (26.5)	1.15 (0.87, 1.52)	0.33	152 (26.1)	166 (29.0)	0.85 (0.64, 1.13)	0.27
Treated with a systemic steroid medication?	178 (31.3)	156 (26.6)	1.28 (0.98, 1.68)	0.07	162 (27.8)	172 (30.1)	0.88 (0.68, 1.16)	0.38
Treated with oxygen at home?	238 (43.5)	206 (36.5)	1.46 (1.11, 1.91)	<0.01*	206 (36.9)	238 (43.1)	0.76 (0.58, 1.00)	0.05*
Have you had to change your plans because of your child's breathing problems?	273 (49.9)	281 (49.7)	1.04 (0.81, 1.34)	0.74	257 (46.0)	297 (53.7)	0.72 (0.56, 0.92)	0.01*

* $p < 0.05$

From: Finer, Neil
To: Newman, Jamie; Wally Carlo, M.D.; Phelps, Dale; mcw3@cwru.edu; mgantz@rti.org; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; Das, Abhik; Do, Barbara; kurt.schibler@cchmc.org; Rich, Wade; 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; Vaucher, Yvonne; ira_adams-chapman@oz.ped.emory.edu; emcgowan@tuftsmedicalcenter.org; Athina Pappas; srhintz@stanford.edu; Michael.Acarregui@providence.org; JaFuller@salud.unm.edu; Ricki Goldstein, M.D.; moshea@wakehealth.edu; cbauer@peds.med.miami.edu; Gary Meyers; (b)(6) @gmail.com; Anna Bodnar
Cc: Stevens, Timothy; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments
Date: Wednesday, December 18, 2013 6:29:58 AM

Hi Tim
This a very complete and appropriate response
The manuscript reads well
Great job
Be well
All the best for the Holiday and the New Year
Neil

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Monday, December 16, 2013 4:46 PM
To: Finer, Neil; Wally Carlo, M.D.; Phelps, Dale; mcw3@cwru.edu; mgantz@rti.org; alaptook@WIHRI.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; Das, Abhik; Do, Barbara; kurt.schibler@cchmc.org; Rich, Wade; 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; Vaucher, Yvonne; ira_adams-chapman@oz.ped.emory.edu; emcgowan@tuftsmedicalcenter.org; Athina Pappas; srhintz@stanford.edu; Michael.Acarregui@providence.org; JaFuller@salud.unm.edu; Ricki Goldstein, M.D.; moshea@wakehealth.edu; cbauer@peds.med.miami.edu; Gary Meyers; (b)(6) @gmail.com; Anna Bodnar
Cc: Stevens, Timothy; higginsr@mail.nih.gov; Archer, Stephanie (NIH/NICHD) [E]
Subject: Please review: Revised Breathing Outcomes manuscript/responses to reviewer comments

Dear Breathing Outcomes manuscript authors,

Dr. Tim Stevens has responded to the reviewer comments (attached). He would like to submit the revised manuscript (also attached) to J Peds by the end of the month so please review and indicate whether you have any questions or comments by Friday, December 20. He can reached at Timothy_Stevens@URMC.Rochester.edu

Thanks, Jamie

Jamie E. Newman, PhD, MPH
RTI International
3040 Cornwallis Road (PO Box 12194)
RTP, NC 27709 USA
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Saturday, December 14, 2013 8:12 PM

To: higginsr@mail.nih.gov; Newman, Jamie
Subject: revised manuscript

Hi Rose and Jamie,

Here is the revised Breathing Outcomes manuscript for re-submission to J Peds. Can you forward to the authors?

I want to submit it by the end of the month, so will need comments by then.

Thanks

Tim

Blansfield, Earl (NIH/NICHD) [E]

From: Shurin, Susan (NIH/NHLBI) [E]
Sent: Tuesday, December 17, 2013 2:13 PM
To: Patterson, Amy (NIH/OD) [E]
Cc: Earle, Melody (NIH/NHLBI) [E]; Wells, Connie (NIH/NHLBI) [E]; Gibbons, Gary (NIH/NHLBI) [E]; Cook, Nakela (NIH/NHLBI) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Gordon, Valery (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]; Hardesty, Rebecca (NIH/OD) [C]
Subject: RE: Planning a Workshop on Ethics of Standard of Care Research
Attachments: Draft Precis-for Workshop on Ethical Issues in SoC Research 12-5-2013 (SBS).docx

Dear Amy,

Gary has asked me to stand in for him on this. I've made a couple of suggested edits to the document. I understand that it is (b)(5)
(b)(5)

This has (b)(5) and is covered in most institutions as QI – quality improvement. The origin of this discussion is the distinction in the Declaration of Helsinki that there is a fundamental difference between research and standard of care. In this area, there is not. One of our major concerns is that (b)(5)
(b)(5)

I've attached my favorite slide commentary on this issue, courtesy of my friend (b)(5) on the three I's of human subject protection: Investigator integrity, IRBs, and informed consent, in increasing order of enforceability and decreasing order of effectiveness. If we (b)(5)
(b)(5)

Susan

From: Wells, Connie (NIH/NHLBI) [E]
Sent: Monday, December 16, 2013 11:02 AM
To: Shurin, Susan (NIH/NHLBI) [E]
Cc: Earle, Melody (NIH/NHLBI) [E]
Subject: FW: Planning a Workshop on Ethics of Standard of Care Research

Susan,

Dr. Gibbons would like to ask if you would participate in this planning committee on his behalf. Would you agree to do this?

If you agree, they would like feedback on the attached items by this Wednesday, Dec. 18, and they are also reaching out now to schedule the first meeting in January (which I will respond to).

Thank you,
Connie

From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, December 05, 2013 8:09 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Gibbons, Gary (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]; Hardesty, Rebecca (NIH/OD) [C]
Subject: Planning a Workshop on Ethics of Standard of Care Research

Dear Colleagues:

I'm writing to ask you to serve on a planning committee to help design and organize an NIH workshop on the ethical issues involved in standard of care research. The workshop will also be used to explore the relevance, validity, and utility of draft guidance that OHRP will be issuing on IRB review and informed consent considerations in research studying standard of care interventions. OHRP is expected to issue the draft guidance for a 60-day public comment period in January 2014. The workshop will likely be scheduled in late February to coincide with the comment period.

We will schedule an in-person meeting of the planning committee for the first week in January. In the meantime, I would appreciate your thoughts and suggestions via email about 1) the initial workshop design which is laid out in the attached précis; 2) case study topics and presenters; and 3) experts and stakeholders who should be invited to attend. Your feedback on these items by **Wednesday, December 18** would be much appreciated.

If you have any questions or are unable to participate in the planning committee, please let me know.

We look forward to working with you on this important meeting.

Many thanks,

Amy

Amy P. Patterson, M.D.
Associate Director for Science Policy, NIH

Page 1691 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1692 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From:	Finer, Neil
To:	Finer, Neil; Lex Doyle; Schmidt, Barbara (Neonatology); (b)(6) @gmail.com; Peter Graham Davis; Higgins@med.usyd.edu.au; Higgins, Rosemary (NIH/NICHD) [E]; Schmidt@med.usyd.edu.au; brian.darlow@otago.ac.nz; henry.halliday@doctors.org.uk; n.marlow@ucl.ac.uk; colin@morleys.net; christian-f.poets@med.uni-tuebingen.de; John@ctc.usyd.edu.au; robin.whyte@dal.ca; peter.brocklehurst@npeu.ox.ac.uk; WCarlo@peds.uab.edu; costan@mcmaster.ca; adas@rti.org; Val@ctc.usyd.edu.au; ed.juszczak@npeu.ox.ac.uk; robertsr@mcmaster.ca; ben.stenson@luht.scot.nhs.uk; Win.Tin@stees.nhs.uk; lisa.askie@ctc.usyd.edu.au; williamtm@med.usyd.edu.au
Subject:	RE: NeOProM Meeting - Item for information: Patient Safety Summit (founded by Masimo) 13 - 14 Jan 2013
Date:	Saturday, December 14, 2013 10:58:34 AM

Sorry – Please ignore this as it is from a year ago
It came up as new mail in my mailbox??
My apologies
Neil

From: Finer, Neil
Sent: Saturday, December 14, 2013 4:53 PM
To: 'Lex Doyle'; Schmidt, Barbara (Neonatology); (b)(6) @gmail.com; Peter Graham Davis; Higgins@med.usyd.edu.au; higginsr@mail.nih.gov; Schmidt@med.usyd.edu.au; brian.darlow@otago.ac.nz; henry.halliday@doctors.org.uk; n.marlow@ucl.ac.uk; colin@morleys.net; christian-f.poets@med.uni-tuebingen.de; John@ctc.usyd.edu.au; robin.whyte@dal.ca; peter.brocklehurst@npeu.ox.ac.uk; WCarlo@peds.uab.edu; costan@mcmaster.ca; adas@rti.org; Val@ctc.usyd.edu.au; ed.juszczak@npeu.ox.ac.uk; robertsr@mcmaster.ca; ben.stenson@luht.scot.nhs.uk; Win.Tin@stees.nhs.uk; lisa.askie@ctc.usyd.edu.au; williamtm@med.usyd.edu.au
Subject: RE: NeOProM Meeting - Item for information: Patient Safety Summit (founded by Masimo) 13 - 14 Jan 2013

Hi Everyone
While I am enthusiastic about completing the NeoProm, I believe that at our last meeting we agreed that we had more work to do. Now that we have funding from 2 sources, we should be aggressively trying to complete the work required. There are significant issues yet to be agreed to, and I would think we should be focusing on these.
While this forum sounds interesting I also believe that there has been entirely too much public attention to SUPPORT which has spun off to the other trials
I am not supportive of attending and presenting at this meeting. If a majority want to see this go forward I would ask that there is an agreed to presentation that has been accepted by all members and it does NOT include anything not already presented/published.
Regards
Neil Finer

From: Lex Doyle [mailto:lwd@unimelb.edu.au]
Sent: Monday, December 03, 2012 5:21 AM
To: Schmidt, Barbara (Neonatology); (b)(6) @gmail.com; Peter Graham Davis; Finer, Neil; Higgins@med.usyd.edu.au; higginsr@mail.nih.gov; Schmidt@med.usyd.edu.au; brian.darlow@otago.ac.nz; henry.halliday@doctors.org.uk; n.marlow@ucl.ac.uk; colin@morleys.net; christian-f.poets@med.uni-tuebingen.de; John@ctc.usyd.edu.au; robin.whyte@dal.ca; peter.brocklehurst@npeu.ox.ac.uk; WCarlo@peds.uab.edu; costan@mcmaster.ca; adas@rti.org; Val@ctc.usyd.edu.au; ed.juszczak@npeu.ox.ac.uk; robertsr@mcmaster.ca; ben.stenson@luht.scot.nhs.uk; Win.Tin@stees.nhs.uk; lisa.askie@ctc.usyd.edu.au; williamtm@med.usyd.edu.au
Subject: RE: NeOProM Meeting - Item for information: Patient Safety Summit (founded by Masimo) 13 - 14 Jan 2013

I agree with Barbara.

Lex

Professor Lex Doyle
Associate Director of Research
The Royal Women's Hospital, and
Professor of Neonatal Paediatrics,
University of Melbourne.

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email lwd@unimelb.edu.au
or lex.doyle@thewomens.org.au

From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: 03 December 2012 01:01
To: (b)(6) @gmail.com; Peter Graham Davis; pfiner@ucsd.edu; Higgins@med.usyd.edu.au; higginsr@mail.nih.gov; Schmidt@med.usyd.edu.au; brian.darlow@otago.ac.nz; henry.halliday@doctors.org.uk; n.marlow@ucl.ac.uk; colin@morleys.net; christian-f.poets@med.uni-tuebingen.de; John@ctc.usyd.edu.au; robin.whyte@dal.ca; peter.brocklehurst@npeu.ox.ac.uk; WCarlo@peds.uab.edu; costan@mcmaster.ca; adas@rti.org; Lex Doyle; Val@ctc.usyd.edu.au; ed.juszczak@npeu.ox.ac.uk; robertsr@mcmaster.ca; ben.stenson@luht.scot.nhs.uk; Win.Tin@stees.nhs.uk; lisa.askie@ctc.usyd.edu.au; williamtm@med.usyd.edu.au
Subject: Re: NeOProM Meeting - Item for information: Patient Safety Summit (founded by Masimo) 13 - 14 Jan 2013

Colleagues,

I am extremely concerned about the direction in which the Neoprom collaboration is being taken.

Enough preliminary data have been made public already. Please let us spend our time and effort now to gather and publish the missing bits in a timely fashion!

It would be especially inappropriate for Lisa to speak at the Masimo summit.

Her role is to summarize the evidence when it is complete! Not to help publicize incomplete data!

Barbara

From: william tarnow-mordi [mailto:wotarnowmordi@gmail.com]
Sent: Sunday, December 02, 2012 08:06 AM

To: 'Peter Graham Davis' <pgd@unimelb.edu.au>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins@med.usyd.edu.au <Higgins@med.usyd.edu.au>; Rosemary [E]' <higginsr@mail.nih.gov>; Schmidt@med.usyd.edu.au <Schmidt@med.usyd.edu.au>; Schmidt, Barbara (Neonatology); 'Brian Darlow' <brian.darlow@otago.ac.nz>; 'Henry Halliday' <henry.halliday@doctors.org.uk>; 'n.marlow@ucl.ac.uk' <n.marlow@ucl.ac.uk>; 'Colin Morley' <colin@morleys.net>; 'Christian Poets' <christian-f.poets@med.uni-tuebingen.de>; John Simes <John@ctc.usyd.edu.au>; 'Robin Whyte' <robin.whyte@dal.ca>; 'peter.brocklehurst@npeu.ox.ac.uk' <peter.brocklehurst@npeu.ox.ac.uk>; 'WCarlo@peds.uab.edu' <WCarlo@peds.uab.edu>; 'Lorrie Costantini' <costan@mcmaster.ca>; 'adas@rti.org' <adas@rti.org>; 'Lex Doyle' <lwd@unimelb.edu.au>; Val Gebski <Val@ctc.usyd.edu.au>; 'Ed Juszczak' <ed.juszczak@npeu.ox.ac.uk>; 'Robin Roberts' <robertsr@mcmaster.ca>; 'ben.stenson@luht.scot.nhs.uk' <ben.stenson@luht.scot.nhs.uk>; 'win.tin@stees.nhs.uk' <win.tin@stees.nhs.uk>; Lisa Askie <lisa.askie@ctc.usyd.edu.au>; william tarnow-mordi <williamtm@med.usyd.edu.au>
Subject: Re: NeOProM Meeting - Item for information: Patient Safety Summit (founded by Masimo) 13 - 14 Jan 2013

(with apologies for earlier incomplete email)

Dear Colleagues

After the NeOProM agenda papers were circulated last week. I received notification of a Patient Safety Science and Technology Summit, founded by Masimo, to be held 13 and 14 Jan 2013. Details are on the meeting website:

http://patientsafetysummit.org/

Keynote speakers include President Bill Clinton, Peter Pronovost MD (VP for Patient Safety and Quality, John Hopkins, who introduced a 5 point checklist responsible for a 66% reduction in catheter related infections in ICU patients NEJM 2006; 355:2725-2732) and Joe Kiani (CEO Masimo)

21 other speakers and panellists include anaesthesiologists, physicians, ICU specialists, hospital administrators and nurses, mostly in adult specialties, with some expertise in pediatric intensive care.

I have registered for the meeting and contacted Joe Kiani to suggest highlighting the NeOProM Collaboration and its potential role in contributing to patient safety in preterm infants. He was positive about this idea.

If any colleagues would be interested and available to join me and Lisa Askie in contributing to a session at this meeting to review already published or presented data related to trials in the NeOProM Collaboration, e.g. the SUPPORT Study, the NeOProM Protocol and the BOOST II interim analyses, please let us know.

It will be important to emphasise that Masimo has had and will continue to have no role in the design or conduct or publication or interpretation of the independent, investigator-initiated studies which are contributing to NeOProM.

Lisa and I would be happy to share any materials for such a session with colleagues in NeOProM before they are finalised.

with kind regards

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:	Luc Brion
To:	Luc Brion; Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne
Subject:	Submitted!! Jackie Levan"s paper
Date:	Thursday, December 12, 2013 11:32:28 AM
Attachments:	20131573R1[1].pdf

This time it WAS submitted!

Thanks for all your comments, including last minute comments from Jaleel, Pablo and Lisa!

Thanks for your collaboration..

Happy Holidays..

Luc

Elsevier Editorial System(tm) for The Journal of Pediatrics
Manuscript Draft

Manuscript Number: 20131573R1

Title: Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Article Type: Original Article

Keywords: very preterm; endotracheal intubation; delivery room; bronchopulmonary dysplasia; retinopathy of prematurity; mortality

Corresponding Author: Dr. Luc P Brion, MD

Corresponding Author's Institution: University of Texas Southwestern Medical Center

First Author: Jaclyn M LeVan, DO

Order of Authors: Jaclyn M LeVan, DO; Luc P Brion, MD; Lisa A Wrage, MPH; Marie G Gantz, PhD; Myra H Wyckoff, MD; Pablo J Sanchez, MD; Roy Heyne, MD; Mambarambath Jaleel, MD; Neil N Finer, MD; Waldemar A Carlo, MD; Abhik Das, PhD; Barbara J Stoll, MD; Rosemary D Higgins, MD

Abstract: Objective
Preterm neonates 240/7-276/7 weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:
This was a retrospective cohort study using the prospective NRN generic database. Infants 240/7-276/7 weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:
DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.89, 95% confidence interval 0.86-0.93) was significantly lower than one.

Conclusions:
After adjustment for baseline variables, infants 240/7-276/7 weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Thursday, December 12, 2013
Clyde J Wright, MD
Associate Editor

William F. Balistreri, M.D.
Editor

Ref.: Ms. No. 20131573
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested.
We have made the revision as short as possible. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text. The Abstract is <250 words. The list of Study Group members and the figures are separate Appendix files. We labeled the third table as online only.
In this revised version we have clarified that this study was designed to test the hypothesis that the proportion of the primary outcome variable, delivery room intubation, would decrease after SUPPORT. This study was not designed to test whether any change in secondary or tertiary variables were associated with the primary outcome variable, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies.
We have entirely revised and streamlined the discussion and emphasized the limitations of the study.
We include an itemized list of responses to the reviewers. Several of these responses are currently not included in the text of the manuscript, to keep in line with your request to make the revision as short as possible. We will be glad to include in the manuscript any additional comments that are currently included only in the itemized list of responses.
We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.
Response: The text of the first version had 2697 words; the revised version has 2612 words. The text of the discussion was shortened by ½ page. We have shortened the results section. We have removed from the text all numbers that were in Figure 1 or in the tables, and all comments on unadjusted results for the primary and secondary variables.

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (http://www.jpeds.com/authorinfo).
Response: We have shortened the abstract; it contains 224 words. The abstract is structured as indicated.

Please upload the list of Study Group members as a separate Appendix file.
Response: the list of Study Group was moved into a separate file.

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.
Response: Figures are submitted as separate files in doc format.

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."
Response: we have changed online documents as requested.

Itemized responses to Reviewers:

Reviewer #1: This study compared neonatal outcomes in centers of the NICHD neonatal research network before and after their participation in the SUPPORT trial. The methodology and discussion are for the most part adequate.
The investigators found a smaller proportion of infants were intubated in the delivery room, less mortality and reduced rates of the composite outcomes of death or BPD and death or severe ROP. There are a few aspects the investigators should consider to further support their findings.

Comments:
- Can these findings and any possible changes in practice be attributed to the publication of the trial or the actual participation of the trial?
Response: In this study we did not obtain any data during participation in the trial; therefore we cannot respond to that question. This is discussed in the first paragraph of the discussion. We replaced "after publication of SUPPORT" with "after SUPPORT." At least in one center of the Neonatal Research Network (Parkland Memorial Hospital), the proportion of delivery room intubation decreased during participation in SUPPORT (LeVan, Pediatrics 2013, reference 16). In another center the proportion of delivery room intubation decreased before participation in SUPPORT (Narendran 2003, reference 17).

- The manuscript would benefit from data on changes in policies/practice implemented in the 11 centers. These data can support the investigators claim that practice indeed changed following SUPPORT. Please see below.
Response: We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.
We provide information on delivery room practice 2 centers (no change in policy in reference 16, and prospective progressive routine change in practice in reference 17).

- The proportion of DR intubations decreased after SUPPORT. Were any changes in policy actually implemented in these 11 centers? Can this be attributed to other changes implemented (e.g. O2 titration in DR, use of PEEP and T piece resuscitators)?

