

**Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms**

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets

	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

\*ARR ( Adjusted relative risk)

\*\* (adjusted mean ± standard error)

\*\*\*(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

**Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups**

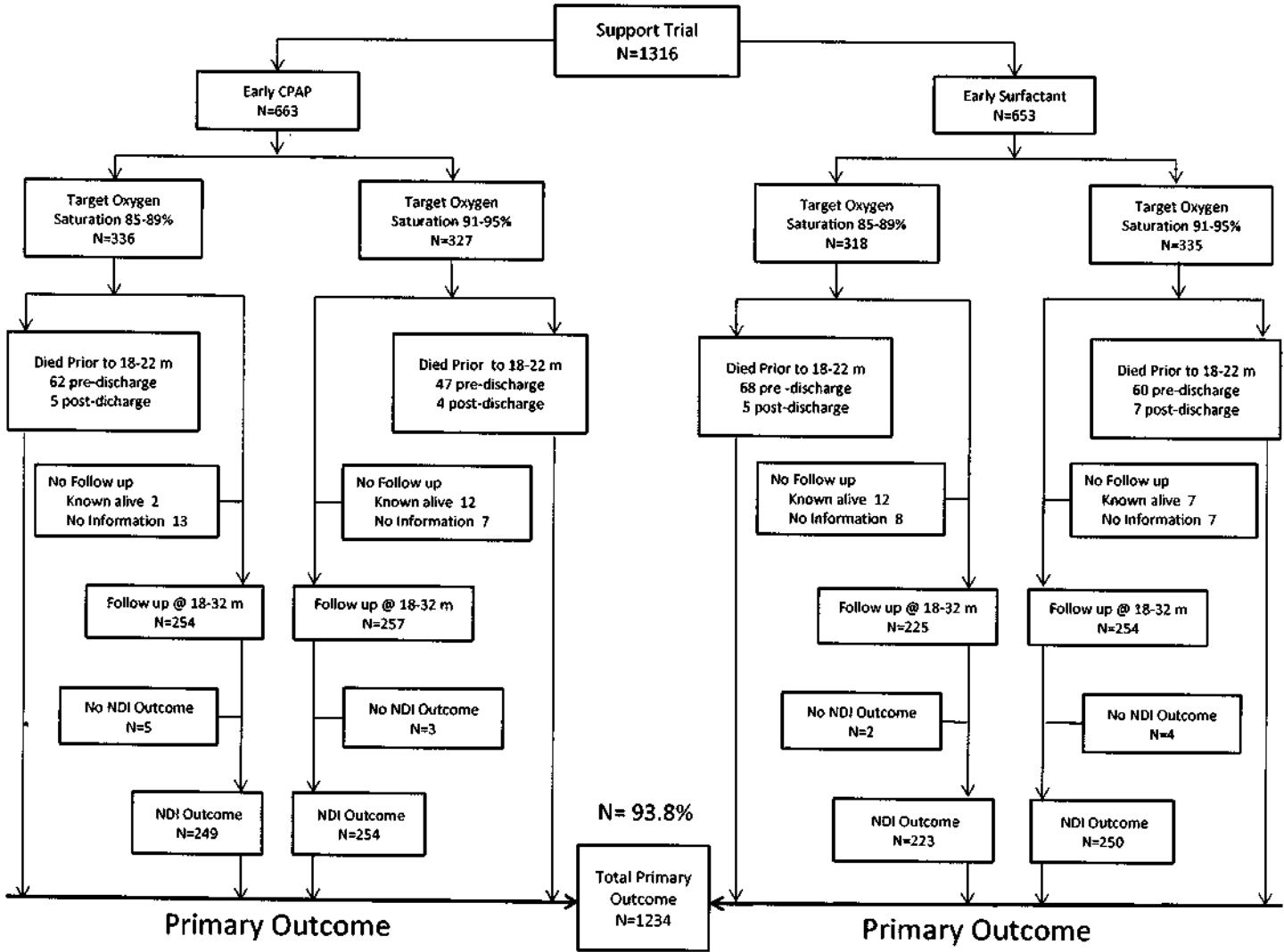
<b>Reason for Eye surgery</b>	<b>Lower N=31</b>	<b>Higher N=67</b>	<b>Total N=98</b>
Retinopathy of Prematurity	26 (84%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)



## References

1. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
2. SUPPORT Manual of Operations, January 4, 2005, Revised March 10, 2005

Figure: Consort Diagram for SUPPORT





YVONNE VAUCHER, M.D., MPH  
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August 11, 2014

Dear Editor:

Thank you for the helpful review of our combined manuscript "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)," (NEJM 12-08506). Following revision we are re-submitting the manuscript as "Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial". We have incorporated all editorial suggestions and have addressed the reviewers' comments. The number of tables/figure and word limits for the title, abstract, and body of the paper comply with the NEJM requirements. The Appendix complies with the supplementary material checklist. Sentences which were added or substantially changed are highlighted.

This study was designed by the SUPPORT subcommittee of the Neonatal Research Network (NRN). Neurodevelopmental outcome data were collected by all participating NRN centers using standardized examinations and data collection tools. Data was submitted to the RTI, the data coordinating center, for data encoding and analysis. Both the NRN and RTI vouch for the data quality and analysis. The paper was written by the two primary authors, Drs. Vaucher and Peralta-Carcelen and the SUPPORT subcommittee. All NRN co-authors reviewed the manuscript and approved publication.

As requested, we are attaching a copy of the study protocol. The study's statistical analysis plan is described in the body of our submitted paper. Details of the limited ventilation strategy and the oximeter blinding strategy are included in the supplementary web appendix.

No part of this manuscript is being considered for publication elsewhere. There are no other manuscripts presently under preparation by the authors or co-authors addressing similar or related research.

**Response to editorial comments:**

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Withheld pursuant to exemption

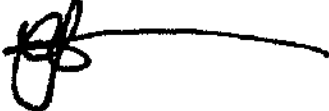
(b)(4)

of the Freedom of Information and Privacy Act

(b)(4)

Thank you for the opportunity to revise and resubmit our manuscript. We believe we have responded satisfactorily to the editor's and reviewer's comments and recommendations.

Sincerely,

A handwritten signature in black ink, consisting of a stylized initial 'Y' followed by a long horizontal stroke.

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatology  
UCSD School of Medicine

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**From:** [Kennedy, Kathleen A](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Tuesday, September 11, 2012 1:47:37 PM

---

Amazing how quickly you get responses. Thanks.

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:** Tuesday, September 11, 2012 12:46 PM  
**To:** Kennedy, Kathleen A  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Onset of ROP Observational Study (SUPPORT Secondary)

Here you go  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Newman, Nancy S [<mailto:Nancy.Newman2@UHhospitals.org>]  
**Sent:** Tuesday, September 11, 2012 1:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)

Hi Rose- I did read the paper when it was originally sent. I do not have any comments. The paper is detailed about the SUPORRT cohort incidence of ROP and I have nothing to add. Thanks for contacting me.

*Nancy*

Nancy Newman, BA, RN  
Case Western Reserve University  
Rainbow Babies and Children's Hospital



nxs5@case.edu

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, September 11, 2012 1:37 PM  
**To:** Nancy Newman  
**Cc:** Kennedy, Kathleen A; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Onset of ROP Observational Study (SUPPORT Secondary)

Nancy

Did you send back comments or should we take your name off the author masthead??

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](mailto:higginsr@mail.nih.gov)

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Friday, July 27, 2012 9:53 AM  
**To:** Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Higgins, Rosemary (NIH/NICHD) [E]; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Das, Abhik; [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [nfinen@ucsd.edu](mailto:nfinen@ucsd.edu); Gantz, Marie; [alaptook@WIHL.org](mailto:alaptook@WIHL.org); [nxs5@cwru.edu](mailto:nxs5@cwru.edu); [wrieh@ucsd.edu](mailto:wrieh@ucsd.edu); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu)  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

**From:** [Kennedy, Kathleen A](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Boilerplate | Kennedy, Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants  
**Date:** Tuesday, September 11, 2012 1:31:24 PM

---

I'm working on a revision of the ROP Secondary paper to send for internal review. After my first email to the author group, I received comments back from everyone except Wade Rich and Nancy Newman. I sent another email to them, again saying that I needed to get comments back if they wanted to be included as authors. I received a reply from Wade (nothing to add) but nothing from Nancy. It's fine with me to remove her name but I don't want to start a battle with the coordinators. What's the precedent here? Do you know if this has been a problem before? Do the coordinators think the authorship rules don't apply to them? (The journals don't see it that way).

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:** Archer, Stephanie (NIH/NICHD) [E] [<mailto:archerst@mail.nih.gov>]  
**Sent:** Monday, July 30, 2012 3:39 PM  
**To:** Kennedy, Kathleen A  
**Subject:** Boilerplate | Kennedy, Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Hi Kathleen,

Sorry to take so long getting this back to you. Based on what you have in the Methods section, I think we can just use the boilerplate from the SUPPORT FU paper (attached). It has already gone through the PIs, so it should be set.

Stephanie

---

Stephanie Wilson Archer  
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
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---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Friday, July 27, 2012 9:53 AM  
**To:** Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Higgins, Rosemary (NIH/NICHD)

[E]; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Das, Abhik; [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Gantz, Marie; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); [nxs5@cwru.edu](mailto:nxs5@cwru.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu)

**Cc:** Archer, Stephanie (NIH/NICHD) [E]

**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

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If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

**From:** [Vaucher, Yvonne](mailto:Yvaucher@uab.edu)  
**To:** [Vaucher, Yvonne](mailto:Yvaucher@uab.edu); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov); [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [Das, Abhik](mailto:Das.Abhik@uab.edu); [Gantz, Marie](mailto:Gantz.Marie@uab.edu); [Finer, Neil](mailto:Finer.Neil@uab.edu); [MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, September 10, 2012 2:59:44 PM  
**Attachments:** [ConsortDiagramSUPPORT\\_10SEP2012\\_RV5.pdf](#)

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Final Consort Diagram

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

**From:** Vaucher, Yvonne  
**Sent:** Monday, September 10, 2012 11:22 AM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Das, Abhik; Gantz, Marie; Finer, Neil; [MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)  
**Subject:** RE: New England Journal of Medicine 12-08506

All,

Yet again.....but this is the last time I sincerely hope.  
Final paper with tables, appendix, consort diagram (as Excel) and letter to editor attached. Waiting to add missing arrows to consort diagram and convert to pdf.  
Appendix is arranged per instructions from NEJM.

Please read letter ASAP as I will upload everything tomorrow AM.

Thanks again,

Yvonne

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, September 10, 2012 5:21 AM  
**To:** Vaucher, Yvonne; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Das, Abhik; Gantz, Marie; Finer, Neil; [MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)  
**Subject:** RE: New England Journal of Medicine 12-08506

Yvonne and all -

Please resubmit and send us what was submitted. We will send to the NRN investigators and co-authors as informational.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

**From:** Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]

Sent: Saturday, September 08, 2012 2:35 AM  
To: wcarlo@peds.uab.edu; Vaucher, Yvonne; Das, Abhik; Gantz, Marie; Finer, Neil; MPeralta@peds.uab.edu; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Re: New England Journal of Medicine 12-08506

All,

Here is the resubmission with answers to editors comments , tables reformatted, web appendix done per specifications and reformatted consort diagram. It just meets the word limit for abstract and paper. The consort diagram is still in Excel. Will put in in PDF.