Response: We are unable to analyze whether changes in DR intubation after SUPPORT were related to changes in DR policy or other changes implemented (e.g. O2 titration in DR, use of PEEP and T piece resuscitators). As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- Were the attempts to avoid intubation successful? What proportion of infants remained non-intubated by day 3 or 7 or were never intubated? The difference in proportion of infants receiving surfactant was smaller than the difference in intubations in DR. Was the technique of surfactant administration changed?
Response: The proportion of babies alive and not requiring artificial ventilation at 7 days was 54.1% before SUPPORT and 60.4% after SUPPORT (Table 2). The proportion of babies who were never intubated was: 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group; this post-hoc analysis is included in the result section.
We do not have information on the technique of surfactant administration. As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- The CPAP/surfactant-intubation component of the SUPPORT trial also reported fewer intubations in DR but did not show significant effects on BPD. Can the reduction in BPD after SUPPORT be attributed to changes/improvements in oxygen saturation targeting?
Response: After adjustment for baseline variables, we found no significant change in the frequency of BPD after SUPPORT, but a significant decrease in combined outcome death or BPD. The CPAP/surfactant randomization in SUPPORT did not affect the frequency of BPD or the frequency of death/BPD.
We do not have information on changes/improvements in oxygen saturation targeting. This information is not collected in the GDB. As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- It is unclear why different exclusion criteria were used for each cohort. The number of infants excluded should be given by cohort. Reasons for withholding or withdrawing support are not mentioned. Were these decisions made before birth? Otherwise these deaths should be reported for each cohort.
Response: Exclusion criteria are different in the 2nd cohort because of a change in GDB field definition. Exclusions for each cohort are now reported separately in the flow diagram. The reasons for withholding or withdrawal of support are not given on the form collected in the GDB.

- Was the analysis adjusted for prenatal factors that clearly differed between cohorts?
Response: Multivariate analysis was adjusted for all factors that differed between cohorts, to which all infants were exposed, and preceded the variable of interest.

Minor comments:
- Gestational age limits in first sentence of Discussion needs to be checked.
Response: Thank you for pointing out this error; we replaced $26^{6/7}$ by $27^{6/7}$

- Table 2 is missing numerator/denominator data in some cells.
Response: We added denominators in all cells.

- 2nd paragraph of Discussion needs to be streamlined and perhaps split by topic.
Response: We have completely revised the discussion. We have split paragraph two. The discussion in streamlined as follows; change in endotracheal intubation, strengths, limitations, changes before/after SUPPORT vs. results of SUPPORT

- The authors state some comparisons of outcome variables reached significance p<0.05) by chance and that they should be considered only exploratory. It is unclear why this would apply only to some variables.
Response: We have clarified this issue. In the statistical analysis we state: "Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory." In the discussion, we have replaced this sentence as follows: "it is likely that some differences reached a significant p value just by chance"

Reviewer #2: The SUPPORT trial was a landmark multicenter factorial-design trial of two interventions for improving outcomes in extremely low gestational age (ELGA) neonates: delivery-room (DR) CPAP vs RD endotracheal intubation (ETI) and surfactant, and a lower vs higher target SpO2 range for oxygen administration. This study reports an analysis of the changes in practice and clinical outcomes that occurred between a 2-year period before and a 3-year period after the publications in 2010 of SUPPORT. It is based on data from 11 centers that contributed to that trial and were members of the NICHD NRN Network during each entire period. This presents an interesting and important opportunity to determine the extent of uptake of important new randomized evidence concerning the clinical effectiveness of these treatments, and to examine the impact on clinical practice and patient outcomes.

Specific comments:
Objectives
1. The primary objective is stated as "to determine if publication of SUPPORT was temporally associated with changes in clinical practice...". "Changes" is vague. What size of absolute effects on the major outcomes of interest were demonstrated in SUPPORT? (These are not stated, but a revised Introduction could make that clear.) At least for the primary outcome, what size of absolute effect did you consider important? What size of absolute effect did your study have the capacity to detect?
Response:
In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough to conduct multivariate analysis with 10 patients per covariate.

Methods
2. Study population, Ascertainment. The eligible infants were born during the stated pre- and post-SUPPORT years. But for each cohort, not all eligible outcomes would have occurred during those stated years. For example, some outcomes for the post-SUPPORT cohort would not be included in the generic database (GDB) during 2003-2012 because they had not yet occurred by end-2012. The duration of follow-up in the GDB to ascertain the later outcomes in the post-SUPPORT cohort needs to be stated. For BPD, severe ROP, days on ventilator, death, was it until 36 wks PMA, hospital discharge, or what?

Response: All this information is included in the GDB. All patients are followed in GDB to ascertain all listed outcomes.
To clarify the exact timing (postnatal age, postmenstrual age or discharge) of each outcome we have revised this paragraph as follows: "Secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, death before discharge or by 36 weeks, BPD, severe ROP before status, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge."
We have also included specific information on GDB in the design section of the manuscript:
The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data is collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data is collected on infants who remain in the hospital at 120 days.

3. Study population, Exclusions. The patient flow diagram (Fig 1) shows the reasons for exclusion of non-eligible patients from each of the two cohorts. Overall, about 42% of the 6601 patients in the two cohorts were not eligible and thus were excluded from analysis. Of potential concern is that there was a higher proportion of ineligible patients in the pre-SUPPORT than in the post-SUPPORT cohort. In fact, the 95% CIs for the respective proportions who were ineligible and thus excluded from analysis do not overlap (by my calculation: pre-SUPPORT, 46.1% [95% CI 44.3, 47.9]; post-SUPPORT, 38.1% [95% CI 36.5, 39.7]). Given this, the specific reasons for exclusion should be given separately for each cohort. Any systematic differences that could bias the comparison of the pre- and post-SUPPORT cohorts as analyzed should be acknowledged when interpreting the results.
Response: The flow diagram was revised to show all exclusions for each cohort separately. The primary imbalance was due to GDB inclusion criteria different re: outborn status.

4. Baseline variables. If the results of SUPPORT are hypothesized to change clinical practice, the baseline variables pertaining to those particular practices need to be identified and ascertained. In the pre-SUPPORT cohort, those critical variables include the numbers and proportion of eligible infants who received DR CPAP rather than DR ETI and surfactant, and the numbers and proportion whose oxygen management was targeted at the lower rather than the higher SpO2 range. I was struck by the absence of those practice variables from the stated list of baseline variables. It was also unclear whether in the post-SUPPORT cohort the numbers and proportion of infants whose oxygen management was targeted at the lower vs higher SpO2 range were to be ascertained.
Response: CPAP and SPO2 target ranges are not part of the variables collected in the GDB. This is listed in limitations of the study.

5. Statistical analyses. For the analysis of change in use of DR CPAP by individual center: the individual centers must have contributed different numbers of patients. Those numbers should be reported. It was not clear if the Spearman correlation was weighted in order to take into account the differing numbers of patients per center.
Response: We calculated a Spearman correlation on center-level aggregate summaries with the center as the unit of analysis. Because the primary interest was in assessing the monotonic association of aggregate center-level rates or prevalence, not in comparing events in individual subjects, weighting these rank-based analyses is not appropriate.

Results

6. a) Primary outcome, DR ETI. This was significantly reduced, adjusted RR 0.88 (95% CI 0.85, 0.91). The absolute risk reduction (ARR), calculated on the numbers presented, was 12.2%, which represents a clinically important effect, NNT = 8. As a matter for Discussion, how does that size of effect compare with what was found in SUPPORT, or was that even reported?

Response: These are not directly comparable. During SUPPORT, all patients in the CPAP arm were started on CPAP immediately and those in the intubation arm were intubated immediately. In contrast, outside a randomized trial such as SUPPORT or COIN, some patients may be started on CPAP or be intubated when respiratory distress develop, some patients may be intubated or placed on CPAP per protocol or policy, and some patients may be started on CPAP and intubated later.

In SUPPORT, the relative risk of intubation in the CPAP arm versus in the intubation arm was 0.37 (0.34–0.42). In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (59%).

Since the Editor has requested to limit the size of the manuscript to a minimum we have not entered absolute risk reduction in the manuscript.

The attempt to further analyze that difference by center did not yield a significant result. In retrospect, it appears that the opportunity to find a significant correlation between the pre- and post-SUPPORT DR ETI rates was limited by the distribution of pre-SUPPORT rates, with 9 of the 11 centers having pre-SUPPORT rates that varied within a narrow range of about 82-97%. Again, a matter possibly for Discussion?

Response: this information was added to the discussion.

b) There was a significant reduction, pre- vs post-SUPPORT, in the composite clinical outcome of BPD or death at 36 weeks, adjusted RR 0.94 (0.89, 0.99). The ARR calculated from table 2 was 5.8%. How does that compare with what was found in SUPPORT?

Response: This study was not designed to test whether any change in secondary or tertiary variables were associated with DR ETI, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies. The composite outcomes in SUPPORT and in the current study are not directly comparable. During SUPPORT, half the patients were randomized to CPAP at the time of randomization and the other half to ETI with surfactant administration, whereas outside a randomized trial such as SUPPORT or COIN, some patients may be started on CPAP either immediately or when respiratory distress develop, whereas other patients may be electively intubated.

In SUPPORT there was no significant adjusted relative risk difference (p=0.07) in death or BPD (defined as O2 need at 36 weeks) between the 2 arms of the study, but the point estimate of the RR was 0.91 (0.83 to 1.01), thus similar to that in the current study.

One possible explanation for the fact that the risk of BPD or death decreased in this study after SUPPORT but not with CPAP during SUPPORT is the larger sample size in this study versus that in SUPPORT (n=3849 vs. 1316). However, several other explanations are possible, including introduction of new policies or changes in processes of care (e.g., antenatal steroids, reduction of exposure to oxygen, lung-protective ventilation strategies, etc).

c) For BPD taken alone, the crude data show a reduction from 50.7% to 45.8%, based evidently on survivors. Calculated from that, the unadjusted RR was 0.90. However the adjusted RR is reported as 1.04 (0.97, 1.1), which is markedly different. Is that an error? Please check.

Response: multivariate analysis took into account multiple baseline variables that were significantly different/ imbalanced by the groups, thereby resulting in a moderate size change in RR. All the numbers were checked once again, and they are correct.

d) Outcomes related to the target SpO2. No results are presented concerning the use of the lower or higher SpO2 target in the pre- vs post-SUPPORT cohorts. However, very highly significant and clinically important reductions were shown for the composite outcome, severe ROP or death (adjusted RR 0.81 [0.73, 0.89], ARR 6.8%; and for severe ROP taken alone, analyzed evidently on survivors (adjusted RR 0.63 [0.52, 0.77]). How do these large reductions compare with the effects of the lower vs higher SpO2 target reported in SUPPORT? (A matter possibly for Discussion?) In the absence of any data on the actual use of the lower vs higher SpO2 target in the pre- and post-SUPPORT cohorts in your study, what if anything can you say about the mechanism of the differences in ROP that you report? What evidence do you have that the differences were in fact associated with the application in practice of evidence from SUPPORT (as distinct, for example, from a secular trend)?
Response: We acknowledge in the discussion that this study was not designed to test whether any change in secondary or tertiary variables were associated with the application in practice of evidence from SUPPORT. On the contrary, many changes over time may be related to other practice changes. We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.

7. Comments on Tables
Table 1
a) I believe the numbers in brackets are percentages; suggest placing (%) at the top
Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

b) The data are sometimes presented as n, sometimes as n/N. Suggest making that uniform. or explaining in a footnote the convention that was followed, eg that the N is given for the denominator when that differs from the N's given at the top (1617 and 2232). These comments pertain also to Table 2.
Response: We added denominators in all cells.

Table 2
a) As noted above, please check the adjusted RR for BPD. The unadjusted point estimate using the data in this row is 0.90. An adjusted value of 1.04 would indicate a huge effect of adjustemnt.
Response: multivariate analysis took into account multiple baseline variables that were significantly different/ imbalanced by the groups, thereby resulting in a moderate size change in RR. All the numbers were checked once again, and they are correct.

b) p values are given to 4 decimal places. Okay if that's the Journal policy, but I would think 2 or 3 places should be enough.
Response: We removed the 2nd number for values with 4 decimals.

c) Bottom row, days on ventilator Pre- and Post-SUPPORT columns. Shown are 3 numbers, the middle one bracketed. The first number is evidently the mean value. What the second and third represent is

unclear. For continuous data, what one would expect are the mean and some measure of the variance. Clarify.

Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables. (%) for categorical variables. We removed the 2nd number for values with 4 decimals

Appendix table.

This is in rough shape. Previous comments apply here too (multiple instances of previous point c). There is evidently an error in the row for Apgar score, 1 min, median (IQR). Identical values are shown, yet p <0.0001

Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables. (%) for categorical variables. We removed the 2nd number for values with 4 decimals
The difference in Apgar scores results from a different distribution, as shown by the percentage of values below 3 (see the next line in the table). All the numbers were checked once again, and they are correct.
If Apgar score were a continuous variable, we would use decimals and parametric statistics as shown below. In this table, we present the values of mean (standard deviation):

{Apgar score, 1 min}	4.4 (2.5)	3.9 (2.4)	<.0001
{Apgar score, 5 min)	6.5 (2.0)	6.3 (2.2)	.0007

However, Apgar score is categorical ordinal variable, for which only integers make sense. Therefore the use of parametric variables is inadequate (Hurley et al, Designing Clinical Research, 2007:p38, Table 4.1). We added in a Footnote in Table 3 the following information: "The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apgar at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those in the pre-SUPPORT cohort. The difference in distribution is shown on the next line in the Table (percentage of Apgar scores < 3)."

8. Discussion

a) This is too long - it needs tightening and focus. The present 2nd paragraph extends over more than 2 pages and includes strengths, weaknesses, cautions and speculations. Break up the paragraphs so as to develop one theme per paragraph.

Response: We shortened, and streamlined the discussion. Strengths, weaknesses and other statements have been split into separate paragraphs.

b) In Discussion you acknowledge that "oxygen saturation was not prospectively collected before and after SUPPORT" and thus it is "impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation". Your point is stated unclearly. Do you mean that the SpO2 target policy was not recorded, that summary measures of the actual SpO2 values achieved were not recorded, or both? In any case, this would seem to comprise a critical limitation in this study's ability to relate the finding of a reduction in severe ROP specifically to a change in oxygen targeting driven by the evidence provided by SUPPORT.

Response: Individual oxygen saturations were not recorded in patients who were not enrolled in SUPPORT. This is listed as one limitation of the study.

As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

To compensate somewhat for the lack of individual patient data on target SpO2 and other relevant aspects of clinical-care policies during the pre- and post-SUPPORT periods, might you determine those policies by reviewing each participating center's clinical guidelines for each period? Would those guidelines provide at least group-level information on changes in relevant care-taking goals that were introduced post SUPPORT?

Response: As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

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List of Abbreviations:

ARR, absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI, endotracheal intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.89, 95% confidence interval 0.86-0.93) was significantly lower than one.

Conclusions:

After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age [PMA]) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of endotracheal intubation and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the

risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of ETI in the DR in each center after the SUPPORT trial would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional

data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003--2012).

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of the SUPPORT trial, i.e., physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related

variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[3] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[4] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone, dexamethasone, no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-14] Since we did not adjust p-values for

multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012.This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1).

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use, antenatal betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

The primary outcome, the proportion of DR ETI, decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. The adjusted risk of DR ETI significantly decreased after the SUPPORT trial, RR 0.89, 95% confidence interval 0.86-0.93 (Table 2).

Secondary outcomes, including the adjusted risk of BPD or death, severe ROP or death, severe ROP, and death or mechanical ventilation at day of life seven were significantly

lower in the post-SUPPORT group (Table 2). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ($P<0.001$).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of the SUPPORT trial in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those born before initiation of the SUPPORT trial. We evaluated changes in ETI for all patients in the cohorts. Since we did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in the SUPPORT trial. The proportion of ETI in one of the participating

centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines. [15] The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a feasibility study prior to initiation of the SUPPORT trial.[17] It is possible that ETI decreased in these 5 centers because of experience with use of T-piece resuscitators and increased use of CPAP in the DR during the feasibility study limiting further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial.

The strengths of this study include the use of a prospective database and a large sample size of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in the SUPPORT trial, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Lack of correlation between the change in the proportion in ETI after the SUPPORT trial and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birth weight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data

on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2

Table 2. Primary and Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Adjusted Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.89 (0.86-0.93)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.03
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.85 (0.77-0.95)	.003
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.93 (0.81-1.1)	0.26
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.02 (0.95-1.1)	0.55
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.66 (0.53-0.82)	.0002
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.96 (0.83-1.1)	0.59
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.83-0.97)	0.004
Days on ventilator survivors[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.2 (-5.7, -2.7)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Table 3 on line only

Table 3- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth, °C	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[5]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[5]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apgar at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those

in the pre-SUPPORT cohort. The difference in distribution is shown on the next line in the Table (percentage of Apgar scores < 3).

[5]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Figure 1
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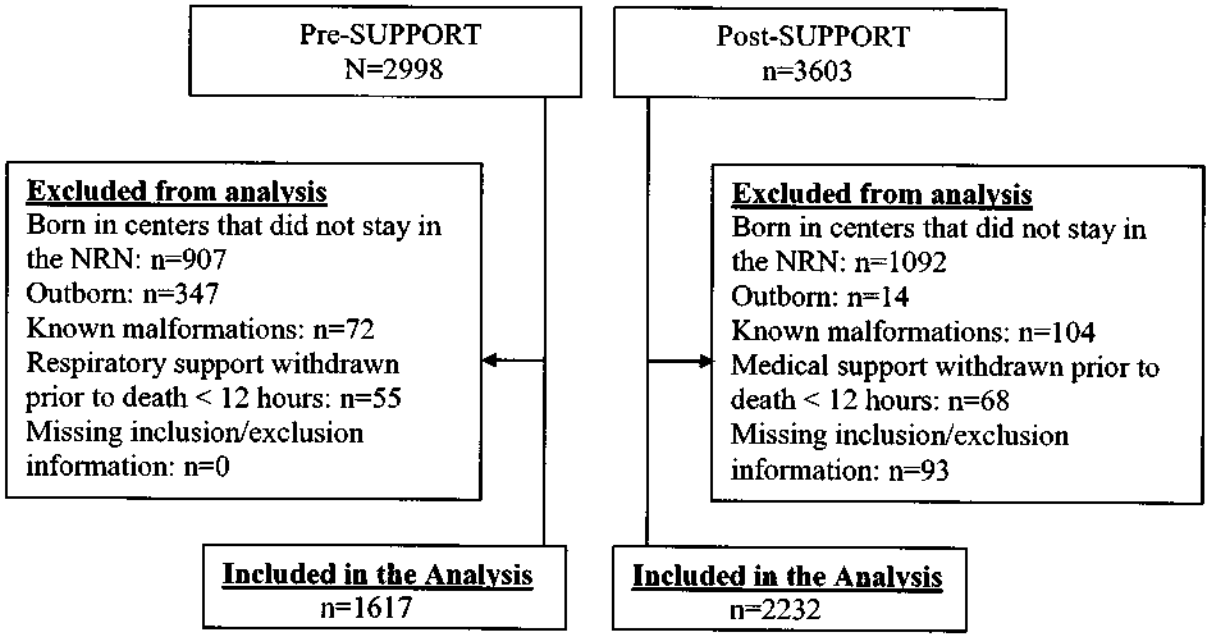

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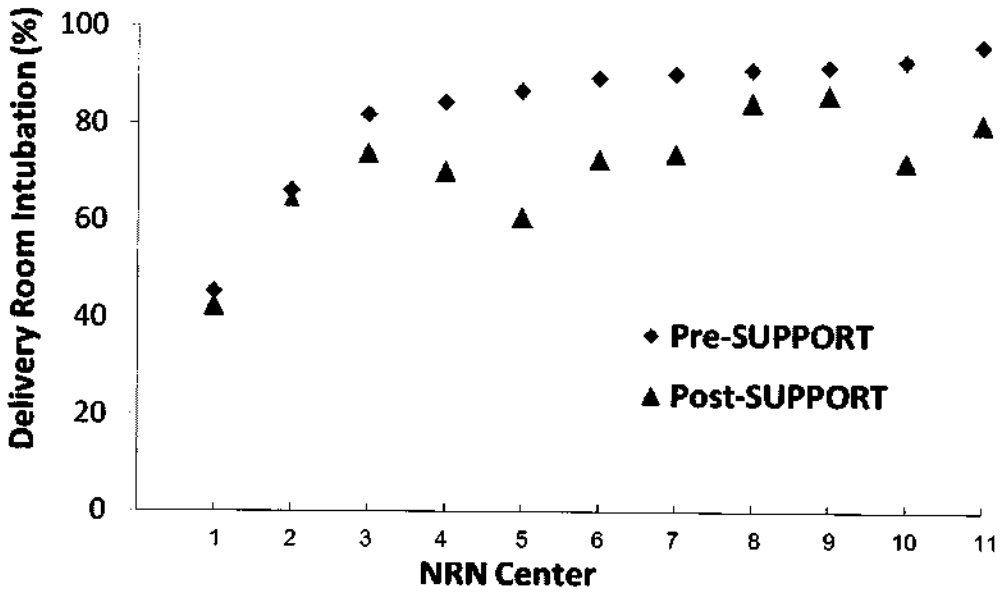

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Thursday, December 12, 2013 11:18 AM
To: Patterson, Amy (NIH/OD) [E]
Subject: RE: Planning a Workshop on Ethics of Standard of Care Research

Amy –

I asked Cathy Spong and Rose Higgins to take a look, too, since they led our trials (pun intended) with the SUPPORT study. I agree with these comments they offered:

(b)(5)

Non Responsive

I imagine you will want (b)(5)

It will be important to include k (b)(5)

(b)(5)

Topics might include:

(b)(5)

I hope that helps - Alan

Alan E. Guttmacher, M.D.
Director

From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, December 05, 2013 8:09 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Gibbons, Gary (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]; Hardesty, Rebecca (NIH/OD) [C]
Subject: Planning a Workshop on Ethics of Standard of Care Research

Dear Colleagues:

I'm writing to ask you to serve on a planning committee to help design and organize an NIH workshop on the ethical issues involved in standard of care research. The workshop will also be used to explore the relevance, validity, and utility of draft guidance that OHRP will be issuing on IRB review and informed consent considerations in research studying standard of care interventions. OHRP is expected to issue the draft guidance for a 60-day public comment period in January 2014. The workshop will likely be scheduled in late February to coincide with the comment period.