I will send the letter to editor/reply to reviewers on Monday.

Rose, Does this have to go out to all the authors again before we upload it?

Yvonne

From: <Higgins>, Rose Higgins <hihigginsr@mail.nih.gov> higginsr@mail.nih.gov <mailto:hihigginsr@mail.nih.gov>  
To: Wally Carlo <wcarlo@peds.uab.edu> wcarlo@peds.uab.edu <mailto:wcarlo@peds.uab.edu>, Yvonne Vaucher <yvaucher@ucsd.edu> yvaucher@ucsd.edu <mailto:yvaucher@ucsd.edu>, "Das, Abhik" <adas@rti.org> adas@rti.org <mailto:adas@rti.org>, "Gantz, Marie" <mgantz@rti.org> mgantz@rti.org <mailto:mgantz@rti.org>, Neil Finer <nfiner@ucsd.edu> nfiner@ucsd.edu <mailto:nfiner@ucsd.edu>, "wcarlo@uab.edu" wcarlo@uab.edu <mailto:wcarlo@uab.edu> <mailto:wcarlo@uab.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu> MPeralta@peds.uab.edu <mailto:MPeralta@peds.uab.edu>  
Cc: "Archer, Stephanie (NIH/NICHD) [E]" <Wally Carlo <wcarlo@peds.uab.edu> wcarlo@peds.uab.edu <mailto:wcarlo@peds.uab.edu>, Yvonne Vaucher <yvaucher@ucsd.edu> yvaucher@ucsd.edu <mailto:yvaucher@ucsd.edu>, "Das, Abhik" <adas@rti.org> adas@rti.org <mailto:adas@rti.org>, "Gantz, Marie" <mgantz@rti.org> mgantz@rti.org <mailto:mgantz@rti.org>, Neil Finer <nfiner@ucsd.edu> nfiner@ucsd.edu <mailto:nfiner@ucsd.edu>, "wcarlo@uab.edu" wcarlo@uab.edu <mailto:wcarlo@uab.edu> <mailto:wcarlo@uab.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu> MPeralta@peds.uab.edu <mailto:MPeralta@peds.uab.edu>  
Subject: RE: New England Journal of Medicine 12-08506

I am fine with the changes

Good Luck

Rose

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

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Thursday, August 23, 2012 8:58 PM  
To: Vaucher, Yvonne; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wcarlo@uab.edu <mailto:wcarlo@uab.edu>; Myriam Peralta, M.D.  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 12-08506

Hi Everyone:

I am including minor tracked changes.

Wally

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu] <mailto:[mailto:yvaucher@ucsd.edu]>  
Sent: Thursday, August 23, 2012 4:44 PM  
To: Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu <mailto:wacarlo@uab.edu>; Myriam Peralta, M.D.; Vaucher, Yvonne  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 12-08506

All,

I have attached 1) NEJM Editor letter with reviewer comments, 2) Original NEJM edited manuscript 3) NEJM edited manuscript with my responses to the editor and reviewers 4) Tables in paper and appendix separately as they are in landscape format 5) Consort diagram

- Title Word/space count (70) is now < 75 but still open to suggestions about wording. I do think "neurodevelopmental" should be included in the title rather than just "outcome" as the latter is too general -Authors are corrected (Brenda added)
  - Abstract word count is 249 (limit 250)
  - Paper word count (2807) now exceeds 2700 word limit.
  - Most of the edits were OK.
  - I have highlighted text changes which I have made in response to the editor/reviewers and left comments in place - Figure needs to be professionally redone for spacing, etc in PDF format including title and legend on same page in portrait layout. We are working on this.
  - Tables need to a major reformat to portrait rather than landscape (I am working on this) -Appendix needs to be completed. Acknowledgements moved to Appendix
- All: Please reread for content and see what you think we can cut to get down to the required 2700 maximum word count. We need to cut 1007 words.
- Myriam: Please address Reviewer 1 comment #5 and Reviewer 2 comment on p. 11.
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Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
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UCSD School of Medicine

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**From:** Myriam Peralta, M.D.  
**To:** "Vaucher, Yvonne"; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, September 10, 2012 1:39:19 PM

---

Also two questions marks next to primary outcome at the bottom, thanks.

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Saturday, September 08, 2012 1:35 AM  
To: Wally Carlo, M.D.; Vaucher, Yvonne; Das, Abhik; Gantz, Marie; Finer, Neil; Myriam Peralta, M.D.; higginsr@mail.nih.gov  
Subject: Re: New England Journal of Medicine 12-08506

All,

Here is the resubmission with answers to editors comments , tables reformatted, web appendix done per specifications and reformatted consort diagram. It just meets the word limit for abstract and paper. The consort diagram is still in Excel. Will put in in PDF.

I will send the letter to editor/reply to reviewers on Monday.

Rose, Does this have to go out t all the authors again before we upload it?