We will schedule an in-person meeting of the planning committee for the first week in January. In the meantime, I would appreciate your thoughts and suggestions via email about 1) the initial workshop design which is laid out in the attached précis; 2) case study topics and presenters; and 3) experts and stakeholders who should be invited to attend. Your feedback on these items by **Wednesday, December 18** would be much appreciated.

If you have any questions or are unable to participate in the planning committee, please let me know.

We look forward to working with you on this important meeting.

Many thanks,

Amy

Amy P. Patterson, M.D.
Associate Director for Science Policy, NIH

From:	Luc Brion
To:	Luc Brion; Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Barbara.Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne
Subject:	Updated Jackie LeVan"s manuscript; ready to submit tomorrow
Date:	Wednesday, December 11, 2013 6:27:46 PM
Attachments:	Jackie LeVan Manuscript NRN 12-11-13.docx Jackie LeVan Manuscript NRN 12-11-13 clean.docx

Dear Colleagues:
Thanks for all your support, comments and patience.
Here is the updated version, which includes all the comments.
The only change in this version is the use of steroids as categorical variable (betamethasone versus dexamethasone versus none) instead of steroids versus none.
This changed one adjusted variable in table 1: note that the death outcome is now non-significant.
All corresponding data were changed in the text.
I will submit this version tomorrow morning.
Best regards and thanks for your collaboration.
Luc

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 2241~~394~~ words
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Revised 12~~1~~/11~~5425~~/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

~~The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which~~ ~~p~~Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. ~~We included i~~Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial ~~(2010-12)~~ at 11 centers that ~~which~~ participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

~~The proportion of~~ DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation

(adjusted RR 0.898, 95% confidence interval 0.865-0.931) was significantly lower than one.

Conclusions:

After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age (PMA)) wasere not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had e-lower proportions of endotracheal intubation ander 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks ~~postmenstrual age (PMA)~~ wereas 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after the ~~SUPPORT~~SUPPORT trial in centers that participated in the trial. We hypothesized that after ~~SUPPORT~~the SUPPORT trial there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before ~~SUPPORT~~the SUPPORT trial. We speculated that the decrease in proportion of ETI in the DR in each center after ~~SUPPORT~~the SUPPORT trial would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after ~~SUPPORT~~the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT ~~t~~Trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are

~~is~~ collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are ~~is~~ collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of~~in~~ the NRN during the entire study period (2003--2012)~~cycles relevant to the two cohorts~~.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). ~~Based on numbers entered in GDB in 2010, we expected to obtain similar numbers of patients in both cohorts.~~

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in ~~SUPPORT~~the SUPPORT trial.[1,2] Specifically, eligible infants were ~~inborn at~~ $24^{0/7}$ to $27^{6/7}$ weeks GA ~~gestational age~~ at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from ~~SUPPORT~~the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks P~~of~~ PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks ~~of~~ PMA, BPD at 36 weeks ~~of~~ PMA, severe ROP at~~as of~~ status~~;~~ or death~~,~~ ~~or~~ mechanical ventilation on day 7, and days on ventilators ~~in survivors~~ until discharge for survivors. The definitions of BPD and ROP ~~for this study~~ were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of ~~SUPPORT~~the SUPPORT trial, i.e., physiological definition of BPD defined as ~~the~~ receipt of more than 30% supplemental oxygen at 36 weeks ~~of~~ PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks ~~of~~ PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until ~~SUPPORT~~the outcome of the SUPPORT trial ~~outcome~~ was reached or resolution occurred.[1,2]

Comment [MW1]: is this correct phrasing. You use it consistently but shouldn't it just be 36 weeks PMA (no 'of' needed)

Comment [MW2]: Are these the same thing? I don't understand what you mean here.

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[35] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[4] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment)[4] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included

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additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same ~~additional~~ variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-143] Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. ~~(Figure 1). The primary imbalance was due to outborn status. The~~ The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1).

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use in general, and specifically more betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less

prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

The primary outcome, ~~For the primary outcome, t~~ the proportion of DR ETI, decreased from 1313/1617 (81%) before ~~SUPPORT~~the SUPPORT trial to 1539/2232 (69%) after ~~SUPPORT~~the SUPPORT trial, $p < 0.0001$. Tthe adjusted risk of DR ETI significantly decreased after ~~SUPPORT~~the SUPPORT trial, ~~adjusted~~ RR 0.89, 95% confidence interval 0.86-0.93 (Table 2).

~~For s~~Secondary outcomes, including the adjusted risk of BPD/death, severe ROP/death, ~~death before discharge,~~ severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 2). By~~In~~ contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after ~~SUPPORT~~the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ($P<0.001$).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, $p=0.18$).

Discussion: ~~The first paragraph is confusing to me and hard to read – started to reword and realize I am not sure what you are saying. You mention the feasibility trial almost in passing. Should that be somewhere in the methods? I think the discussion still needs some work~~

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of the ~~-~~SUPPORT trial in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those ~~infants~~ born before ~~the~~ initiation of ~~the SUPPORT~~the SUPPORT trial. We evaluated changes in ETI for all patients in the cohorts. ~~In this study we compared data before SUPPORT with data after SUPPORT~~ Since we~~and~~ did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in ~~SUPPORT~~the SUPPORT trial~~decrease in ETI in some among these 11 centers~~. The proportion of ETI in one of the ~~the other centers participating in SUPPORT~~ participating centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[15] The proportion of DR ETI in this ~~latter~~center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center ~~among the 11 NRN centers~~ that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a~~the~~

feasibility study ~~Feasibility Trial~~ prior to initiation of ~~SUPPORT~~the SUPPORT trial; ~~which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003,[15] i.e., before SUPPORT and before the current study.~~[17] It is possible that ~~Possible explanations for the decrease in~~ -ETI decreased in these 5 centers ~~The proportion of ETI in each center could have decreased with increasing use of CPAP and~~ because of experience with use of T-piece resuscitators ~~connectors~~ and increased use of CPAP in the DR during the feasibility study limiting ~~in the DR during the Feasibility trial, thereby before, during or after participation in the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),[15] during participation or after publication of the results of SUPPORT. limiting any~~ further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial ~~in the current study. The proportion of ETI in one of the centers participating in SUPPORT decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010), in the absence of any change in DR policy or practice guideline. The proportion of ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[16] In another center among the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after the neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before SUPPORT.[17] The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between the change in the proportion in ETI after SUPPORT and baseline ETI proportion may have resulted from the limited number of centers in this~~

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Comment [R3]: This sentence is not clear to me, even with Barbara's addition

Comment [R4]: "subset" and the whole sentence may be more confusing than helpful here

~~study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.~~

The strengths of this study include ~~a large sample size,~~ the use of a prospective database and a large sample size ~~and~~ of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in ~~SUPPORT~~the SUPPORT trial, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Lack of correlation between the change in the proportion in ETI after ~~SUPPORT~~the SUPPORT trial and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in ~~SUPPORT~~the SUPPORT trial ~~but remained in the NRN during the study period~~, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time. ~~This finding contrasts with previous published reports from the NICHD NRN~~[18,19] , but a more recent ~~but is consistent with a recent~~ review of ~~among~~ extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen ~~O2~~ delivery or oxygen~~O2~~ saturation targets or limits, or with the application in practice of evidence from ~~SUPPORT~~the SUPPORT trial or ~~from~~ other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in ~~SUPPORT~~the SUPPORT trial, the decreased risk observed after ~~SUPPORT~~the SUPPORT trial may be related to practice changes, ~~based on evidence from other~~ studies. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes,[~~22-31~~][2] [~~2-31~~] . We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but ~~in the 11 NRN centers participating in this study. We~~ decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. ~~Experience in the network has shown that such surveys often are not very accurate even on current practices.~~

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This study did not address how generalizable the study results might be to centers that did not participate in ~~SUPPORT~~the SUPPORT trial. It is possible that centers participating in ~~SUPPORT~~the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~SUPPORT~~the SUPPORT trial and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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);
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Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, M01 RR39, UL1 TR454) – Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Linda L. Wright, MD; Stephanie Wilson Archer, MA.

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Stanford University and Lucile Packard Children's Hospital (U10 HD27880, M01 RR70, UL1 TR93) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Melinda S. Proud, RCP.

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.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) – Neil N. Finer, MD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Pablo J. Sánchez, MD; Myra Wyckoff, MD; Luc P. Brion, MD; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Melissa Martin, RN; Nancy A. Miller, RN; Lizette E. Torres, RN; Jackie Hickman, RN; Diana M Vasil, RNC-NIC; Lijun Chen, PhD RN; Araceli Solis, RRT; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School, 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; Katrina Burson, RN BSN; Patricia Ann Orekoya, RN BSN; Susan E. Dieterich, PhD; Patricia W. Evans, MD; Claudia I. Franco, RNC MSN; Charles E. Green, PHD; Margarita Jiminez, MD MPH; Terri L. Major-Kincade, MD MPH; Anna E. Lis, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; M. Layne Poundstone, RN BSN; Peggy Robichaux, RN BSN; Saba Khan Siddiki, MD; Maegan C. Simmons, RN; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT(ASCP).

Wayne State University, University of Michigan, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; John Barks, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN, Geraldine Muran, RN BSN.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations inby pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

~~Figure 1 If I understand this correctly this flow diagram represents all infants in the GDB during the 2 study periods. would clarify that in a title for the figure~~

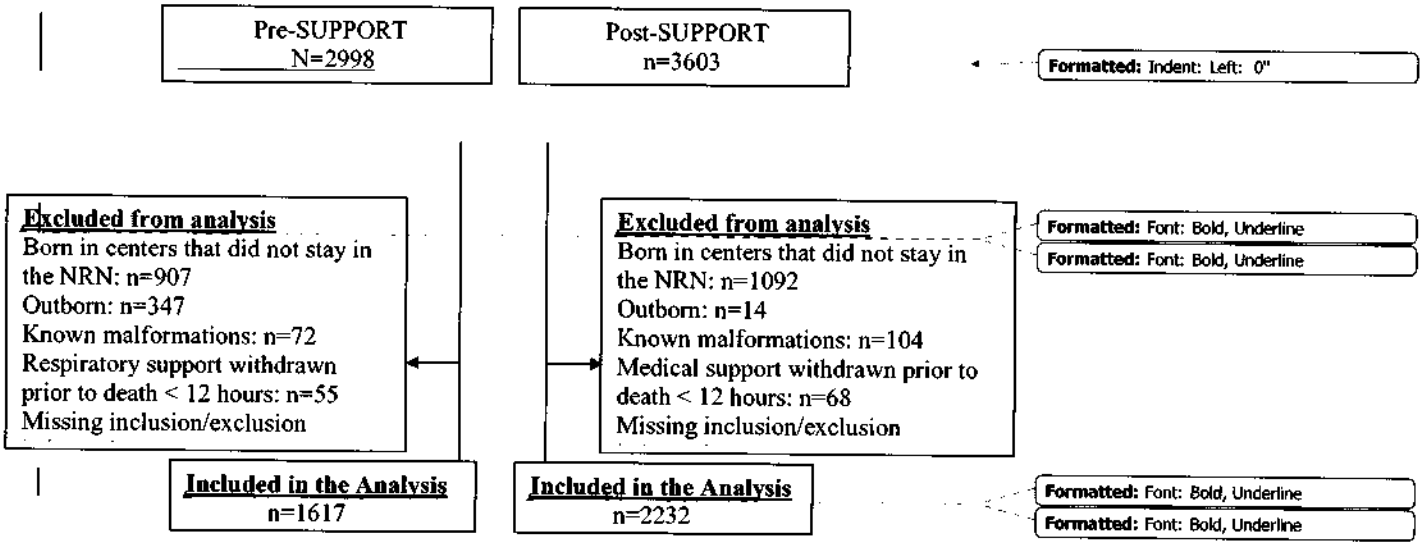

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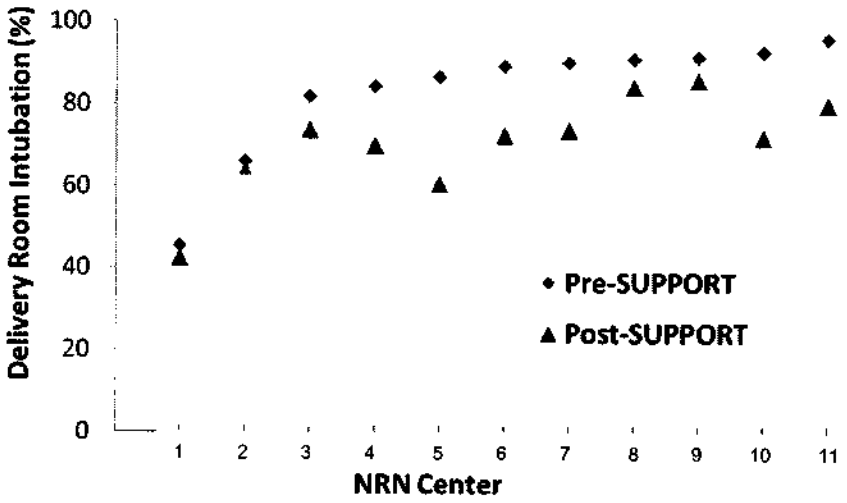
Figure 2


Delivery Room Intubation (%)
100
80
60
40
20
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1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

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Table 2. Primary and Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Adjusted Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.898 (0.865-0.931)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.032
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.851 (0.773-0.9589)	<0.0001,003
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 93 (0.7681-1.1098)	0.0226
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.024 (0.9795-1.1)	0.2655
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.63 66 (0.5253-0.7782)	<0.0001,002
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 96 (0.7683-1.001)	0.060.59
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.8483-0.97)	0.0043
Days on ventilator survivors[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 2 (-6.15.7, -3.22.7)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Table 3- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth, °C	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[5,4]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[5,4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

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[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apgar at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those in the pre-SUPPORT cohort.

[54]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 224 words
Article length: 2,613 words
Revised 12/11/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial at 11 centers that participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.89, 95% confidence interval 0.86-0.93) was significantly lower than one.

Conclusions:

After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risk of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age (PMA)) was not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had lower proportions of endotracheal intubation and 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks PMA 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the

risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after the SUPPORT trial in centers that participated in the trial. We hypothesized that after the SUPPORT trial there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before the SUPPORT trial. We speculated that the decrease in proportion of ETI in the DR in each center after the SUPPORT trial would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional

data are collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of the NRN during the entire study period (2003--2012).

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in the SUPPORT trial.[1,2] Specifically, eligible infants were $24^{0/7}$ to $27^{6/7}$ weeks GA at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks PMA, BPD at 36 weeks PMA, severe ROP at status or death, mechanical ventilation on day 7, and days on ventilator until discharge for survivors. The definitions of BPD and ROP were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of the SUPPORT trial, i.e., physiological definition of BPD defined as receipt of more than 30% supplemental oxygen at 36 weeks PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until the outcome of the SUPPORT trial was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related

variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[3] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants[4] [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids] (GA, antenatal corticosteroids [treated as categorical variable: betamethasone vs. dexamethasone vs. no corticosteroids], gender, singleton vs. multiple, birth weight by 100 g increment) as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained the same variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-14] Since we did not adjust p-values for

multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012.This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1).

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use in general, and specifically more betamethasone use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

The primary outcome, the proportion of DR ETI, decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. The adjusted risk of DR ETI significantly decreased after the SUPPORT trial, RR 0.89, 95% confidence interval 0.86-0.93 (Table 2).

Secondary outcomes, including the adjusted risk of BPD/death, severe ROP/death, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in

the post-SUPPORT group (Table 2). By contrast, the adjusted risks of BPD, death before discharge, and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ($P<0.001$).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, $p=0.18$).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of the SUPPORT trial in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those born before initiation of the SUPPORT trial. We evaluated changes in ETI for all patients in the cohorts. Since we did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in the SUPPORT trial. The proportion of ETI in one of the participating

centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines. [15] The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a feasibility study prior to initiation of the SUPPORT trial.[17] It is possible that ETI decreased in these 5 centers because of experience with use of T-piece resuscitators and increased use of CPAP in the DR during the feasibility study limiting further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial.