Yvonne

From: <Higgins>, Rose Higgins <hibigginsr@mail.nih.gov> [mailto:hibigginsr@mail.nih.gov] <mailto:hibigginsr@mail.nih.gov>  
To: Wally Carlo <wcarlo@peds.uab.edu> [mailto:wcarlo@peds.uab.edu], Yvonne Vaucher <yvaucher@ucsd.edu> [mailto:yvaucher@ucsd.edu], "Das, Abhik" <adas@rti.org> [mailto:adas@rti.org], "Gantz, Marie" <mgantz@rti.org> [mailto:mgantz@rti.org], Neil Finer <nfiner@ucsd.edu> [mailto:nfiner@ucsd.edu], "wacarlo@uab.edu" <mailto:wacarlo@uab.edu> <wacarlo@uab.edu> [mailto:wacarlo@uab.edu], "Myriam Peralta, M.D." <MPeralta@peds.uab.edu> [mailto:MPeralta@peds.uab.edu]  
Cc: "Archer, Stephanie (NIH/NICHD) [E]" <Wally Carlo <wcarlo@peds.uab.edu> [mailto:wcarlo@peds.uab.edu], Yvonne Vaucher <yvaucher@ucsd.edu> [mailto:yvaucher@ucsd.edu], "Das, Abhik" <adas@rti.org> [mailto:adas@rti.org], "Gantz, Marie" <mgantz@rti.org> [mailto:mgantz@rti.org], Neil Finer <nfiner@ucsd.edu> [mailto:nfiner@ucsd.edu], "wacarlo@uab.edu" <mailto:wacarlo@uab.edu> <wacarlo@uab.edu> [mailto:wacarlo@uab.edu], "Myriam Peralta, M.D." <MPeralta@peds.uab.edu> [mailto:MPeralta@peds.uab.edu]  
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I am fine with the changes

Good Luck

Rose

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Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
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Sent: Thursday, August 23, 2012 8:58 PM  
To: Vaucher, Yvonne; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu<mailto:wacarlo@uab.edu>; Myriam Peralta, M.D.  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
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To: Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu<mailto:wacarlo@uab.edu>; Myriam Peralta, M.D.; Vaucher, Yvonne  
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**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, September 10, 2012 2:22:30 PM  
**Attachments:** SUPPORTWeb Appendix 090812Final.docx  
SUPPORTConsortDiagramyey090812.xlsx  
SUPPORTPaperResubmission090912CleanHighlightedTablesNEJM090812Final.docx  
SUPPORTEditorialReplyLtrNEJMResubmission090812.docx

---

All,

Yet again.....but this is the last time I sincerely hope.

Final paper with tables, appendix, consort diagram (as Excel) and letter to editor attached. Waiting to add missing arrows to consort diagram and convert to pdf.

Appendix is arranged per instructions from NEJM.

Please read letter ASAP as I will upload everything tomorrow AM.

Thanks again,

Yvonne

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, September 10, 2012 5:21 AM  
**To:** Vaucher, Yvonne; wcarlo@peds.uab.edu; Das, Abhik; Gantz, Marie; Finer, Neil; MPeralta@peds.uab.edu  
**Subject:** RE: New England Journal of Medicine 12-08506

Yvonne and all -

Please resubmit and send us what was submitted. We will send to the NRN investigators and co-authors as informational.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
and Perinatology Branch CDBPM, NIH  
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## **Investigators**

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – William Oh, MD; Angelita M. Hensman, RN BSN; Bonnie E. Stephens, MD; Barbara Alksninis, PNP; Dawn Andrews, RN; Kristen Angela, RN; Susan Barnett, RRT; Bill Cashore, MD; Melinda Caskey, MD; Kim Francis, RN;

Dan Gingras, RRT; Regina A. Gargus, MD FAAP; Katharine Johnson, MD; Shabnam Lainwala, MD; Theresa M. Leach, MEd CAES; Martha R. Leonard, BA BS; Sarah Lillie, RRT; Kalida Mehta; James R. Moore, MD; Lucy Noel; Suzy Ventura; Rachel V. Walden; Victoria E. Watson, MS CAS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

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Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

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National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Rene Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN;

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University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia,

MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O.

Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD;

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University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama

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Lisa Augustino; Julie Babish Johnson, MSW; Erica Burnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen;

Emily Kushner, MA; Joan Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD;

Kelley Yost, PhD.

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Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A.

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Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman,

MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann

Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia

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University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

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Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD;  
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Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children’s National Medical Center;  
Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University  
School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National  
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PhD, The EMMES Corporation; Mary E. D’Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI  
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School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner,  
MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National  
Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester;  
Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman,

### **Methodology for limited ventilator strategy**

#### **CPAP Arm -**

NICU management: CPAP infants could be intubated if they met any of the following criteria: an  $FiO_2 > .50$  required to maintain an indicated  $SpO_2 > 88\%$  for one hour, an arterial  $PaCO_2 > 65$  torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a  $PaCO_2 < 65$  torr with a  $pH > 7.20$ , an  $SpO_2 > 88\%$  with an  $FiO_2 < 50\%$ , a mean airway pressure (MAP)  $< 10$  cm  $H_2O$ , ventilator rate  $< 20$  bpm, an amplitude  $< 2X$  MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

**Surfactant Arm:** All infants were to be extubated within 24 hours of meeting all of the following criteria:  $PaCO_2 < 50$  torr and  $pH > 7.30$ ,  $FiO_2 \leq .35$  with a  $SpO_2 > 88\%$ , a MAP  $< 8$  cm  $H_2O$ , ventilator rate  $< 20$  bpm, an amplitude  $< 2X$  MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.<sup>1</sup>

### **Methodology for oximeter blinding strategy**

Infants were also randomized to a prospective comparison of a lower target  $SpO_2$  range (85% to 89%) with a higher more conventional target  $SpO_2$  range (91% to 95%) until the infant was 36 weeks or no longer received ventilatory support or oxygen.<sup>2</sup>

**Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u> <u>Saturation</u>	<u>Higher</u> <u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) <sup>δ</sup>	849±186	852±193	858±186	844±192
Gestational age (weeks) <sup>δ</sup>	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10 <sup>th</sup> %) <sup>ε</sup>	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male <sup>ε</sup>	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White <sup>ε</sup>	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black <sup>ε</sup>	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic <sup>ε</sup>	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown <sup>ε</sup>	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation <sup>ε</sup>	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any <sup>ε</sup>	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section <sup>ε</sup>	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only <sup>ε</sup>	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married <sup>ε</sup>	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents <sup>ε</sup>	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < highschool	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

**Comment [CS1]:** We ask that table fit on one page in print version and this looks questionable. Recommend shorten number of rows in print version to focus on what you consider the more important variables (eg would remove English as primary language, whether both parents at home (or marriage status.) etc.) Recommend include retain table with all variables in web appendix and in text can refer to this for more details re baseline data.  
  