The strengths of this study include the use of a prospective database and a large sample size of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in the SUPPORT trial, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Lack of correlation between the change in the proportion in ETI after the SUPPORT trial and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in the SUPPORT trial, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time,[18,19] but a more recent review of extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen delivery or oxygen saturation targets or limits, or with the application in practice of evidence from the SUPPORT trial or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in the SUPPORT trial, the decreased risk observed after the SUPPORT trial may be related to practice changes. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data

on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. This study did not address how generalizable the study results might be to centers that did not participate in the SUPPORT trial. It is possible that centers participating in the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during the SUPPORT trial and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

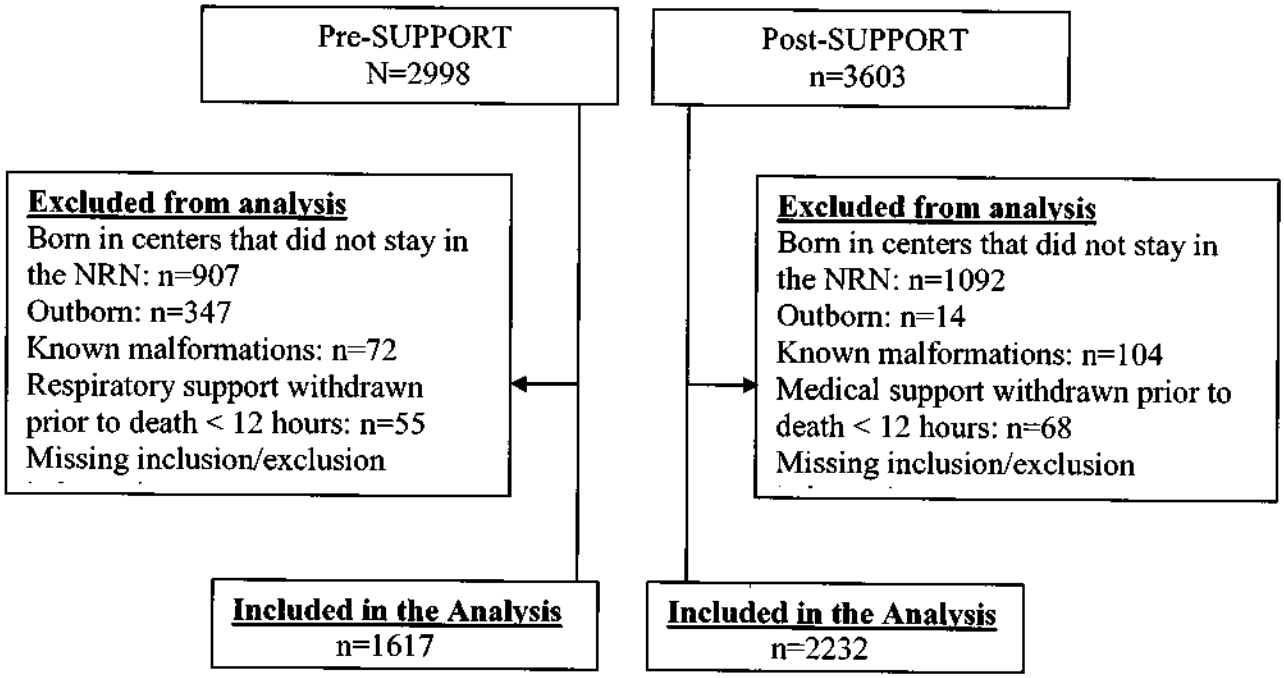
Pre-SUPPORT
N=2998
Post-SUPPORT
n=3603
Excluded from analysis
Born in centers that did not stay in the NRN: n=907
Outborn: n=347
Known malformations: n=72
Respiratory support withdrawn prior to death < 12 hours: n=55
Missing inclusion/exclusion
Excluded from analysis
Born in centers that did not stay in the NRN: n=1092
Outborn: n=14
Known malformations: n=104
Medical support withdrawn prior to death < 12 hours: n=68
Missing inclusion/exclusion
Included in the Analysis
n=1617
Included in the Analysis
n=2232

Figure 2

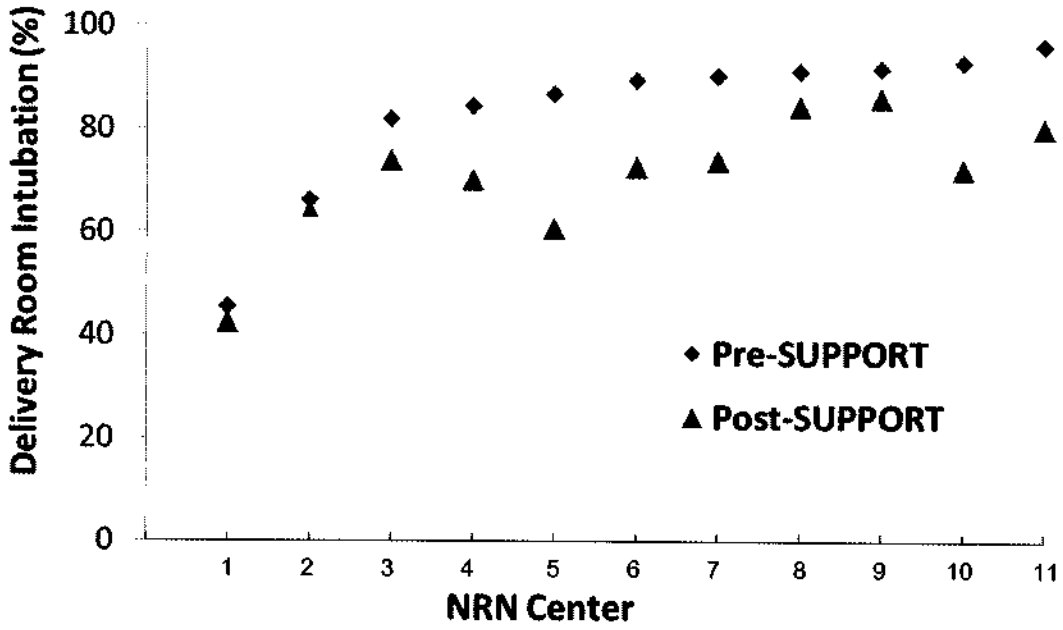
Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids:			
Betamethasone[3]	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Dexamethasone	383/1614 (23.7)	18/2229 (0.8)	
None	278/1614 (17.2)	231/2229 (10.4)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

[3] includes 24 infants whose mothers received a combination of betamethasone and dexamethasone.

Table 2. Primary and Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Adjusted Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.89 (0.86-0.93)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.03
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.85 (0.77-0.95)	.003
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.93 (0.81-1.1)	0.26
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.02 (0.95-1.1)	0.55
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.66 (0.53-0.82)	.0002
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.96 (0.83-1.1)	0.59
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.83-0.97)	0.004
Days on ventilator survivors[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.2 (-5.7, -2.7)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Table 3- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth, °C	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[5]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[5]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apger at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those in the pre-SUPPORT cohort.

[5]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

From: Luc Brion
To: Luc Brion; Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(5) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne
Subject: revised Jackie Levan"s manuscript
Date: Monday, December 09, 2013 2:21:40 PM
Attachments: Jackie LeVan Manuscript NRN 12-09-13.docx

Here is the latest version, including Roy's suggestion.
Best regards,
Luc

Change in Practice After
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 224~~1394~~ words
Article length: 2,585~~47752~~ words
Revised 12~~1~~/05~~425~~/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

~~The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which~~ ~~p~~Preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. ~~We included i~~Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial ~~(2010-12)~~ at 11 centers that ~~which~~ participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

~~The proportion of~~ DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for

baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval 0.85-0.91) was significantly lower than one.

Conclusions:

After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age (PMA)) wasere not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportions of endotracheal intubation and~~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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks ~~postmenstrual age (~~PMA~~)~~ wereas 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after the ~~SUPPORT~~SUPPORT trial in centers that participated in the trial. We hypothesized that after ~~SUPPORT~~the SUPPORT trial there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before ~~SUPPORT~~the SUPPORT trial. We speculated that the decrease in proportion of ETI in the DR in each center after ~~SUPPORT~~the SUPPORT trial would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after ~~SUPPORT~~the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT tTrial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are

~~is~~ collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are ~~is~~ collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of~~in~~ the NRN during the entire study period (2003--2012)~~cycles relevant to the two cohorts~~.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). ~~Based on numbers entered in GDB in 2010, we expected to obtain similar numbers of patients in both cohorts.~~

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in ~~SUPPORT~~the SUPPORT trial.[1,2] Specifically, eligible infants were ~~inborn at~~ $24^{0/7}$ to $27^{6/7}$ weeks GA ~~gestational age~~ at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from ~~SUPPORT~~the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks P~~of~~ PMA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks ~~of~~ PMA, BPD at 36 weeks~~of~~ PMA, severe ROP at~~es of~~ status~~,~~ or death~~,~~ ~~or~~ mechanical ventilation on day 7, and days on ventilators ~~in survivors~~ until discharge for survivors. The definitions of BPD and ROP ~~for this study~~ were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of ~~SUPPORT~~the SUPPORT trial, i.e., physiological definition of BPD defined as ~~the~~ receipt of more than 30% supplemental oxygen at 36 weeks ~~of~~ PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks ~~of~~ PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until ~~SUPPORT~~the outcome of the SUPPORT trial ~~outcome~~ was reached or resolution occurred.[1,2]

Comment [MW1]: is this correct phrasing. You use it consistently but shouldn't it just be 36 weeks PMA (no 'of' needed)

Comment [MW2]: Are these the same thing? I don't understand what you mean here.

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[4] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but

not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same ~~additional~~ variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-14~~2~~] Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. ~~(Figure 1). The primary imbalance was due to outborn status. The~~ The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1).

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

The primary outcome, ~~For the primary outcome, t~~ the proportion of DR ETI, decreased from 1313/1617 (81%) before ~~SUPPORT~~the SUPPORT trial to 1539/2232 (69%) after

~~SUPPORT~~the SUPPORT trial, $p < 0.0001$. T~~t~~he adjusted risk of DR ETI significantly decreased after ~~SUPPORT~~the SUPPORT trial, ~~adjusted~~ RR 0.88, 95% confidence interval 0.85-0.91 (Table 2).

~~For s~~Secondary outcomes, including the adjusted risk of BPD/death, severe ROP/death, death before discharge, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 2). By~~In~~ contrast, the adjusted risks of BPD and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after ~~SUPPORT~~the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ($P<0.001$).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, $p=0.18$).

Discussion: ~~The first paragraph is confusing to me and hard to read – started to reword and realize I am not sure what you are saying. You mention the feasibility trial almost in passing. Should that be somewhere in the methods? I think the discussion still needs some work~~

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of the -SUPPORT trial in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those ~~infants~~ born before ~~the~~ initiation of ~~the SUPPORT~~the SUPPORT trial. We evaluated changes in ETI for all patients in the cohorts. ~~In this study we compared data before SUPPORT with data after SUPPORT~~ Since we~~and~~ did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in ~~SUPPORT~~the SUPPORT trial~~decrease in ETI in some among these 11 centers~~. The proportion of ETI in one of the ~~the other centers participating in SUPPORT~~ participating centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[15] The proportion of DR ETI in this ~~latter~~center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center ~~among the 11 NRN centers~~ that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a~~the~~ feasibility study ~~Feasibility Trial~~ prior to initiation of ~~SUPPORT~~the SUPPORT trial, ~~which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003,[15] i.e., before SUPPORT and before the current study~~.[17] It is possible that ~~Possible explanations for the decrease in~~ -ETI decreased in these 5 centers ~~The proportion of ETI~~

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~~in each center could have decreased with increasing use of CPAP and~~ because of experience with use of T-piece resuscitators ~~connectors~~ and increased use of CPAP in the DR during the feasibility study limiting ~~in the DR during the Feasibility trial, thereby before, during or after participation in the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),[15] during participation or after publication of the results of SUPPORT. limiting any~~ further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial ~~in the current study. The proportion of ETI in one of the centers participating in SUPPORT decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010), in the absence of any change in DR policy or practice guideline. The proportion of ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[16] In another center among the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after the neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before SUPPORT.[17] The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between the change in the proportion in ETI after SUPPORT and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.~~

The strengths of this study include ~~a large sample size,~~ the use of a prospective database and a large sample size ~~and~~ of inborn patients which limits incomplete/missing data and

Comment [R3]: This sentence is not clear to me, even with Barbara's addition

Comment [R4]: "subset" and the whole sentence may be more confusing than helpful here

information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in ~~SUPPORT~~the SUPPORT trial, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Lack of correlation between the change in the proportion in ETI after ~~SUPPORT~~the SUPPORT trial and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in ~~SUPPORT~~the SUPPORT trial ~~but remained in the NRN during the study period~~, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time. ~~This finding contrasts with previous published reports from the NICHD NRN~~[18,19] ~~,~~but a more recent~~but is consistent with a~~

~~recent~~ review of~~among~~ extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen ~~O2~~ delivery or oxygen~~O2~~ saturation targets or limits, or with the application in practice of evidence from ~~SUPPORT~~the SUPPORT trial or ~~from~~ other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in ~~SUPPORT~~the SUPPORT trial, the decreased risk observed after ~~SUPPORT~~the SUPPORT trial may be related to practice changes~~, based on evidence from other studies.~~ Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes[22,31,32,34]. We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but~~in the 11 NRN centers participating in this study. We~~ decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. ~~Experience in the network has shown that such surveys often are not very accurate even on current practices.~~

This study did not address how generalizable the study results might be to centers that did not participate in ~~SUPPORT~~the SUPPORT trial. It is possible that centers participating in ~~SUPPORT~~the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~SUPPORT~~the SUPPORT trial and thus might

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have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Linda L. Wright, MD; Stephanie Wilson Archer, MA.

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The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in~~by~~ pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

~~Figure 1 If I understand this correctly this flow diagram represents all infants in the GDB during the 2 study periods. would clarify that in a title for the figure~~

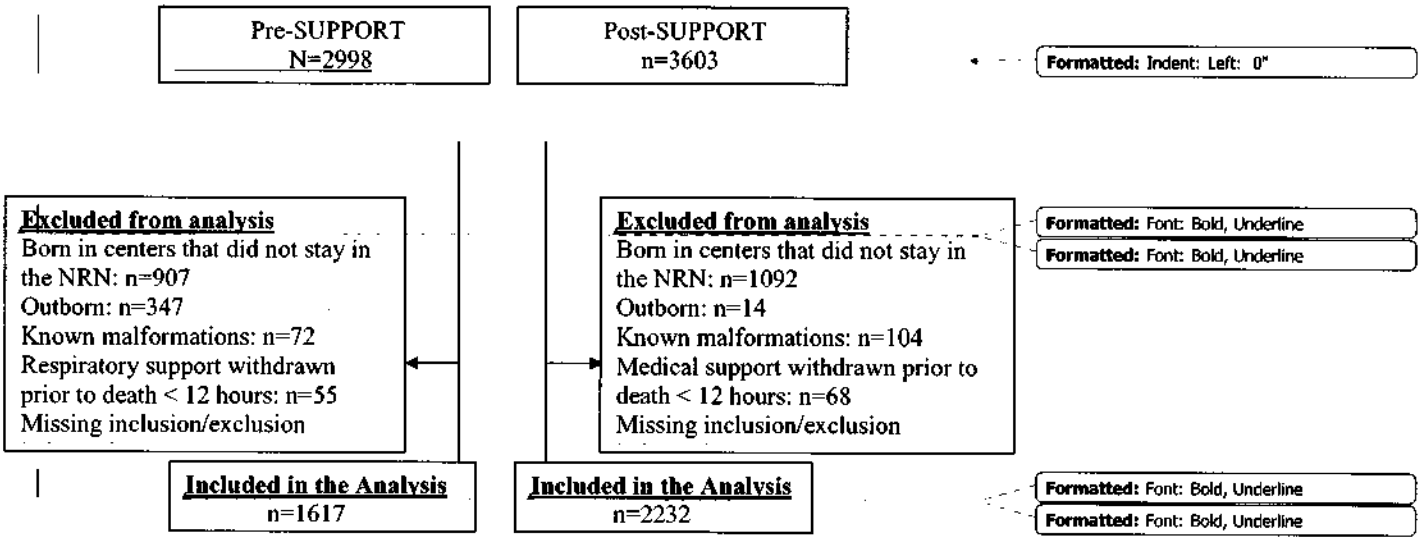

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Figure 2

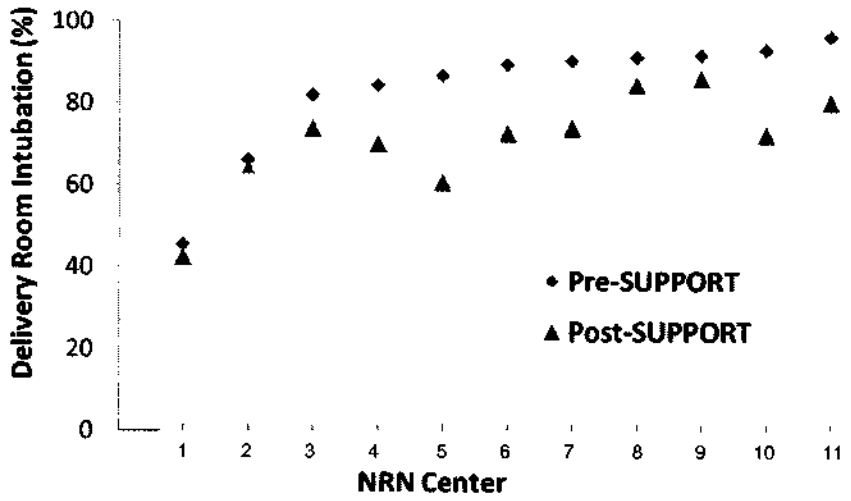
Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120/2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary and Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Adjusted Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.003
Days on ventilator survivors[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Table 3- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth, °C	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[5,4]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[5,4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Comment [I5]: See below; The distribution was different despite identical median and IQR.

Comment [MW6]: Is this correct that they are different statistically?

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Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apgar at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those in the pre-SUPPORT cohort.

[54]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

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From: Luc Brion
To: Roy Heyne; Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(5) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Updated version with Myra"s comments
Date: Monday, December 09, 2013 2:06:37 PM

Roy:
Thanks for your comments.
I removed "after publication of" SUPPORT to reflect our lack of serial data. We really can't say that changes occurred after publication of SUPPORT. See response to the reviewers.
I will change the text according to your other suggestions.
Best regards,
Luc

From: Roy Heyne
Sent: Monday, December 09, 2013 12:12 PM
To: Luc Brion; Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(5) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov)
Subject: RE: Updated version with Myra's comments

All changes look good. The first paragraph of the Discussion is much improved. One minor thing in that paragraph: "The proportion of ETI in one of participating centers" needs a "the" before participating. Regarding the revised wording "after the SUPPORT trial" the changes do aid consistency, but I wonder whether either in Objective statement at the end of the Introduction, or in the methods section, one needs to more explicitly define "after the SUPPORT trial" as tantamount to "after the publication of the SUPPORT trial" . The three places the latter wording is used in Conclusion of the abstract, in the Methods, and in the first paragraph of the Discussion.

From: Luc Brion
Sent: Saturday, December 07, 2013 12:09 PM
To: Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(5) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov)
Subject: Updated version with Myra's comments

Here is the latest version, after Myra's comments and suggestions.
Luc

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Subject: Updated version with Myra"s comments
Date: Saturday, December 07, 2013 1:09:14 PM
Attachments: Jackie LeVan Manuscript NRN 12-07-13.docx

Here is the latest version, after Myra's comments and suggestions.
Luc

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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Conflict of Interest Statement: There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 224~~1~~394 words
Article length: 2,585~~47~~752 words
Revised 12~~1~~/054~~25~~/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

~~The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which~~ pPreterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. ~~We included i~~Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial ~~(2010-12)~~ at 11 centers that ~~which~~ participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

~~The proportion of~~ DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for

baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval 0.85-0.91) was significantly lower than one.

Conclusions:

After adjustment for baseline variables, infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age (PMA)) wasere not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportions of endotracheal intubation ander 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks ~~postmenstrual age (~~PMA~~)~~ wereas 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after the ~~SUPPORT~~SUPPORT trial in centers that participated in the trial. We hypothesized that after ~~SUPPORT~~the SUPPORT trial there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before ~~SUPPORT~~the SUPPORT trial. We speculated that the decrease in proportion of ETI in the DR in each center after ~~SUPPORT~~the SUPPORT trial would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after ~~SUPPORT~~the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT ~~t~~Trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are

~~is~~ collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are ~~is~~ collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of~~in~~ the NRN during the entire study period (2003--2012)~~cycles relevant to the two cohorts~~.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). ~~Based on numbers entered in GDB in 2010, we expected to obtain similar numbers of patients in both cohorts.~~

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in ~~SUPPORT~~the SUPPORT trial.[1,2] Specifically, eligible infants were ~~inborn at~~ $24^{0/7}$ to $27^{6/7}$ weeks GA ~~gestational age~~ at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from ~~SUPPORT~~the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included (1) the composite of death or BPD (oxygen use at 36 weeks ~~P~~of ~~P~~MA, as defined in the SUPPORT trial), (2) the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and (3) death before discharge. Additional secondary outcomes included death by 36 weeks ~~of~~ PMA, BPD at 36 weeks ~~of~~ PMA, severe ROP at ~~as of~~ status ~~:~~ or death, ~~or~~ mechanical ventilation on day 7, and days on ventilators ~~in survivors~~ until discharge for survivors. The definitions of BPD and ROP ~~for this study~~ were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of ~~SUPPORT~~the SUPPORT trial, i.e., physiological definition of BPD defined as ~~the~~ receipt of more than 30% supplemental oxygen at 36 weeks ~~of~~ PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks ~~of~~ PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until ~~SUPPORT~~the outcome of the SUPPORT trial ~~outcome~~ was reached or resolution occurred.[1,2]

Comment [MW1]: is this correct phrasing. You use it consistently but shouldn't it just be 36 weeks PMA (no 'of needed)

Comment [MW2]: Are these the same thing? I don't understand what you mean here.

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[4] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but

not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same ~~additional~~ variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-14~~3~~] Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. ~~This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. (Figure 1). The primary imbalance was due to outborn status. The~~ The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1).

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

The primary outcome, ~~For the primary outcome, t~~ the proportion of DR ETI, decreased from 1313/1617 (81%) before ~~SUPPORT~~ the SUPPORT trial to 1539/2232 (69%) after

~~SUPPORT~~the SUPPORT trial, $p < 0.0001$. T~~t~~he adjusted risk of DR ETI significantly decreased after ~~SUPPORT~~the SUPPORT trial, ~~adjusted~~ RR 0.88, 95% confidence interval 0.85-0.91 (Table 2).

~~For s~~Secondary outcomes, including the adjusted risk of BPD/death, severe ROP/death, death before discharge, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 2). By~~In~~ contrast, the adjusted risks of BPD and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after ~~SUPPORT~~the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion: ~~The first paragraph is confusing to me and hard to read—started to reword and realize I am not sure what you are saying. You mention the feasibility trial almost in passing. Should that be somewhere in the methods? I think the discussion still needs some work~~

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of the ~~-~~SUPPORT trial in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those ~~infants~~ born before ~~the~~ initiation of ~~the SUPPORT~~the SUPPORT trial. We evaluated changes in ETI for all patients in the cohorts. ~~In this study we compared data before SUPPORT with data after SUPPORT~~ Since we~~and~~ did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in ~~SUPPORT~~the SUPPORT trial~~decrease in ETI in some among these 11 centers~~. The proportion of ETI in one of ~~the other centers participating in~~ SUPPORT participating centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[15] The proportion of DR ETI in this ~~latter~~center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center ~~among the 11 NRN centers~~ that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a~~the~~ feasibility study ~~Feasibility Trial~~ prior to initiation of ~~SUPPORT~~the SUPPORT trial~~, which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003,~~[15] ~~i.e., before SUPPORT and before the current study~~.[17] It is possible that ~~Possible explanations for the decrease in~~ -ETI decreased in these 5 centers ~~The proportion of ETI~~

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~~in each center could have decreased with increasing use of CPAP and~~ because of experience with use of T-piece resuscitators ~~connectors~~ and increased use of CPAP in the DR during the feasibility study limiting ~~in the DR during the Feasibility trial, thereby before, during or after participation in the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),[15] during participation or after publication of the results of SUPPORT. limiting any~~ further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial ~~in the current study. The proportion of ETI in one of the centers participating in SUPPORT decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010), in the absence of any change in DR policy or practice guideline. The proportion of ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[16] In another center among the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after the neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before SUPPORT.[17] The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between the change in the proportion in ETI after SUPPORT and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.~~

The strengths of this study include ~~a large sample size,~~ the use of a prospective database and a large sample size ~~and~~ of inborn patients which limits incomplete/missing data and

Comment [R3]: This sentence is not clear to me, even with Barbara's addition

Comment [R4]: "subset" and the whole sentence may be more confusing than helpful here

information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in ~~SUPPORT~~the SUPPORT trial, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Lack of correlation between the change in the proportion in ETI after ~~SUPPORT~~the SUPPORT trial and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in ~~SUPPORT~~the SUPPORT trial ~~but remained in the NRN during the study period~~, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time.~~This finding contrasts with previous published reports from the NICHD NRN~~[18,19] ~~,~~but a more recent~~but is consistent with a~~

~~recent~~ review ofamong extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen ~~O2~~ delivery or oxygen~~O2~~ saturation targets or limits, or with the application in practice of evidence from ~~SUPPORT~~the SUPPORT trial or ~~from~~ other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in ~~SUPPORT~~the SUPPORT trial, the decreased risk observed after ~~SUPPORT~~the SUPPORT trial may be related to practice changes~~, based on evidence from other studies.~~ Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes,[22-31] ~~-~~ -We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but~~in the 11 NRN centers participating in this study. We~~ decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. ~~Experience in the network has shown that such surveys often are not very accurate even on current practices.~~

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This study did not address how generalizable the study results might be to centers that did not participate in ~~SUPPORT~~the SUPPORT trial. It is possible that centers participating in ~~SUPPORT~~the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~SUPPORT~~the SUPPORT trial and thus might

have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie G. Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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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. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations inby pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

~~Figure 1 If I understand this correctly this flow diagram represents all infants in the GDB during the 2 study periods. would clarify that in a title for the figure~~

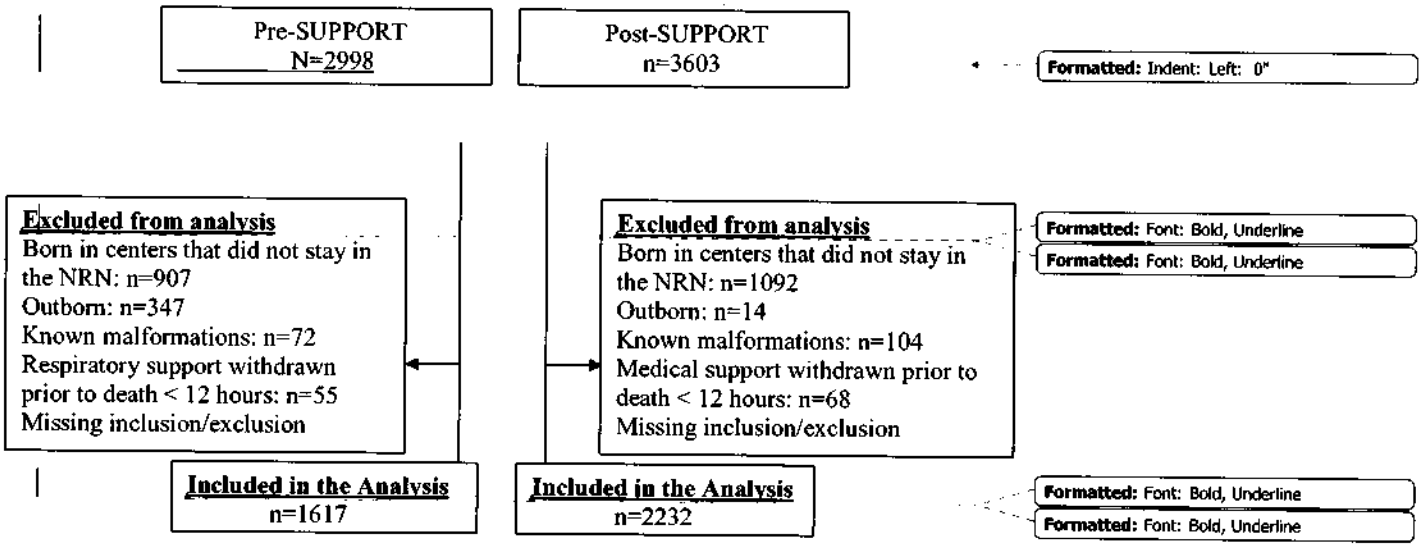

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Figure 2

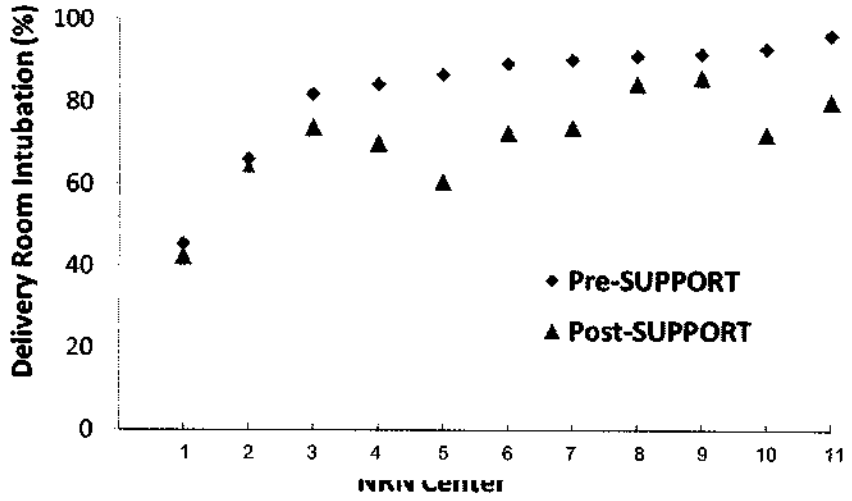
Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary and Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Adjusted Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.003
Days on ventilator survivors[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Table 3- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)[4]	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth, °C	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Comment [I5]: See below; The distribution was different despite identical median and IQR.

Comment [MW6]: Is this correct that they are different statistically?

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Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-values for Apgar scores are significant despite identical (Apgar at 1 minute) or almost identical (Apger at 5 minutes) medians and IQRs in both cohorts because the distributions of the values in the post-SUPPORT cohort were different from those in the pre-SUPPORT cohort.

[54] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

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From:	Luc Brion
To:	Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(5) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]
Subject:	Updated version for Jackie LeVan"s manuscript
Date:	Friday, December 06, 2013 11:20:54 PM
Attachments:	Responses to reviewers 12-6-2013.docx Jackie LeVan Manuscript NRN 12-06-13.docx

Dear Colleagues:

This version takes into account comments and edits from Jaleel, Marie, Roy, Barbara, Wally, and

Thanks a lot for your contribution.

Neil: I am waiting for Lisa' s response about whether adjustment was done for betamethasone.

Best regards,

Luc

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Tuesday, September 02, 2014~~Tuesday, January 01, 2002Friday, December 06, 2013Monday, November 25, 2013~~

Clyde J Wright, MD
Associate Editor

William F. Balistreri, M.D.
Editor

Ref.: Ms. No. 20131573
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested.
We have made the revision as short as possible. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text. The Abstract is <250 words. The list of Study Group members and the figures are separate Appendix files. We labeled the third table as online only.
In this revised version we have clarified that this study was designed to test the hypothesis that the proportion of the primary outcome variable, delivery room intubation, would decrease after SUPPORT. This study was not designed to test whether any change in secondary or tertiary variables were associated with the primary outcome variable, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies.
We have entirely revised and streamlined the discussion and emphasized the limitations of the study.
We include an itemized list of responses to the reviewers. Several of these responses are currently not included in the text of the manuscript, to keep in line with your request to make the revision as short as possible. We will be glad to include in the manuscript any additional comments that are currently included only in the itemized list of responses.
We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.
Response: The text of the first version had 2697 words; the revised version has 2452 words. The text of the discussion was shortened by ½ page. We have shortened the results section. We have -removed from the text all numbers that were in Figure 1 or in the tables, and all comments on unadjusted results for the primary and secondary variables.

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (http://www.jpeds.com/authorinfo).
Response: We have shortened the abstract; it contains 194 words. The abstract is structured as indicated.

Please upload the list of Study Group members as a separate Appendix file.
Response: the list of Study Group was moved into a separate file.

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.
Response: Figures are submitted as separate files in doc format.

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."
Response: we have changed online documents as requested.

Itemized responses to Reviewers:

Reviewer #1: This study compared neonatal outcomes in centers of the NICHD neonatal research network before and after their participation in the SUPPORT trial. The methodology and discussion are for the most part adequate.
The investigators found a smaller proportion of infants were intubated in the delivery room, less mortality and reduced rates of the composite outcomes of death or BPD and death or severe ROP. There are a few aspects the investigators should consider to further support their findings.

Comments:
- Can these findings and any possible changes in practice be attributed to the publication of the trial or the actual participation of the trial?

Response: In this study we did not obtain any serial data ~~during participation in the trial~~; therefore we cannot respond to that question. ~~This is discussed in the first paragraph of the discussion.~~ We replaced "after publication of SUPPORT" with "after SUPPORT." This is discussed in the first paragraph of the discussion. "Since we did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in the SUPPORT trial. The proportion of ETI in one of participating centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines. The proportion of DR ETI in this center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[16] In another center that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[17] ~~*At least in one center of the Neonatal Research Network (Parkland Memorial Hospital), the proportion of delivery room intubation decreased during participation in SUPPORT (LeVan, Pediatrics 2013, reference 16). In another center the proportion of delivery room intubation decreased before participation in SUPPORT (Narendran 2003, reference 17).*~~

Comment [MJ1]: I think the question is being misunderstood. Is the reviewer suggesting that the results of the trial made these centers comfortable with using more CPAP vs. the comfort of their experience during the trial? And if so, I guess you have answered that in the last paragraph of the discussion section.

- The manuscript would benefit from data on changes in policies/practice implemented in the 11 centers. These data can support the investigators claim that practice indeed changed following SUPPORT. Please see below.
Response: We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.
We provide information on delivery room practice 2 centers (no change in policy in reference 16, and prospective progressive routine change in practice in reference 17).

- The proportion of DR intubations decreased after SUPPORT. Were any changes in policy actually implemented in these 11 centers? Can this be attributed to other changes implemented (e.g. O2 titration in DR, use of PEEP and T piece resuscitators)?
Response: We are unable to analyze whether changes in DR intubation after SUPPORT were related to changes in DR policy or other changes implemented (e.g. O2 titration in DR, use of PEEP and T piece resuscitators). As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- Were the attempts to avoid intubation successful? What proportion of infants remained non-intubated by day 3 or 7 or were never intubated? The difference in proportion of infants receiving surfactant was smaller than the difference in intubations in DR. Was the technique of surfactant administration changed?
Response: The proportion of babies alive and not requiring artificial ventilation at 7 days was 54.1% before SUPPORT and 60.4% after SUPPORT (Table 2). The proportion of babies who were never intubated was: 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group; this post-hoc analysis is included in the result section.
We do not have information on the technique of surfactant administration. As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- The CPAP/surfactant-intubation component of the SUPPORT trial also reported fewer intubations in DR but did not show significant effects on BPD. Can the reduction in BPD after SUPPORT be attributed to changes/improvements in oxygen saturation targeting?
Response: After adjustment for baseline variables, we found no significant change in the frequency of BPD after SUPPORT, but a significant decrease in combined outcome death or BPD. The CPAP/surfactant randomization in SUPPORT did not affect the frequency of BPD or the frequency of death/BPD.
We do not have information on changes/improvements in oxygen saturation targeting. This information is not collected in the GDB. As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- It is unclear why different exclusion criteria were used for each cohort. The number of infants excluded should be given by cohort. Reasons for withholding or withdrawing support are not mentioned. Were these decisions made before birth? Otherwise these deaths should be reported for each cohort.

Response: Exclusion criteria are different in the 2nd cohort because of a change in GDB field definition. Exclusions for each cohort are now reported separately in the flow diagram. The reasons for withholding or withdrawal of support are not given on the form collected in the GDB.

- Was the analysis adjusted for prenatal factors that clearly differed between cohorts?
Response: Multivariate analysis was adjusted for all factors that differed between cohorts, to which all infants were exposed, and preceded the variable of interest.

Minor comments:
- Gestational age limits in first sentence of Discussion needs to be checked.
Response: Thank you for pointing out this error; we replaced $26^{6/7}$ by $27^{6/7}$

- Table 2 is missing numerator/denominator data in some cells.
Response: We added denominators in all cells.

- 2nd paragraph of Discussion needs to be streamlined and perhaps split by topic.
Response: We have completely revised the discussion. We have split paragraph two. The discussion in streamlined as follows; change in endotracheal intubation, strengths, limitations, changes before/after SUPPORT vs. results of SUPPORT

- The authors state some comparisons of outcome variables reached significance p<0.05) by chance and that they should be considered only exploratory. It is unclear why this would apply only to some variables.
Response: We have clarified this issue. In the statistical analysis we state: "Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory." In the discussion, we have replaced this sentence as follows: "it is likely that some differences reached a significant p value just by chance"

Reviewer #2: The SUPPORT trial was a landmark multicenter factorial-design trial of two interventions for improving outcomes in extremely low gestational age (ELGA) neonates: delivery-room (DR) CPAP vs RD endotracheal intubation (ETI) and surfactant, and a lower vs higher target SpO2 range for oxygen administration. This study reports an analysis of the changes in practice and clinical outcomes that occurred between a 2-year period before and a 3-year period after the publications in 2010 of SUPPORT. It is based on data from 11 centers that contributed to that trial and were members of the NICHD NRN Network during each entire period. This presents an interesting and important opportunity to determine the extent of uptake of important new randomized evidence concerning the clinical effectiveness of these treatments, and to examine the impact on clinical practice and patient outcomes.

Specific comments:
Objectives
1. The primary objective is stated as "to determine if publication of SUPPORT was temporally associated with changes in clinical practice...". "Changes" is vague. What size of absolute effects on the major outcomes of interest were demonstrated in SUPPORT? (These are not stated, but a revised Introduction could make that clear.) At least for the primary outcome, what size of absolute effect did you consider important? What size of absolute effect did your study have the capacity to detect?
Response:

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough to conduct multivariate analysis with 10 patients per covariate.

Methods

2. Study population, Ascertainment. The eligible infants were born during the stated pre- and post-SUPPORT years. But for each cohort, not all eligible outcomes would have occurred during those stated years. For example, some outcomes for the post-SUPPORT cohort would not be included in the generic database (GDB) during 2003-2012 because they had not yet occurred by end-2012. The duration of follow-up in the GDB to ascertain the later outcomes in the post-SUPPORT cohort needs to be stated. For BPD, severe ROP, days on ventilator, death, was it until 36 wks PMA, hospital discharge, or what?
Response: All this information is included in the GDB. All patients are followed in GDB to ascertain all listed outcomes.
To clarify the exact timing (postnatal age, postmenstrual age or discharge) of each outcome we have revised this paragraph as follows: "Secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, death before discharge or by 36 weeks, BPD, severe ROP before status, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge."
We have also included specific information on GDB in the design section of the manuscript:
The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data is collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data is collected on infants who remain in the hospital at 120 days.

3. Study population, Exclusions. The patient flow diagram (Fig 1) shows the reasons for exclusion of non-eligible patients from each of the two cohorts. Overall, about 42% of the 6601 patients in the two cohorts were not eligible and thus were excluded from analysis. Of potential concern is that there was a higher proportion of ineligible patients in the pre-SUPPORT than in the post-SUPPORT cohort. In fact, the 95% CIs for the respective proportions who were ineligible and thus excluded from analysis do not overlap (by my calculation: pre-SUPPORT, 46.1% [95% CI 44.3, 47.9]; post-SUPPORT, 38.1% [95% CI 36.5, 39.7]). Given this, the specific reasons for exclusion should be given separately for each cohort. Any systematic differences that could bias the comparison of the pre- and post-SUPPORT cohorts as analyzed should be acknowledged when interpreting the results.
Response: The flow diagram was revised to show all exclusions for each cohort separately. The primary imbalance was due to GDB inclusion criteria different re: outborn status.

4. Baseline variables. If the results of SUPPORT are hypothesized to change clinical practice, the baseline variables pertaining to those particular practices need to be identified and ascertained. In the pre-SUPPORT cohort, those critical variables include the numbers and proportion of eligible infants who received DR CPAP rather than DR ETI and surfactant, and the numbers and proportion whose oxygen management was targeted at the lower rather than the higher SpO2 range. I was struck by the absence of those practice variables from the stated list of baseline variables. It was also unclear whether in the post-SUPPORT cohort the numbers and proportion of infants whose oxygen management was targeted at the lower vs higher SpO2 range were to be ascertained.

Response: CPAP and SPO2 target ranges are not part of the variables collected in the GDB. This is listed in limitations of the study.

5. Statistical analyses. For the analysis of change in use of DR CPAP by individual center: the individual centers must have contributed different numbers of patients. Those numbers should be reported. It was not clear if the Spearman correlation was weighted in order to take into account the differing numbers of patients per center.
Response: We calculated a Spearman correlation on center-level aggregate summaries with the center as the unit of analysis. Because the primary interest was in assessing the monotonic association of aggregate center-level rates or prevalence, not in comparing events in individual subjects, weighting these rank-based analyses is not appropriate.

Results
6. a) Primary outcome, DR ETI. This was significantly reduced, adjusted RR 0.88 (95% CI 0.85, 0.91). The absolute risk reduction (ARR), calculated on the numbers presented, was 12.2%, which represents a clinically important effect, NNT = 8. As a matter for Discussion, how does that size of effect compare with what was found in SUPPORT, or was that even reported?
Response: These are not directly comparable. During SUPPORT, all patients in the CPAP arm were started on CPAP immediately and those in the intubation arm were intubated immediately. In contrast, outside a randomized trial such as SUPPORT or COIN, some patients may be started on CPAP or be intubated when respiratory distress develop, some patients may be intubated or placed on CPAP per protocol or policy, and some patients may be started on CPAP and intubated later.
In SUPPORT, the relative risk of intubation in the CPAP arm versus in the intubation arm was 0.37 (0.34–0.42). In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (59%).
Since the Editor has requested to limit the size of the manuscript to a minimum we have not entered absolute risk reduction in the manuscript.

The attempt to further analyze that difference by center did not yield a significant result. In retrospect, it appears that the opportunity to find a significant correlation between the pre- and post-SUPPORT DR ETI rates was limited by the distribution of pre-SUPPORT rates, with 9 of the 11 centers having pre-SUPPORT rates that varied within a narrow range of about 82-97%. Again, a matter possibly for Discussion?
Response: this information was added to the discussion.

b) There was a significant reduction, pre- vs post-SUPPORT, in the composite clinical outcome of BPD or death at 36 weeks, adjusted RR 0.94 (0.89, 0.99). The ARR calculated from table 2 was 5.8%. How does that compare with what was found in SUPPORT?
Response: This study was not designed to test whether any change in secondary or tertiary variables were associated with DR ETI, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies. The composite outcomes in SUPPORT and in the current study are not directly comparable. During SUPPORT, half the patients were randomized to CPAP at the time of randomization and the other half to ETI with surfactant administration, whereas outside a randomized trial such as SUPPORT or COIN, some patients may be started on CPAP either immediately or when respiratory distress develop, whereas other patients may be electively intubated.