Also would note in footnote that data are mean ± SD or n (%) (or just % depending on space in the print version.) (and then can remove the details after each entry.)

degree <sup>€</sup>				
Income < \$30,000/year <sup>€</sup>	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language <sup>€</sup>	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP <sup>€</sup>	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD <sup>¶</sup> <sup>€</sup>	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL <sup>€</sup>	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC <sup>€</sup>	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis <sup>€</sup>	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids <sup>€</sup>	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) <sup>δ</sup>	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

<sup>δ</sup> Mean ± SD

<sup>€</sup> no./total no.(%)

<sup>¶</sup> At 36 weeks postmenstrual age

\*p<0.05, \*\* p<0.01, \*\*\*p<0.001 (Comparison for groups within each intervention arm)

Comparisons adjusted for stratification by center and gestational age and for familial clustering

Comment [CGS2]: Per our format for table 1... Also probably useful to specify that this is for comparison between the two groups

**Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT**

<u>24 0/7-25 6/7 weeks</u>	CPAP*	Surfactant *	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07
<u>26 0/7-27 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31



Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

\*no./total no. (%)

\*\* Adjusted Relative Risk ( 95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS**

<u>24 0/7-25 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22
<u>26 0/7-27 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97

NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level $\geq$ 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral palsy	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78

\*no./total no. (%)

\*\* Adjusted Relative Risk ( 95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small

N)

**Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms**

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets

	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

\*ARR ( Adjusted relative risk)

\*\* (adjusted mean ± standard error)

\*\*\*(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

**Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups**

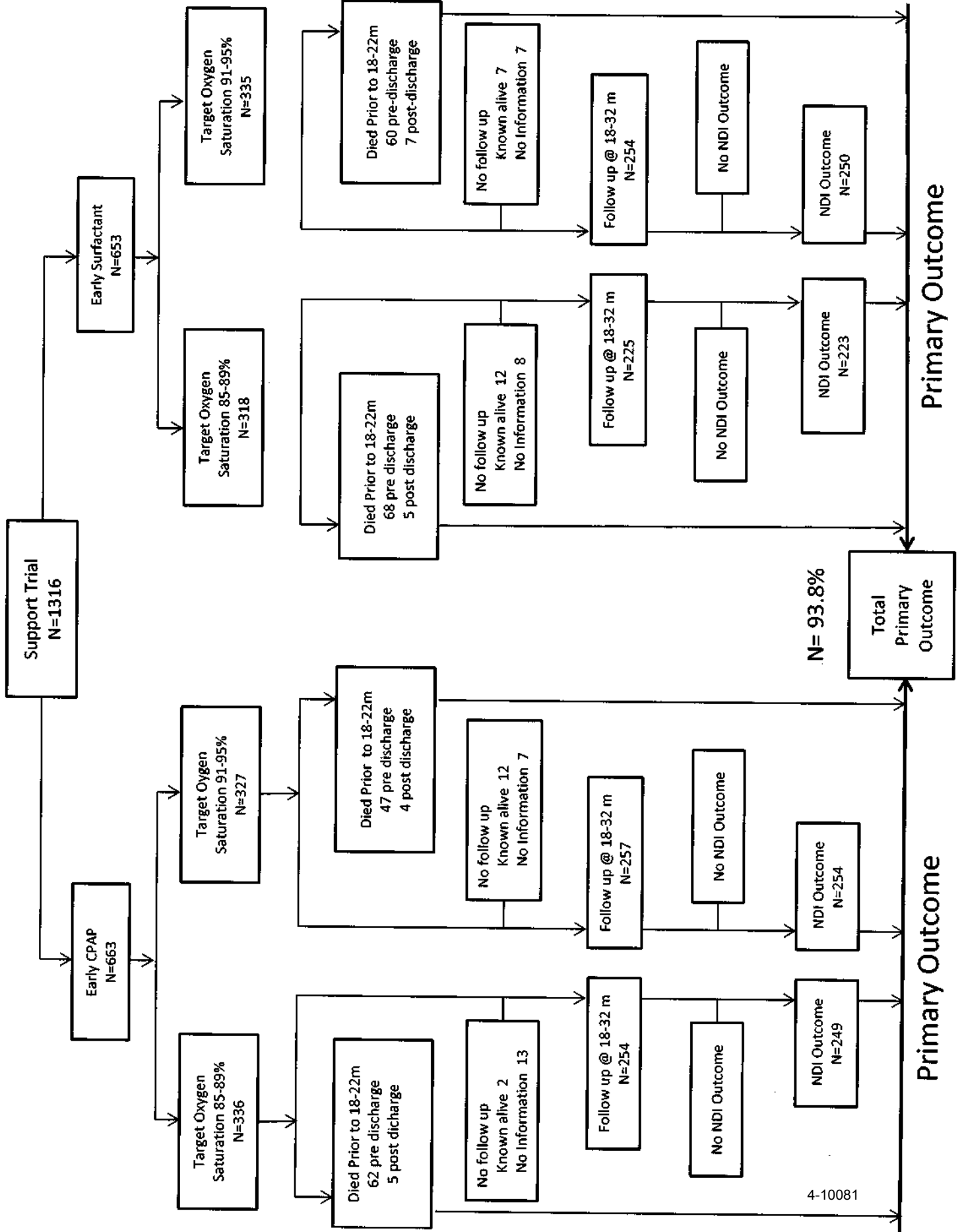
<b>Reason for Eye surgery</b>	<b>Lower N=31</b>	<b>Higher N=67</b>	<b>Total N=98</b>
Retinopathy of Prematurity	26 (83%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)

## References

1. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.

2. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.

Consort Diagram for SUPPORT



N=93.8%

## Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

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**Word count:**

**Text: MeSH terms:**

**Cerebral palsy**

**Infant, Newborn**

**Infant, Low Birth Weight**

**Infant, Extremely Low Birth Weight**

**Infant, Premature**

**Infant, Extremely Low Gestational Age**

**Infant mortality**

**Intellectual disability**

**Intensive care, neonatal**

**Neurodevelopmental outcome**

**Oximetry**

**Randomized controlled trial**

**Continuous Positive Airway Pressure**

**Intubation, intratracheal**

**Pulmonary surfactants/therapeutic use**

**Oxygen inhalation therapy/methods**

**Oxygen administration & dosage**

**Retinopathy of prematurity, epidemiology**

**Child development**

**Developmental disabilities, epidemiology**

**Psychomotor disorders, epidemiology**

**Follow-up studies**

## **ABSTRACT**

**BACKGROUND:** Early results of the SUPPORT trial showed no significant difference in the outcome of death or BPD between infants receiving early CPAP versus early surfactant, and showed lower rates of severe retinopathy but higher mortality with lower (versus higher) oxygen saturation targets. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI).

**METHODS:** Infants born at 24 0/7 through 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP with a limited ventilation strategy versus early surfactant administration and to lower (85-89%) versus higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months corrected age.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants; 93.6% (990/1058) of survivors were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621)] of infants in the CPAP group vs. 29.9% (183/613) in the surfactant group (RR 0.93, 95% CI 0.78 to 1.1, p=0.38); and in 30.2% (185/612)] of the lower oxygen saturation group versus 27.5% (171/622)] of the higher oxygen saturation groups (RR 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality was greater in the lower oxygen saturation group (18.2% versus 22.1%; RR 1.25, 95% CI 1.004 to 1.55, p=0.046).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

Word Count: 249

## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have not demonstrated significant reductions in mortality and morbidity or improved developmental outcomes with any of these treatments.<sup>13-17</sup> Likewise, we previously reported results of the multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants (24 through 27 weeks gestation), demonstrating that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth, as compared with early intubation and surfactant administration, did not reduce rates of death or BPD or other major morbidities at 36 weeks postmenstrual age.<sup>18</sup>

Although for many preterm oxygen supplementation is necessary for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between infants randomized to a lower (85-89%) versus higher (91-95%) oxygen saturation target. However, the risk of retinopathy of prematurity among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

We now report results of our longer term follow-up of the infants in SUPPORT, assessing whether 1) early, non-invasive CPAP with a limited ventilation strategy, compared to early surfactant administration and 2)

lower, compared to higher, oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age(CA).

## **METHODS**

### Study Design

SUPPORT was a randomized controlled trial including 1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, who were enrolled at delivery. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation.<sup>18</sup> Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygen saturation target group) using specially designed blinded oximeters.<sup>24</sup> Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18,24</sup> The trial was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

## Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability. Cognitive function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>26</sup> Moderate to severe cerebral palsy was defined as a nonprogressive disorder having abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture which was associated with a GMFCS  $\geq 2$ .<sup>27,28</sup> Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification, and visual impairment, defined as vision  $< 20/200$ ), were based upon examination and parental report.

Certified research staff collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, sex, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage or periventricular leukomalacia, late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Socioeconomic data were updated during the 18-22 month visit; these data were used if data from the neonatal period were not available.

## Outcome

The pre-specified, primary composite outcome for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score < 70, GMFCS  $\geq$  2, moderate or severe CP, or hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality and NDI among survivors. Exploratory secondary outcomes included the individual components of NDI, levels of cognitive delay and a comparison of outcomes within higher and lower gestational age strata.

### Statistical Analysis

The sample size calculations were based on Neonatal Research Network data for infants born in the year 2000; details have been previously reported.<sup>18,24</sup> While the sample size for the study was estimated based on hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in the composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Data were entered on standard forms and were transmitted to RTI International, the Data Coordinating Center for the Neonatal Research Network, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson

regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator used to calculate the frequency of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted, where missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes<sup>29</sup>. Two-sided p values of  $< 0.05$  were considered significant for all analyses; no adjustments were made for multiple comparisons.

## RESULTS

The primary composite outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children missing a neurodevelopmental assessment, 33 were known to be alive. A neurodevelopmental assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. The presence or absence of NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months corrected age, mothers of the 68 children who were not assessed were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

Demographic and clinical characteristics of the follow-up population are summarized in Table 1 and Appendix S1. Almost all mothers received antenatal corticosteroids. At follow up there were more small for gestational age children and children with severe ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had necrotizing enterocolitis and less likely to have been exposed to postnatal corticosteroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room; 65% received surfactant with limited ventilation.

#### Primary outcome

The frequency of the composite outcome of death or NDI did not significantly differ between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months corrected age (Table 2 a and b). Results from the sensitivity analysis using multiple imputations were virtually identical to the analysis of the non-missing cases. (Results not shown). There were no significant differences in the primary outcome between treatment groups in subgroup analyses stratified by gestational age at birth (Appendix).

The mortality rate was not significantly different between the CPAP and Surfactant arms but was significantly higher in the lower versus higher oxygen saturation target group. There was no significant interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all  $p$  values  $> 0.7$ ).