In SUPPORT there was no significant adjusted relative risk difference (p=0.07) in death or BPD (defined as O2 need at 36 weeks) between the 2 arms of the study, but the point estimate of the RR was 0.91 (0.83 to 1.01), thus similar to that in the current study.
One possible explanation for the fact that the risk of BPD or death decreased in this study after SUPPORT but not with CPAP during SUPPORT is the larger sample size in this study versus that in SUPPORT (n=3849 vs. 1316). However, several other explanations are possible, including introduction of new policies or changes in processes of care (e.g., antenatal steroids, reduction of exposure to oxygen, lung-protective ventilation strategies, etc).

c) For BPD taken alone, the crude data show a reduction from 50.7% to 45.8%, based evidently on survivors. Calculated from that, the unadjusted RR was 0.90. However the adjusted RR is reported as 1.04 (0.97, 1.1), which is markedly different. Is that an error? Please check.
Response: multivariate analysis took into account multiple baseline variables that were significantly different/ imbalanced by the groups, thereby resulting in a moderate size change in RR. All the numbers were checked once again, and they are correct.

d) Outcomes related to the target SpO2. No results are presented concerning the use of the lower or higher SpO2 target in the pre- vs post-SUPPORT cohorts. However, very highly significant and clinically important reductions were shown for the composite outcome, severe ROP or death (adjusted RR 0.81 [0.73, 0.89], ARR 6.8%; and for severe ROP taken alone, analyzed evidently on survivors (adjusted RR 0.63 [0.52, 0.77]). How do these large reductions compare with the effects of the lower vs higher SpO2 target reported in SUPPORT? (A matter possibly for Discussion?) In the absence of any data on the actual use of the lower vs higher SpO2 target in the pre- and post-SUPPORT cohorts in your study, what if anything can you say about the mechanism of the differences in ROP that you report? What evidence do you have that the differences were in fact associated with the application in practice of evidence from SUPPORT (as distinct, for example, from a secular trend)?
Response: We acknowledge in the discussion that this study was not designed to test whether any change in secondary or tertiary variables were associated with the application in practice of evidence from SUPPORT. On the contrary, many changes over time may be related to other practice changes. We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.

7. Comments on Tables
Table **1**
a) I believe the numbers in brackets are percentages; suggest placing (%) at the top
Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

b) The data are sometimes presented as n, sometimes as n/N. Suggest making that uniform. or explaining in a footnote the convention that was followed, eg that the N is given for the denominator when that differs from the N's given at the top (1617 and 2232). These comments pertain also to Table 2.
Response: We added denominators in all cells.

Table 2

a) As noted above, please check the adjusted RR for BPD. The unadjusted point estimate using the data in this row is 0.90. An adjusted value of 1.04 would indicate a huge effect of adjustemnt.
Response: multivariate analysis took into account multiple baseline variables that were significantly different/ imbalanced by the groups, thereby resulting in a moderate size change in RR. All the numbers were checked once again, and they are correct.

b) p values are given to 4 decimal places. Okay if that's the Journal policy, but I would think 2 or 3 places should be enough.
Response: We removed the 2nd number for values with 4 decimals.

c) Bottom row, days on ventilator Pre- and Post-SUPPORT columns. Shown are 3 numbers, the middle one bracketed. The first number is evidently the mean value. What the second and third represent is unclear. For continuous data, what one would expect are the mean and some measure of the variance. Clarify.
Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables. (%) for categorical variables. We removed the 2nd number for values with 4 decimals

Appendix table.
This is in rough shape. Previous comments apply here too (multiple instances of previous point c). There is evidently an error in the row for Apgar score, 1 min, median (IQR). Identical values are shown, yet p <0.0001
Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables. (%) for categorical variables. We removed the 2nd number for values with 4 decimals
The difference in Apgar scores results from a different distribution, as shown by the percentage of values below 3 (see the next line in the table). All the numbers were checked once again, and they are correct.

8. Discussion
a) This is too long - it needs tightening and focus. The present 2nd paragraph extends over more than 2 pages and includes strengths, weaknesses, cautions and speculations. Break up the paragraphs so as to develop one theme per paragraph.
Response: We shortened, and streamlined the discussion. Strengths, weaknesses and other statements have been split into separate paragraphs.

b) In Discussion you acknowledge that "oxygen saturation was not prospectively collected before and after SUPPORT" and thus it is "impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation". Your point is stated unclearly. Do you mean that the SpO2 target policy was not recorded, that summary measures of the actual SpO2 values achieved were not recorded, or both? In any case, this would seem to comprise a critical limitation in this study's ability to relate the finding of a reduction in severe ROP specifically to a change in oxygen targeting driven by the evidence provided by SUPPORT.
Response: Individual oxygen saturations were not recorded in patients who were not enrolled in SUPPORT. This is listed as one limitation of the study.
As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

To compensate somewhat for the lack of individual patient data on target SpO2 and other relevant aspects of clinical-care policies during the pre- and post-SUPPORT periods, might you determine those policies by reviewing each participating center's clinical guidelines for each period? Would those guidelines provide at least group-level information on changes in relevant care-taking goals that were introduced post SUPPORT?

Response: As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

Change in Practice After
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M. LeVan, DO,[1,2] Luc P. Brion, MD,[1] Lisa Wrage, MPH,[3] Marie G. Gantz, PhD,[3] Myra H. Wyckoff, MD,[1] Pablo Sánchez, MD,[1,4] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[5] Waldemar A. Carlo, MD,[6] Abhik Das, PhD,[3] Barbara Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

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No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Statement: No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Conflict of Interest Statement: There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 2091~~394~~ words
Article length: 2,471~~752~~ words
Revised 12~~1~~/0542~~5~~/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

~~The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which~~ pPreterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) enrolled in the NICHD Neonatal Research Network (NRN) SUPPORT trial were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after the SUPPORT trial within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. ~~We included i~~Infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after (2010-12) the SUPPORT trial ~~(2010-12)~~ at 11 centers that ~~which~~ participated in the SUPPORT trial and were part of the NRN in 2003-12 were studied. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

~~The proportion of~~ DR intubation decreased from 1313/1617 (81%) before the SUPPORT trial to 1539/2232 (69%) after the SUPPORT trial, $p < 0.0001$. After adjustment for

baseline variables, the relative risk (RR) (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval 0.85-0.91) was significantly lower than one.

Conclusions:

After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of the SUPPORT trial had significantly lower percentages of DR intubation compared to infants born before the SUPPORT trial.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD] at 36 weeks postmenstrual age (PMA)) wasere not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportions of endotracheal intubation ander 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risks of death during hospitalization and at 36 weeks ~~postmenstrual age (~~PMA) wereas 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target

groups. However, the risk of death during hospitalization was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after the ~~SUPPORT~~SUPPORT trial in centers that participated in the trial. We hypothesized that after ~~SUPPORT~~the SUPPORT trial there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before ~~SUPPORT~~the SUPPORT trial. We speculated that the decrease in proportion of ETI in the DR in each center after ~~SUPPORT~~the SUPPORT trial would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after ~~SUPPORT~~the SUPPORT trial. The most important secondary outcomes were the composite of death or BPD at 36 weeks PMA, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT ~~t~~Trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data are

~~is~~ collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data are ~~is~~ collected on infants who remain in the hospital at 120 days. We included the eleven centers that participated in the SUPPORT trial and were part of~~in~~ the NRN during the entire study period (2003--2012)~~cycles relevant to the two cohorts~~.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). ~~Based on numbers entered in GDB in 2010, we expected to obtain similar numbers of patients in both cohorts.~~

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in ~~SUPPORT~~the SUPPORT trial.[1,2] Specifically, eligible infants were ~~inborn at~~ $24^{0/7}$ to $27^{6/7}$ weeks GA ~~gestational age~~ at birth by best obstetrical estimate, delivered at an NRN center participating in the SUPPORT trial, and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from ~~SUPPORT~~the SUPPORT trial, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, as defined in the SUPPORT trial), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks of PMA, BPD at 36 weeks of PMA, severe ROP as of status, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of ~~SUPPORT~~the SUPPORT trial, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks of PMA or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks of PMA after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until ~~SUPPORT~~the outcome of the SUPPORT trial ~~outcome~~ was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in adjusted means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[4] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but

not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same ~~additional~~ variables that preceded birth as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-14~~3~~] Since we did not adjust p-values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012. This number included outborn infants and infants born in centers that did not participate in the SUPPORT trial. ~~(Figure 1). The primary imbalance was due to outborn status. The~~ The study population included 3,849 inborn infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group (Figure 1).

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

The primary outcome, ~~For the primary outcome, t~~the proportion of DR ETI, decreased from 1313/1617 (81%) before ~~SUPPORT~~the SUPPORT trial to 1539/2232 (69%) after

~~SUPPORT~~the SUPPORT trial, $p < 0.0001$. T~~t~~he adjusted risk of DR ETI significantly decreased after ~~SUPPORT~~the SUPPORT trial, ~~adjusted~~ RR 0.88, 95% confidence interval 0.85-0.91 (Table 2).

~~For s~~Secondary outcomes, including the adjusted risk of BPD/death, severe ROP/death, death before discharge, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 2). By~~In~~ contrast, the adjusted risks of BPD and death at 36 weeks of PMA were not significantly different between groups. The average number of ventilator days among survivors decreased after ~~SUPPORT~~the SUPPORT trial.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ($P<0.001$).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, $p=0.18$).

Discussion: ~~The first paragraph is confusing to me and hard to read—started to reword and realize I am not sure what you are saying. You mention the feasibility trial almost in passing. Should that be somewhere in the methods? I think the discussion still needs some work~~

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of the ~~-~~SUPPORT trial in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before ~~the~~ initiation of ~~the SUPPORT~~the SUPPORT trial. We evaluated changes in ETI for all patients in the cohorts. ~~In this study we compared data before SUPPORT with data after SUPPORT~~ Since weand did not analyze serial changes in the proportion of ETI in each participating center, the data from this study do not allow us to determine when ETI decreased in each center. However, data from other studies provide more precise information on the timing of changes in ETI practices at a subset of the 11 centers that participated in ~~SUPPORT~~the SUPPORT trial~~decrease in ETI in some among these 11 centers~~. The proportion of ETI in one of ~~the other centers participating in SUPPORT~~ participating centers decreased in non-enrolled patients from baseline before the SUPPORT trial (2003-2005) to epochs during the SUPPORT trial (2005-2009) and before its publication (2009-2010), in the absence of any changes in DR policy or practice guidelines.[15] The proportion of DR ETI in this ~~latter~~center decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[15] In another center ~~among the 11 NRN centers~~ that participated in the SUPPORT trial, the proportion of ETI decreased after neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before the SUPPORT trial and before the current study.[16] Five of the 11 centers participated in a~~the~~ feasibility study ~~Feasibility Trial~~ prior to initiation of ~~SUPPORT~~the SUPPORT trial, ~~which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003,[15] i.e., before SUPPORT and before the current study~~.[17] It is possible that ~~Possible explanations for the decrease in~~ -ETI decreased in these 5 centers ~~The proportion of ETI~~

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~~in each center could have decreased with increasing use of CPAP and~~ because of experience with use of T-piece resuscitators ~~connectors~~ and increased use of CPAP in the DR during the feasibility study limiting ~~in the DR during the Feasibility trial, thereby before, during or after participation in the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),[15] during participation or after publication of the results of SUPPORT, limiting any~~ further decrease in DR ETI that could be observed in the current analysis of changes after the SUPPORT trial ~~in the current study. The proportion of ETI in one of the centers participating in SUPPORT decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010), in the absence of any change in DR policy or practice guideline. The proportion of ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[16] In another center among the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after the neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before SUPPORT.[17] The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between the change in the proportion in ETI after SUPPORT and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.~~

The strengths of this study include ~~a large sample size,~~ the use of a prospective database and a large sample size ~~and~~ of inborn patients which limits incomplete/missing data and

Comment [R1]: This sentence is not clear to me, even with Barbara's addition

Comment [R2]: "subset" and the whole sentence may be more confusing than helpful here

information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in ~~SUPPORT~~the SUPPORT trial, and the inclusion of study centers that remained in the NICHD NRN during the entire study period including the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies. Lack of correlation between the change in the proportion in ETI after ~~SUPPORT~~the SUPPORT trial and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions (required to restrict the cohorts to match the SUPPORT enrollment criteria as closely as possible); lack of serial data and lack of data from centers that did not participate in ~~SUPPORT~~the SUPPORT trial ~~but remained in the NRN during the study period~~, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. Earlier studies from the NRN reporting outcomes of infants born prior to 2008 failed to show a decrease in ELBW mortality over time.~~This finding contrasts with previous published reports from the NICHD NRN~~[18,19] ~~,~~but a more recent~~but is consistent with a~~

~~recent~~ review of~~among~~ extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011 did show a decrease in mortality.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with a change in DR ETI, with changes in oxygen ~~O2~~ delivery or oxygen~~O2~~ saturation targets or limits, or with the application in practice of evidence from ~~SUPPORT~~the SUPPORT trial or ~~from~~ other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in ~~SUPPORT~~the SUPPORT trial, the decreased risk observed after ~~SUPPORT~~the SUPPORT trial may be related to practice changes. ~~based on evidence from other studies.~~ Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We have no data on standard clinical practices in the 11 participating NRN centers. We considered conducting a survey of clinical practices but~~in the 11 NRN centers participating in this study. We~~ decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. ~~Experience in the network has shown that such surveys often are not very accurate even on current practices.~~

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This study did not address how generalizable the study results might be to centers that did not participate in ~~SUPPORT~~the SUPPORT trial. It is possible that centers participating in ~~SUPPORT~~the SUPPORT trial might have developed experience with T-piece connectors and with tight oxygen monitoring during ~~SUPPORT~~the SUPPORT trial and thus might

have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before the SUPPORT trial.

Acknowledgments:

Jaclyn M. LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P. Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

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Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

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Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram representing all infants in the GDB during the two study periods and those included in the study

Figure 2. Percent delivery room intubations in~~by~~ pre/post SUPPORT periods for the eleven Neonatal Research Network Centers included in this study

~~Figure 1 If I understand this correctly this flow diagram represents all infants in the GDB during the 2 study periods. would clarify that in a title for the figure~~

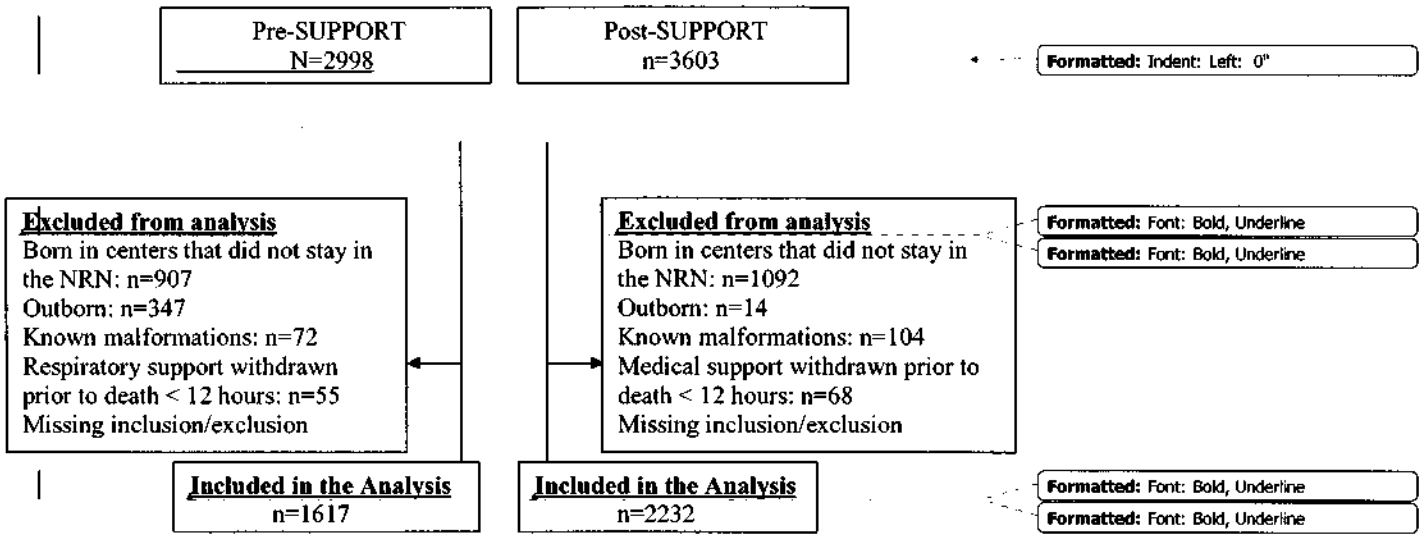

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Figure 2

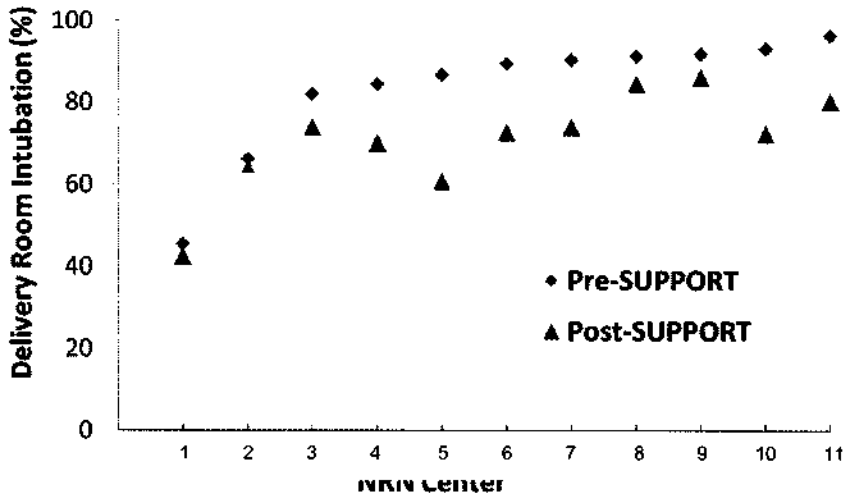
Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
Pre-SUPPORT
Post-SUPPORT

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary and Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Adjusted Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.003
Days on ventilator survivors[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Table 3- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)[4]	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[24]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[24]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

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Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] The p-value for Apgar score is significant despite identical median and IQR because the distribution of the values changed after the SUPPORT trial.

[5][4]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

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From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Proposed revised Jackie Levan"s Manucript for J Peds
Date: Friday, December 06, 2013 9:51:48 AM

Thanks
Luc

Sent from my iPhone

On Dec 6, 2013, at 7:26 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Luc I am ok with the resubmission
>
> Thanks for all the hard work and effort!
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
> 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
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> higginsr@mail.nih.gov
>
> ---
>
> **From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
> **Sent:** Thursday, December 05, 2013 8:43 PM
> **To:** Finer, Neil; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]
> **Subject:** RE: Proposed revised Jackie Levan's Manucript for J Peds
>
> Neil:
> Thanks for your email.
> Data were adjusted for antenatal steroids.
> I asked Lisa Wrage to check if data were adjusted for betamethasone.
> Best regards,
> 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
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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, December 05, 2013 5:29 AM
To: Luc Brion; Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov)
Subject: RE: Proposed revised Jackie Levan's Manucript for J Peds

Hi Luc
Thanks for sending this latest revision
The message is very clear and you have addressed the issues raised by the reviewers
I am always a bit skeptical of adjusted analyses and the particular concern is the increased use of ANS, and especially betamethasone- This looks dramatic but I assume that adjusting for betamethasone was done
I am not sure if it is essential but this issue has always been there for me
In the main trial of course the ANS use was even higher than the post cohort
I think this version is good
Good luck
Neil

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, December 05, 2013 12:16 AM
To: Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie'

(mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); Finer, Neil
Subject: RE: Proposed revised Jackie Levan's Manucript for J Peds

Wally:
Thanks a lot for your suggestion.
I made the change you suggested both in the abstract and the text.
Best regards,
Luc

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, December 04, 2013 2:21 PM
To: Luc Brion; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); nfiner@ucsd.edu
Subject: RE: Proposed revised Jackie Levan's Manucript for J Peds

Hi Luc and Jackie:

I like your changes a lot.

My only important (though simple) suggestion is to keep the unadjusted result for the primary outcome so readers do not have to guess if we had to adjust the results to get significance. In doing this change, it seems like I changed to abstract too much but that was not my intention.

Should you emphasize the raw data on DR intubation in the abstract? This would give the readers exact information of what rates of intubation and effect size we observed.

Wally

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, December 04, 2013 9:58 AM
To: Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Wally Carlo, M.D.; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); Luc Brion; nfiner@ucsd.edu
Subject: FW: Proposed revised Jackie Levan's Manucript for J Peds

I hope all of you had a wonderful Thanksgiving.
Just a reminder, could you please email me your comments by Friday so I can prepare the submission to Journal of Pediatrics.
Thanks a lot
Best regards,
Luc

From: Luc Brion
Sent: Monday, November 25, 2013 2:48 PM
To: Wrage, Lisa Ann (wrage@rti.org); (b)(6) gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); Luc Brion; nfiner@ucsd.edu
Subject: Proposed revised Jackie Levan's Manucript for J Peds

Dear Colleagues:

I attach Jackie LeVan's manuscript (previous submission in September, revised tracked version and revised clean version), and the proposed letter to editor with responses to reviewers.

Please review the attached documents

Could you please send me the comments using wordtracking on the clean version by December 6th.

Once this is completed I will split the manuscript in its parts (text, figures, etc).

Thanks for your collaboration

Best regards and Happy Thanksgiving

Luc

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "srhintz@stanford.edu"
Cc: "Abhik Das (adas@rti.org)"
Subject: NEJM
Date: Friday, December 06, 2013 8:37:37 AM
Attachments: image003.png

Susan

I was on the NEJM site this morning and looked up the SUPPORT Neuro Paper:

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13-15067	Neonatal Neuroimaging and Neurodevelopmental Outcomes at 18-22 Months Corrected Age in Extremely Preterm Infants: The NEURO Study [View Submission]	28-Nov-2013	29-Nov-2013	*Out for Review

The editors sent it for review – we will keep our fingers crossed!!

Thanks for all the hard work!

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Blansfield, Earl (NIH/NICHD) [E]

From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, December 05, 2013 8:09 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Gibbons, Gary (NIH/NHLBI) [E]; Briggs, Josephine (NIH/NCCAM) [E]; Hodes, Richard (NIH/NIA) [E]; Grady, Christine (NIH/CC/BEP) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]; Hardesty, Rebecca (NIH/OD) [C]
Subject: Planning a Workshop on Ethics of Standard of Care Research
Attachments: Draft Precis-for Workshop on Ethical Issues in SoC Research 12-5-2013.docx

Dear Colleagues:

I'm writing to ask you to serve on a planning committee to help design and organize an NIH workshop on the ethical issues involved in standard of care research. The workshop will also be used to explore the relevance, validity, and utility of draft guidance that OHRP will be issuing on IRB review and informed consent considerations in research studying standard of care interventions. OHRP is expected to issue the draft guidance for a 60-day public comment period in January 2014. The workshop will likely be scheduled in late February to coincide with the comment period.

We will schedule an in-person meeting of the planning committee for the first week in January. In the meantime, I would appreciate your thoughts and suggestions via email about 1) the initial workshop design which is laid out in the attached précis; 2) case study topics and presenters; and 3) experts and stakeholders who should be invited to attend. Your feedback on these items by **Wednesday, December 18** would be much appreciated.

If you have any questions or are unable to participate in the planning committee, please let me know.

We look forward to working with you on this important meeting.

Many thanks,

Amy

Amy P. Patterson, M.D.
Associate Director for Science Policy, NIH

Page 1940 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1941 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Archer, Stephanie (NIH/NICHD) [E]
To: Hirschfeld, Steven (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Clinicaltrials.gov | SUPPORT results
Date: Thursday, December 05, 2013 10:04:31 AM

Hi Steven,

Just a reminder about this. We still need to get the SUPPORT results posted on ClinicalTrials.gov.

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

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From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Wednesday, November 13, 2013 2:20 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: clinicaltrials.gov

Will follow up early next when I return from Australia.

Steven Hirschfeld, MD PhD
Captain, USPHS
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
Rapid Deployment Force PHS-1

On Nov 14, 2013, at 1:26 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Steven
> We now have the clinicaltrials.gov NCT numbers for the two studies – inositol and hydrocortisone for hypotension. We still do not have the SUPPORT results posted – do you have a time frame for these results to be posted? Does RTI need to provide a

different format?
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
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higginsr@mail.nih.gov

From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Tuesday, September 24, 2013 12:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: clinicaltrials.gov

Will get back to you on all three. I anticipate that all will be resolved before the end of the this week but will confirm.

Kind regards,

Steven H.

Steven Hirschfeld, MD PhD
Captain, U.S. Public Health Service
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
U.S. Public Health Service Rapid Deployment Force PHS-1

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, September 24, 2013 12:46 PM
To: Hirschfeld, Steven (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: clinicaltrials.gov

Steven
RTI entered two trials into clinicaltrials.gov that have not yet been posted. One is a

(b)(5)

(b)(5)

Also when will the SUPORT data be posted?

Thanks for your help

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Wednesday, September 11, 2013 4:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: clinicaltrials.gov

See below.

Steven Hirschfeld, MD PhD
Captain, U.S. Public Health Service
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
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Chief Medical Officer
U.S. Public Health Service Rapid Deployment Force PHS-1

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, September 11, 2013 2:07 PM
To: Hirschfeld, Steven (NIH/NICHD) [E]
Subject: clinicaltrials.gov

Steven –
Were you able to get the SUPPORT results posted on clinicaltrials.gov?

--Still pendind.

Do you need anything else from the data coordinating center?

--No, so far so good.

Also, once the records are totally switched to RTI, the NRN would like to list the sponsor as "NICHD Neonatal Research Network." There are a few other neonatal research networks around the world and we would like to avoid confusion. Let me know if this is appropriate.

--Seems perfect. Please proceed.

Thanks
Rose

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higginsr@mail.nih.gov

From: Finer, Neil
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics
Date: Thursday, December 05, 2013 6:32:45 AM

Marie
Have you tried to remove the 13 or so infants who died within 48 hrs and always had SpO2 < 80
None of these infants would have been in any of the other trials
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, December 02, 2013 10:14 PM
To: Wally Carlo, M.D.; Rosemary Higgins; Finer, Neil
Subject: RE: Hot Topics

Hi all,

Today is my first day back from (b)(6) and I wanted to follow up to see what needs to be done for the analysis proposed below and what the timeline is. From graphs I have produced previously, our data look very similar to Figure 1 of the BOOST II paper when similar graphing methods are used.

Marie

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

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, October 28, 2013 1:25 PM
To: Rosemary Higgins; Finer, Neil; Gantz, Marie
Subject: FW: Hot Topics

Hi Rose, Neil, and Marie:

One of the concerns of how we reported O2 sat distribution in SUPPORT is that we used median sat per baby rather than % of time at each oxygen saturation.

Enclosed is the BOOST II paper. See how they reported their O2 sat data on Figure 1. Can we get our analysis done that way for Hot Topics? Ben thinks we could compare better O2 separation that way.

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 (b)(6)

From: Stenson, Ben [mailto:Ben.Stenson@nhslothian.scot.nhs.uk]
Sent: Monday, October 28, 2013 12:19 PM
To: Wally Carlo, M.D.
Subject: RE: Hot Topics

Yes.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: 28 October 2013 17:17
To: Stenson, Ben
Subject: RE: Hot Topics

Hi Ben:

Do you mean to report it as you did in your Fig 1 with average % of time spent by infants at each saturation?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
1700 6th Avenue South
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Cell: (b)(6)

From: Stenson, Ben [mailto:Ben.Stenson@nhslothian.scot.nhs.uk]
Sent: Monday, October 28, 2013 11:59 AM
To: Wally Carlo, M.D.
Subject: RE: Hot Topics

Hi Wally
It appears that there are still important differences of view about the effect of the different oximeters on saturation. Did you find out whether you would be able to show the saturation distributions of your Support babies in the same way that was done in BOOST as well as in the way that you did in the support paper so that there is a comparison that goes beyond the median sats histograms?
Ben

****

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****

From:	Luc Brion
To:	Wally Carlo, M.D.; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Subject:	RE: Proposed revised Jackie Levan"s Manucript for J Peds
Date:	Wednesday, December 04, 2013 6:17:08 PM
Attachments:	Jackie LeVan Manuscript NRN 12-04-13.docx Responses to reviewers 120413 rev.docx

Wally:

Thanks a lot for your suggestion.

I made the change you suggested both in the abstract and the text.

Best regards,

Luc

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, December 04, 2013 2:21 PM
To: Luc Brion; Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); nfiner@ucsd.edu
Subject: RE: Proposed revised Jackie Levan's Manucript for J Peds

Hi Luc and Jackie:

I like your changes a lot.

My only important (though simple) suggestion is to keep the unadjusted result for the primary outcome so readers do not have to guess if we had to adjust the results to get significance. In doing this change, it seems like I changed to abstract too much but that was not my intention.

Should you emphasize the raw data on DR intubation in the abstract? This would give the readers exact information of what rates of intubation and effect size we observed.

Wally

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Wednesday, December 04, 2013 9:58 AM
To: Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Wally Carlo, M.D.; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); Luc Brion; nfiner@ucsd.edu
Subject: FW: Proposed revised Jackie Levan's Manucript for J Peds

I hope all of you had a wonderful Thanksgiving.

Just a reminder, could you please email me your comments by Friday so I can prepare the submission to Journal of Pediatrics.

Thanks a lot

Best regards,

Luc

From: Luc Brion
Sent: Monday, November 25, 2013 2:48 PM
To: Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); Luc Brion; nfiner@ucsd.edu
Subject: Proposed revised Jackie Levan's Manucript for J Peds

Dear Colleagues:

I attach Jackie LeVan's manuscript (previous submission in September, revised tracked version and revised clean version), and the proposed letter to editor with responses to reviewers.

Please review the attached documents

Could you please send me the comments using wordtracking on the clean version by December 6th.

Once this is completed I will split the manuscript in its parts (text, figures, etc).

Thanks for your collaboration

Best regards and Happy Thanksgiving

Luc

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1,4] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[5] Waldemar A. Carlo, MD,[6] Abhik Das, PhD,[3] Barbara Stoll, MD,[7] Rosemary D. Higgins, MD,[8] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]Department of Pediatrics, University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3] Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [4]Current affiliation: The Ohio State University - Nationwide Children's Hospital; [5]Division of Neonatology, University of California, San Diego, CA; [6]Division of Neonatology, University of Alabama, Birmingham, AL; [7]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [8]*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu
No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Statement: No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Conflict of Interest Statement: There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 21394 words
Article length: 2,47752 words
Revised 121/0425/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Abstract

Objective

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to test the hypothesis that DR intubation decreased after SUPPORT within NICUs in NRN centers.

Study Design:

This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

Results:

The proportion of DR intubation decreased from 1313/1617 (81%) before SUPPORT to 1539/2232 (69%) after SUPPORT, $p < 0.0001$. After adjustment for baseline variables, the RR (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval 0.85-0.91) was significantly lower than one.

Conclusions:

After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportion of endotracheal 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 seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was 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 risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after SUPPORT in centers that participated in the trial. We hypothesized that after SUPPORT there would be a decrease in ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after SUPPORT. The most important secondary outcomes were the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data is collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data is collected on infants who remain in the hospital at 120 days. We

included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain similar numbers of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in SUPPORT.[1,2] Specifically, eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from SUPPORT, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, 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.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks, BPD at 36 weeks, severe ROP as of status, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.[1,2]

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature

within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes,to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[4] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.[5-13] Since we did not adjust p-values for multiple comparisons, all secondary and

tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). The primary imbalance was due to outborn status. The study population included 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, the proportion of DR ETI decreased from 1313/1617 (81%) before SUPPORT to 1539/2232 (69%) after SUPPORT, $p < 0.0001$. The adjusted risk of DR ETI significantly decreased after SUPPORT, adjusted RR 0.88, 95% confidence interval 0.85-0.91 (Table 2).

For secondary outcomes, the adjusted risk of BPD/death, severe ROP/death, death before discharge, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 2). In contrast, the adjusted risk

of BPD and death at 36 weeks were not significantly different between groups. The average number of ventilator days among survivors decreased after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $27^{6/7}$ weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before the initiation of the SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and did not analyze serial changes in the proportion of ETI in each participating center. The proportion of ETI in each center could have decreased with increasing use of CPAP and experience with T-piece connectors before, during or after participation in the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),[15] during participation or after publication of the results of SUPPORT. The proportion of ETI in one of the centers participating in SUPPORT decreased in non-enrolled patients from baseline before SUPPORT (2003-

2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010), in the absence of any change in DR policy or practice guideline. The proportion of ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).[16] In another center among the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after the neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before SUPPORT.[17] The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between the change in the proportion in ETI after SUPPORT and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

The strengths of this study include a large sample size, the use of a prospective database and of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in SUPPORT, and the inclusion of study centers that remained in the NICHD NRN during the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions; lack of serial data and of data from centers that did not participate in SUPPORT but remained in the NRN during the study period, thereby preventing analysis of secular trends; lack of

information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. This finding contrasts with previous published reports from the NICHD NRN[18,19] but is consistent with a recent review among extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011.[20] Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.[21]

This study was not designed to test whether any change in secondary or tertiary variables were associated with DR ETI, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in SUPPORT, the decreased risk observed after SUPPORT may be related to practice changes based on evidence from other studies. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.[22-31] We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. Experience in the network has shown that such surveys often are not very accurate even on current practices.

This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during SUPPORT and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before SUPPORT.

Acknowledgments:

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

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Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

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The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

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12.

Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

Figure 1

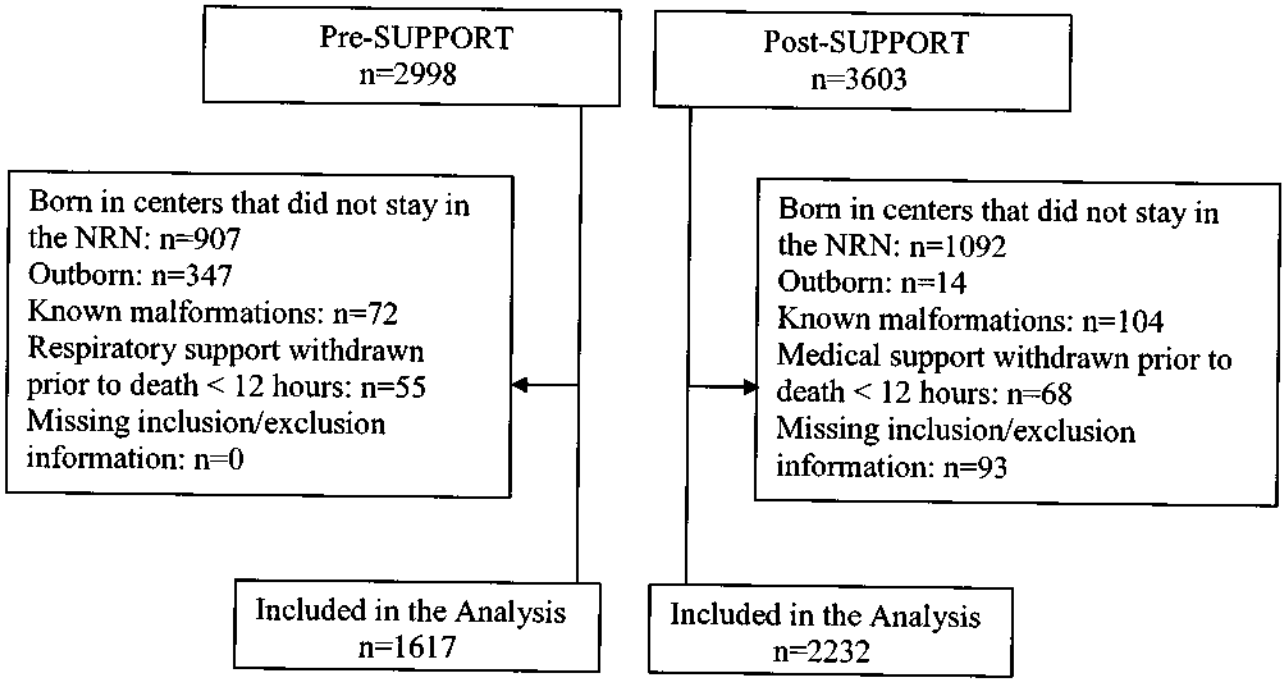
Pre-SUPPORT
n=2998
Post-SUPPORT
n=3603
Born in centers that did not stay in the NRN: n=907
Outborn: n=347
Known malformations: n=72
Respiratory support withdrawn prior to death < 12 hours: n=55
Missing inclusion/exclusion information: n=0
Born in centers that did not stay in the NRN: n=1092
Outborn: n=14
Known malformations: n=104
Medical support withdrawn prior to death < 12 hours: n=68
Missing inclusion/exclusion information: n=93
Included in the Analysis
n=1617
Included in the Analysis
n=2232

Figure 2

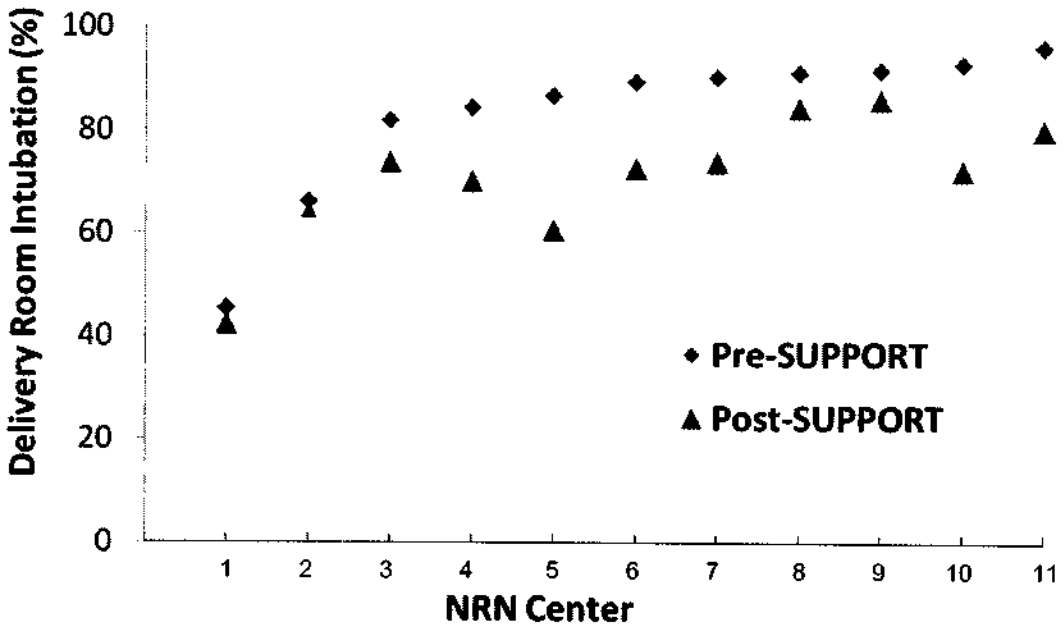
Delivery Room Intubation (%)
100
80
60
40
20
0
1
2
3
4
5
6
7
8
9
10
11
NRN Center
Pre-SUPPORT
Post-SUPPORT

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.

[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary and Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[3]
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP[4]	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.003
Days on ventilator survivors[5]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable). All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

[4] for infants who had an ROP exam with complete information

[5] survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Table 3- Online only. Tertiary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication[3]	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

[1] presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4]survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Tuesday, September 02, 2014~~Wednesday, December 04, 2013Monday, November 25, 2013~~
Clyde J Wright, MD
Associate Editor

William F. Balistreri, M.D.
Editor

Ref.: Ms. No. 20131573
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested.
We have made the revision as short as possible. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text, except for the primary outcome. The Abstract is <250 words. The list of Study Group members and the figures are separate Appendix files. We labeled the third table as online only.
In this revised version we have clarified that this study was designed to test the hypothesis that the proportion of the primary outcome variable, delivery room intubation, would decrease after SUPPORT. This study was not designed to test whether any change in secondary or tertiary variables were associated with the primary outcome variable, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies.
We have entirely revised and streamlined the discussion and emphasized the limitations of the study.
We include an itemized list of responses to the reviewers. Several of these responses are currently not included in the text of the manuscript, to keep in line with your request to make the revision as short as possible. We will be glad to include in the manuscript any additional comments that are currently included only in the itemized list of responses.
We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.
Response: The text of the first version had 2697 words; the revised version has 2477~~52~~ words. The text of the discussion was shortened by ½ page. We have shortened the results section. We have removed from the text all numbers that were in Figure 1 or in the tables, and all comments on unadjusted results for the primary and secondary variables.