**Other outcomes:** The incidences of individual components of NDI [cognitive impairment (BSID-III cognitive composite score < 70), gross motor function level  $\geq 2$ , moderate/severe cerebral palsy, hearing impairment, and blindness] among survivors were not significantly different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Tables 2 and 3). Neither were there differences in individual components of NDI between treatment arms when stratified by gestational age (Appendix). However, in the lower gestational age stratum, mortality was higher in the Surfactant treatment arm compared to the CPAP arm. Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were greater in the higher versus lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye, or other vision impairment did not significantly differ between groups at 18 to 22 months corrected age. (Table 4) There were no significant differences between the CPAP and Surfactant arms or between the lower and higher oxygen saturation target groups in rates of the composite outcome of death or *individual* NDI components (results not shown), mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix). Sixty percent (583/977) of children evaluated at 18-22 months corrected age had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations.

## **DISCUSSION**

In this large multicenter trial of very high risk, extremely premature infants, we found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP versus early intubation and surfactant administration or between those randomized to the lower versus higher oxygen saturation target groups. Consistent with our earlier results, the mortality rate did not differ significantly between infants randomized to CPAP versus surfactant, and remained significantly higher in the lower compared to the higher oxygen saturation target

group.<sup>18,24</sup> There were no significant differences between the early CPAP versus surfactant group, or between the higher versus lower oxygen saturation groups, in the frequencies among survivors of NDI or its components including, severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq 2$ ), hearing impairment, and bilateral blindness.

Recent trials have raised concerns about using lower oxygen saturation targets because of the possibility of increased mortality in extremely premature infants.<sup>21,30</sup> In SUPPORT, mortality during initial hospitalization was increased among neonates randomized to the lower oxygen-saturation target as well as in the most immature gestational age stratum of the surfactant administration group. As previously reported, the causes of death did not differ significantly between the lower and higher oxygen saturation groups.<sup>24</sup> Although significant differences in mortality persisted at 18 to 22 months corrected age, these differences reflected higher mortality that had occurred before hospital discharge. Additional information concerning neurodevelopmental outcome and mortality will be available in 2014 when the results of five individual trials which randomized infants to higher versus lower oxygen saturation targets, including SUPPORT, are combined in a meta-analysis.<sup>31</sup>

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>32,33</sup> In this study, infants in the lower oxygen saturation target arm who survived to discharge had a lower incidence of severe retinopathy of prematurity (8.6% vs. 17.9% in the higher saturation group).<sup>24</sup> Although eye surgery was significantly less frequent in the lower oxygen saturation target group, there were no significant differences between saturation groups in unilateral and bilateral blindness, nystagmus, strabismus or the use of corrective lenses. We did not collect detailed data on visual function at the 18 to 22 months visit.

The strengths of this study include the large initial sample size, providing sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the high percentage of survivors who had comprehensive, standardized neurodevelopmental evaluation at 18-22 months corrected age. Antenatal consent, which is associated with enrollment bias, may limit generalizability.<sup>34,35</sup> In this study, the incidence of NDI in extremely premature infants is substantially lower than that previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>36</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no significant differences between treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome. In comparing several secondary outcomes between treatment groups for both arms of this factorial design trial, no adjustments were made for multiple comparisons; appropriate caution should be used in interpreting the reported results. Neurodevelopmental outcome differences may have been blunted by there being less difference in oxygen saturation between the higher and lower saturation target groups.<sup>24</sup> Although a large proportion of the Early CPAP intervention arm ultimately required intubation for respiratory care, the purpose of SUPPORT was not to compare the outcome of CPAP versus intubation per se, but rather to determine whether an initially less invasive respiratory strategy would improve neurodevelopmental outcome.<sup>18</sup>

In summary, there were no significant differences in the composite outcome of death or NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher oxygen saturation targets. Thus, early CPAP with a limited ventilation strategy can be considered an alternative to early surfactant even in

**infants as immature as 24 weeks. Lower mortality and comparable rates of neurodevelopmental impairment and major adverse visual outcomes at 18-22 months corrected age in the higher oxygen saturation group argue against lower oxygen saturation targets in these extremely preterm infants.**

Word Count: 2685

**Figure: Consort Diagram for SUPPORT**

**Table 1: Demographic and neonatal characteristics of follow-up cohorts**

**Table 2: Primary outcome (Death or NDI) and component outcomes: CPAP vs. Surfactant**

**Table 3: Primary outcome (Death or NDI) and component outcomes: Lower vs. Higher Oxygen Saturation**

**Target groups**

**Table 4: Visual outcome: Lower vs. Higher Oxygen Saturation Target groups**

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Lupton AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.

23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
27. Amiel-Tison C GJ. Neurological Development from Birth to Six Years. Baltimore: The Johns Hopkins University Press; 1998.
28. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8-14.
29. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
30. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
31. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
32. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
33. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
34. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
35. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
36. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.

**Table 1: Demographic and Clinical Characteristics of the Follow-up Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u> <u>Saturation</u>	<u>Higher</u> <u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) <sup>δ</sup>	849±186	852±193	858±186	844±192
Gestational age (weeks) <sup>δ</sup>	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
SGA (birthweight < 10 <sup>th</sup> %) <sup>δ</sup> €	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male <sup>€</sup>	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Multiple gestation <sup>€</sup>	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any <sup>€</sup>	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section <sup>€</sup>	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Severe ROP <sup>€</sup>	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD <sup>€¶</sup>	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL <sup>€</sup>	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC <sup>€</sup>	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis <sup>€</sup>	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids <sup>€</sup>	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months)	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

<sup>δ</sup> Mean ± SD

<sup>€</sup> no./total no.(%)

<sup>δ</sup> birthweight < 10<sup>th</sup> centile

¶ At 36 weeks postmenstrual age; Comparisons adjusted for stratification by center and gestational age and for familial clustering