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (http://www.jpeds.com/authorinfo).
Response: We have shortened the abstract; it contains 213~~94~~ words. The abstract is structured as indicated.

Please upload the list of Study Group members as a separate Appendix file.
Response: the list of Study Group was moved into a separate file.

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.
Response: Figures are submitted as separate files in doc format.

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."
Response: we have changed online documents as requested.

Itemized responses to Reviewers:

Reviewer #1: This study compared neonatal outcomes in centers of the NICHD neonatal research network before and after their participation in the SUPPORT trial. The methodology and discussion are for the most part adequate.
The investigators found a smaller proportion of infants were intubated in the delivery room, less mortality and reduced rates of the composite outcomes of death or BPD and death or severe ROP. There are a few aspects the investigators should consider to further support their findings.

Comments:
- Can these findings and any possible changes in practice be attributed to the publication of the trial or the actual participation of the trial?
Response: In this study we did not obtain any data during participation in the trial; therefore we cannot respond to that question. This is discussed in the first paragraph of the discussion. We replaced "after publication of SUPPORT" with "after SUPPORT." At least in one center of the Neonatal Research Network (Parkland Memorial Hospital), the proportion of delivery room intubation decreased during participation in SUPPORT (LeVan, Pediatrics 2013, reference 16). In another center the proportion of delivery room intubation decreased before participation in SUPPORT (Narendran 2003, reference 17).

- The manuscript would benefit from data on changes in policies/practice implemented in the 11 centers. These data can support the investigators claim that practice indeed changed following SUPPORT. Please see below.
Response: We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.
We provide information on delivery room practice 2 centers (no change in policy in reference 16, and prospective progressive routine change in practice in reference 17).

- The proportion of DR intubations decreased after SUPPORT. Were any changes in policy actually implemented in these 11 centers? Can this be attributed to other changes implemented (e.g. O2 titration in DR, use of PEEP and T piece resuscitators)?

Response: We are unable to analyze whether changes in DR intubation after SUPPORT were related to changes in DR policy other changes implemented (e.g. O2 titration in DR, use of PEEP and T piece resuscitators). As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- Were the attempts to avoid intubation successful? What proportion of infants remained non-intubated by day 3 or 7 or were never intubated? The difference in proportion of infants receiving surfactant was smaller than the difference in intubations in DR. Was the technique of surfactant administration changed?
Response: The proportion of babies alive and not requiring artificial ventilation at 7 days was 54.1% before SUPPORT and 60.4% after SUPPORT (Table 2). The proportion of babies who were never intubated was: 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group; this post-hoc analysis is included in the result section.
We do not have information on the technique of surfactant administration. As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- The CPAP/surfactant-intubation component of the SUPPORT trial also reported fewer intubations in DR but did not show significant effects on BPD. Can the reduction in BPD after SUPPORT be attributed to changes/improvements in oxygen saturation targeting?
Response: After adjustment for baseline variables, we found no significant change in the frequency of BPD after SUPPORT, but a significant decrease in combined outcome death or BPD. The CPAP/surfactant randomization in SUPPORT did not affect the frequency of BPD or the frequency of death/BPD.
We do not have information on changes/improvements in oxygen saturation targeting. This information is not collected in the GDB. As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

- It is unclear why different exclusion criteria were used for each cohort. The number of infants excluded should be given by cohort. Reasons for withholding or withdrawing support are not mentioned. Were these decisions made before birth? Otherwise these deaths should be reported for each cohort.
Response: Exclusion criteria are different in the 2nd cohort because of a change in GDB field definition. Exclusions for each cohort are now reported separately in the flow diagram. The reasons for withholding or withdrawal of support are not given on the form collected in the GDB.

- Was the analysis adjusted for prenatal factors that clearly differed between cohorts?
Response: Multivariate analysis was adjusted for all factors that differed between cohorts, to which all infants were exposed, and preceded the variable of interest.

Minor comments:
- Gestational age limits in first sentence of Discussion needs to be checked.
Response: Thank you for pointing out this error; we replaced $26^{6/7}$ by $27^{6/7}$

- Table 2 is missing numerator/denominator data in some cells.
Response: We added denominators in all cells.

- 2nd paragraph of Discussion needs to be streamlined and perhaps split by topic.
Response: We have completely revised the discussion. We have split paragraph two. The discussion in streamlined as follows; change in endotracheal intubation, strengths, limitations, changes before/after SUPPORT vs. results of SUPPORT

- The authors state some comparisons of outcome variables reached significance p<0.05) by chance and that they should be considered only exploratory. It is unclear why this would apply only to some variables.
Response: We have clarified this issue. In the statistical analysis we state: "Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory." In the discussion, we have replaced this sentence as follows: "it is likely that some differences reached a significant p value just by chance"

Reviewer #2: The SUPPORT trial was a landmark multicenter factorial-design trial of two interventions for improving outcomes in extremely low gestational age (ELGA) neonates: delivery-room (DR) CPAP vs RD endotracheal intubation (ETI) and surfactant, and a lower vs higher target SpO2 range for oxygen administration. This study reports an analysis of the changes in practice and clinical outcomes that occurred between a 2-year period before and a 3-year period after the publications in 2010 of SUPPORT. It is based on data from 11 centers that contributed to that trial and were members of the NICHD NRN Network during each entire period. This presents an interesting and important opportunity to determine the extent of uptake of important new randomized evidence concerning the clinical effectiveness of these treatments, and to examine the impact on clinical practice and patient outcomes.

Specific comments:
Objectives
1. The primary objective is stated as "to determine if publication of SUPPORT was temporally associated with changes in clinical practice...". "Changes" is vague. What size of absolute effects on the major outcomes of interest were demonstrated in SUPPORT? (These are not stated, but a revised Introduction could make that clear.) At least for the primary outcome, what size of absolute effect did you consider important? What size of absolute effect did your study have the capacity to detect?
Response:
In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%. Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a reduction in ETI from 80% to 60% with an alpha error less than 5% and a power greater than 99%. The sample size was large enough to conduct multivariate analysis with 10 patients per covariate.

Methods
2. Study population, Ascertainment. The eligible infants were born during the stated pre- and post-SUPPORT years. But for each cohort, not all eligible outcomes would have occurred during those stated years. For example, some outcomes for the post-SUPPORT cohort would not be included in the generic database (GDB) during 2003-2012 because they had not yet occurred by end-2012. The duration of follow-up in the GDB to ascertain the later outcomes in the post-SUPPORT cohort needs to be stated. For BPD, severe ROP, days on ventilator, death, was it until 36 wks PMA, hospital discharge, or what?

Response: All this information is included in the GDB. All patients are followed in GDB to ascertain all listed outcomes.
To clarify the exact timing (postnatal age, postmenstrual age or discharge) of each outcome we have revised this paragraph as follows: "Secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, death before discharge or by 36 weeks, BPD, severe ROP before status, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge."
We have also included specific information on GDB in the design section of the manuscript:
The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data is collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data is collected on infants who remain in the hospital at 120 days.

3. Study population, Exclusions. The patient flow diagram (Fig 1) shows the reasons for exclusion of non-eligible patients from each of the two cohorts. Overall, about 42% of the 6601 patients in the two cohorts were not eligible and thus were excluded from analysis. Of potential concern is that there was a higher proportion of ineligible patients in the pre-SUPPORT than in the post-SUPPORT cohort. In fact, the 95% CIs for the respective proportions who were ineligible and thus excluded from analysis do not overlap (by my calculation: pre-SUPPORT, 46.1% [95% CI 44.3, 47.9]; post-SUPPORT, 38.1% [95% CI 36.5, 39.7]). Given this, the specific reasons for exclusion should be given separately for each cohort. Any systematic differences that could bias the comparison of the pre- and post-SUPPORT cohorts as analyzed should be acknowledged when interpreting the results.
Response: The flow diagram was revised to show all exclusions for each cohort separately. The primary imbalance was due to GDB inclusion criteria different re: outborn status.

4. Baseline variables. If the results of SUPPORT are hypothesized to change clinical practice, the baseline variables pertaining to those particular practices need to be identified and ascertained. In the pre-SUPPORT cohort, those critical variables include the numbers and proportion of eligible infants who received DR CPAP rather than DR ETI and surfactant, and the numbers and proportion whose oxygen management was targeted at the lower rather than the higher SpO2 range. I was struck by the absence of those practice variables from the stated list of baseline variables. It was also unclear whether in the post-SUPPORT cohort the numbers and proportion of infants whose oxygen management was targeted at the lower vs higher SpO2 range were to be ascertained.
Response: CPAP and SPO2 target ranges are not part of the variables collected in the GDB. This is listed in limitations of the study.

5. Statistical analyses. For the analysis of change in use of DR CPAP by individual center: the individual centers must have contributed different numbers of patients. Those numbers should be reported. It was not clear if the Spearman correlation was weighted in order to take into account the differing numbers of patients per center.
Response: We calculated a Spearman correlation on center-level aggregate summaries with the center as the unit of analysis. Because the primary interest was in assessing the monotonic association of aggregate center-level rates or prevalence, not in comparing events in individual subjects, weighting these rank-based analyses is not appropriate.

Results

6. a) Primary outcome, DR ETI. This was significantly reduced, adjusted RR 0.88 (95% CI 0.85, 0.91). The absolute risk reduction (ARR), calculated on the numbers presented, was 12.2%, which represents a clinically important effect, NNT = 8. As a matter for Discussion, how does that size of effect compare with what was found in SUPPORT, or was that even reported?

Response: These are not directly comparable. During SUPPORT, all patients in the CPAP arm were started on CPAP immediately and those in the intubation arm were intubated immediately. In contrast, outside a randomized trial such as SUPPORT or COIN, some patients may be started on CPAP or be intubated when respiratory distress develop, some patients may be intubated or placed on CPAP per protocol or policy, and some patients may be started on CPAP and intubated later.

In SUPPORT, the relative risk of intubation in the CPAP arm versus in the intubation arm was 0.37 (0.34–0.42). In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (59%).

Since the Editor has requested to limit the size of the manuscript to a minimum we have not entered absolute risk reduction in the manuscript.

The attempt to further analyze that difference by center did not yield a significant result. In retrospect, it appears that the opportunity to find a significant correlation between the pre- and post-SUPPORT DR ETI rates was limited by the distribution of pre-SUPPORT rates, with 9 of the 11 centers having pre-SUPPORT rates that varied within a narrow range of about 82-97%. Again, a matter possibly for Discussion?

Response: this information was added to the discussion.

b) There was a significant reduction, pre- vs post-SUPPORT, in the composite clinical outcome of BPD or death at 36 weeks, adjusted RR 0.94 (0.89, 0.99). The ARR calculated from table 2 was 5.8%. How does that compare with what was found in SUPPORT?

Response: This study was not designed to test whether any change in secondary or tertiary variables were associated with DR ETI, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies. The composite outcomes in SUPPORT and in the current study are not directly comparable. During SUPPORT, half the patients were randomized to CPAP at the time of randomization and the other half to ETI with surfactant administration, whereas outside a randomized trial such as SUPPORT or COIN, some patients may be started on CPAP either immediately or when respiratory distress develop, whereas other patients may be electively intubated.

In SUPPORT there was no significant adjusted relative risk difference (p=0.07) in death or BPD (defined as O2 need at 36 weeks) between the 2 arms of the study, but the point estimate of the RR was 0.91 (0.83 to 1.01), thus similar to that in the current study.

One possible explanation for the fact that the risk of BPD or death decreased in this study after SUPPORT but not with CPAP during SUPPORT is the larger sample size in this study versus that in SUPPORT (n=3849 vs. 1316). However, several other explanations are possible, including introduction of new policies or changes in processes of care (e.g., antenatal steroids, reduction of exposure to oxygen, lung-protective ventilation strategies, etc).

c) For BPD taken alone, the crude data show a reduction from 50.7% to 45.8%, based evidently on survivors. Calculated from that, the unadjusted RR was 0.90. However the adjusted RR is reported as 1.04 (0.97, 1.1), which is markedly different. Is that an error? Please check.

Response: multivariate analysis took into account multiple baseline variables that were significantly different/ imbalanced by the groups, thereby resulting in a moderate size change in RR. All the numbers were checked once again, and they are correct.

d) Outcomes related to the target SpO2. No results are presented concerning the use of the lower or higher SpO2 target in the pre- vs post-SUPPORT cohorts. However, very highly significant and clinically important reductions were shown for the composite outcome, severe ROP or death (adjusted RR 0.81 [0.73, 0.89], ARR 6.8%; and for severe ROP taken alone, analyzed evidently on survivors (adjusted RR 0.63 [0.52, 0.77]). How do these large reductions compare with the effects of the lower vs higher SpO2 target reported in SUPPORT? (A matter possibly for Discussion?) In the absence of any data on the actual use of the lower vs higher SpO2 target in the pre- and post-SUPPORT cohorts in your study, what if anything can you say about the mechanism of the differences in ROP that you report? What evidence do you have that the differences were in fact associated with the application in practice of evidence from SUPPORT (as distinct, for example, from a secular trend)?
Response: We acknowledge in the discussion that this study was not designed to test whether any change in secondary or tertiary variables were associated with the application in practice of evidence from SUPPORT. On the contrary, many changes over time may be related to other practice changes. We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago. Experience in the network has shown that such surveys often are not very accurate even on current practices.

7. Comments on Tables
Table 1
a) I believe the numbers in brackets are percentages; suggest placing (%) at the top
Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

b) The data are sometimes presented as n, sometimes as n/N. Suggest making that uniform. or explaining in a footnote the convention that was followed, eg that the N is given for the denominator when that differs from the N's given at the top (1617 and 2232). These comments pertain also to Table 2.
Response: We added denominators in all cells.

Table 2
a) As noted above, please check the adjusted RR for BPD. The unadjusted point estimate using the data in this row is 0.90. An adjusted value of 1.04 would indicate a huge effect of adjustemnt.
Response: multivariate analysis took into account multiple baseline variables that were significantly different/ imbalanced by the groups, thereby resulting in a moderate size change in RR. All the numbers were checked once again, and they are correct.

b) p values are given to 4 decimal places. Okay if that's the Journal policy, but I would think 2 or 3 places should be enough.
Response: We removed the 2nd number for values with 4 decimals.

c) Bottom row, days on ventilator Pre- and Post-SUPPORT columns. Shown are 3 numbers, the middle one bracketed. The first number is evidently the mean value. What the second and third represent is

unclear. For continuous data, what one would expect are the mean and some measure of the variance. Clarify.
Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables. (%) for categorical variables. We removed the 2nd number for values with 4 decimals

Appendix table.
This is in rough shape. Previous comments apply here too (multiple instances of previous point c). There is evidently an error in the row for Apgar score, 1 min, median (IQR). Identical values are shown, yet p <0.0001
Response: This information is provided in a footnote, noted in the title of the table: Primary and Secondary Outcomes [1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables. (%) for categorical variables. We removed the 2nd number for values with 4 decimals
The difference in Apgar scores results from a different distribution, as shown by the percentage of values below 3 (see the next line in the table). All the numbers were checked once again, and they are correct.

8. Discussion
a) This is too long - it needs tightening and focus. The present 2nd paragraph extends over more than 2 pages and includes strengths, weaknesses, cautions and speculations. Break up the paragraphs so as to develop one theme per paragraph.
Response: We shortened, and streamlined the discussion. Strengths, weaknesses and other statements have been split into separate paragraphs.

b) In Discussion you acknowledge that "oxygen saturation was not prospectively collected before and after SUPPORT" and thus it is "impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation". Your point is stated unclearly. Do you mean that the SpO2 target policy was not recorded, that summary measures of the actual SpO2 values achieved were not recorded, or both? In any case, this would seem to comprise a critical limitation in this study's ability to relate the finding of a reduction in severe ROP specifically to a change in oxygen targeting driven by the evidence provided by SUPPORT.
Response: Individual oxygen saturations were not recorded in patients who were not enrolled in SUPPORT. This is listed as one limitation of the study.
As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

To compensate somewhat for the lack of individual patient data on target SpO2 and other relevant aspects of clinical-care policies during the pre- and post-SUPPORT periods, might you determine those policies by reviewing each participating center's clinical guidelines for each period? Would those guidelines provide at least group-level information on changes in relevant care-taking goals that were introduced post SUPPORT?
Response: As discussed above, we decided not conduct a survey of clinical practices in the 11 NRN centers participating in this study because it is extremely unlikely that such a survey would accurately reflect what actually happened 10 years ago.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Clinicaltrials.gov | SUPPORT results
Date: Wednesday, December 04, 2013 11:06:13 AM

Still not posted

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: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, December 04, 2013 11:06 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Clinicaltrials.gov | SUPPORT results

Was this resolved?

From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Wednesday, November 13, 2013 2:20 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: clinicaltrials.gov

Will follow up early next when I return from Australia.

Steven Hirschfeld, MD PhD
Captain, USPHS
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
Rapid Deployment Force PHS-1

On Nov 14, 2013, at 1:26 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Steven
> We now have the clinicaltrials.gov NCT numbers for the two studies – inositol and hydrocortisone for hypotension. We still do not have the SUPPORT results posted – do

you have a time frame for these results to be posted? Does RTI need to provide a different format?
Thanks
Rose

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

From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Tuesday, September 24, 2013 12:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: clinicaltrials.gov

Will get back to you on all three. I anticipate that all will be resolved before the end of the this week but will confirm.

Kind regards,

Steven H.

Steven Hirschfeld, MD PhD
Captain, U.S. Public Health Service
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, September 24, 2013 12:46 PM
To: Hirschfeld, Steven (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: clinicaltrials.gov

Steven
RTI entered two trials into clinicaltrials.gov that have not yet been posted. One is a

(b)(5)

(b)(5)

Also when will the SUPORT data be posted?

Thanks for your help

Rose

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From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Wednesday, September 11, 2013 4:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: clinicaltrials.gov

See below.

Steven Hirschfeld, MD PhD
Captain, U.S. Public Health Service
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
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Chief Medical Officer
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, September 11, 2013 2:07 PM
To: Hirschfeld, Steven (NIH/NICHD) [E]
Subject: clinicaltrials.gov

Steven –
Were you able to get the SUPPORT results posted on clinicaltrials.gov?

--Still pendind.

Do you need anything else from the data coordinating center?

--No, so far so good.

Also, once the records are totally switched to RTI, the NRN would like to list the sponsor as "NICHD Neonatal Research Network." There are a few other neonatal research networks around the world and we would like to avoid confusion. Let me know if this is appropriate.

--Seems perfect. Please proceed.

Thanks
Rose

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From:	Luc Brion
To:	Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; "Gantz, Marie" (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion; nfiner@ucsd.edu
Subject:	FW: Proposed revised Jackie Levan"s Manucript for J Peds
Date:	Wednesday, December 04, 2013 10:58:13 AM
Attachments:	Jackie LeVan Manuscript NRN 11-25-13 clean.docx Responses to reviewers 112513 rev.docx JPEDS-S-13-01998[2].pdf Jackie LeVan Manuscript NRN 11-25-13.docx

I hope all of you had a wonderful Thanksgiving.
Just a reminder, could you please email me your comments by Friday so I can prepare the submission to Journal of Pediatrics.
Thanks a lot
Best regards,
Luc

From: Luc Brion
Sent: Monday, November 25, 2013 2:48 PM
To: Wrage, Lisa Ann (wrage@rti.org); (b)(6) @gmail.com; Das, Abhik (adas@rti.org); Myra Wyckoff; Mambarambath Jaleel; 'Gantz, Marie' (mgantz@rti.org); Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Wally Carlo (WCarlo@peds.uab.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Rosemary Higgins (higginsr@mail.nih.gov); Luc Brion; nfiner@ucsd.edu
Subject: Proposed revised Jackie Levan's Manucript for J Peds

Dear Colleagues:
I attach Jackie LeVan's manuscript (previous submission in September, revised tracked version and revised clean version), and the proposed letter to editor with responses to reviewers.
Please review the attached documents
Could you please send me the comments using wordtracking on the clean version by December 6th.
Once this is completed I will split the manuscript in its parts (text, figures, etc).
Thanks for your collaboration
Best regards and Happy Thanksgiving
Luc

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Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

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Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 2000 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act