\*p<0.05, \*\* p<0.01, \*\*\*p<0.001 (Comparison for groups within each intervention arm)



**See web appendix, Table S1 for additional cohort demographics**

**Table 2: Rates and Relative Risks of Death or NDI in the CPAP versus Surfactant Groups**

	<u>CPAP*</u>	<u>Surfactant*</u>	<u>ARR**</u>	<u>p</u>
Death or NDI	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

\*no./total no. (%)

\*\* Adjusted Relative Risk ( 95% CI)

**Table 3: Rates and Relative Risks of Death or NDI in the Lower versus Higher Oxygen Saturation Groups**

	<u>Lower*</u>	<u>Higher*</u>	<u>ARR**</u>	<u>p</u>
Death or NDI	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

\*no./total no. (%)

\*\* Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Table 4: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower*	Higher*	ARR**	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes¶	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes¶	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes¶	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings¶	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Blind in at least one eye¶	5/479 (1.0)	8/511 (1.6)	0.67 (0.22, 2.02)	0.48
Eye surgery€	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002

\*no./total no. (%)

\*\* Adjusted Relative Risk (95% CI)

¶versus normal

€ See web appendix for reasons for surgery

Dear Editor:

Thank you for the helpful review of our combined manuscript "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)," (NEJM 12-08506). Following revision we are re-submitting the manuscript as "**Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial**". We have incorporated all editorial suggestions and have addressed the reviewers' comments. The number of tables/figure and word limits for the title, abstract, and body of the paper comply with the NEJM requirements. The Appendix complies with the supplementary material checklist. Sentences which were added or substantially changed are highlighted.

This study was designed by the SUPPORT subcommittee of the Neonatal Research Network (NRN). Neurodevelopmental outcome data were collected by all participating NRN centers using standardized examinations and data collection tools. Data was submitted to the RTI, the data coordinating center, for data encoding and analysis. Both the NRN and RTI vouch for the data quality and analysis. The paper was written by the two primary authors, Drs. Vaucher and Peralta-Carcelen and the SUPPORT subcommittee. All NRN co-authors reviewed the manuscript and approved publication.

As requested, we are attaching a copy of the study protocol. The study's statistical analysis plan is described in the body of our submitted paper. Details of the limited ventilation strategy and the oximeter blinding strategy are included in the supplementary web appendix.

No part of this manuscript is being considered for publication elsewhere. There are no other manuscripts presently under preparation by the authors or co-authors addressing similar or related research.

**Response to editorial comments:**

(b)(4)



Page 0104 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

(b)(4)

**Thank you for the opportunity to revise and resubmit our manuscript. We believe we have responded satisfactorily to the editor's and reviewer's comments and recommendations.**

**Sincerely,**

**Yvonne E. Vaucher, M.D., M.P.H.  
Professor of Pediatrics  
Division of Neonatology  
UCSD School of Medicine**

**From:** Myriam Peralta, M.D.  
**To:** "Vaucher, Yvonne"; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, September 10, 2012 1:38:21 PM

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Yvonne: a minor comment on the consort diagram. You are missing the arrows on the side of early surfactant after the target oxygen saturation boxes. Also there is a question mark left on the first box on death on the left side that needs to be deleted. Thanks.

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

**From:** Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
**Sent:** Saturday, September 08, 2012 1:35 AM  
**To:** Wally Carlo, M.D.; Vaucher, Yvonne; Das, Abhik; Gantz, Marie; Finer, Neil; Myriam Peralta, M.D.; higginsr@mail.nih.gov  
**Subject:** Re: New England Journal of Medicine 12-08506

All,

Here is the resubmission with answers to editors comments , tables reformatted, web appendix done per specifications and reformatted consort diagram. It just meets the word limit for abstract and paper. The consort diagram is still in Excel. Will put in in PDF.

I will send the letter to editor/reply to reviewers on Monday.

Rose, Does this have to go out t all the authors again before we upload it?

Yvonne

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I am fine with the changes

Good Luck  
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I would like to resubmit the paper by September 6th

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SUPPORTPaperResubmissionwcsccommentswith TablesNEJM090712Final.docx  
SUPPORTWeb Appendix\_090712Final.docx

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All,

Here is the resubmission with answers to editors comments , tables reformatted, web appendix done per specifications and reformatted consort diagram. It just meets the word limit for abstract and paper. The consort diagram is still in Excel. Will put in in PDF.

I will send the letter to editor/reply to reviewers on Monday.

Rose, Does this have to go out t all the authors again before we upload it?

Yvonne

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

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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## **Methodology for limited ventilator strategy**

### **CPAP Arm -**

NICU management: CPAP infants could be intubated if they met any of the following criteria: an  $FiO_2 > .50$  required to maintain an indicated  $SpO_2 > 88\%$  for one hour, an arterial  $PaCO_2 > 65$  torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a  $PaCO_2 < 65$  torr with a  $pH > 7.20$ , an  $SpO_2 > 88\%$  with an  $FiO_2 < 50\%$ , a mean airway pressure (MAP)  $< 10$  cm H<sub>2</sub>O, ventilator rate  $< 20$  bpm, an amplitude  $< 2X$  MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

**Surfactant Arm:** All infants were to be extubated within 24 hours of meeting all of the following criteria:  $PaCO_2 < 50$  torr and  $pH > 7.30$ ,  $FiO_2 \leq .35$  with a  $SpO_2 > 88\%$ , a MAP  $< 8$  cm H<sub>2</sub>O, ventilator rate  $< 20$  bpm, an amplitude  $< 2X$  MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.

These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.<sup>1</sup>

## **Methodology for oximeter blinding strategy**

Infants were also randomized to a prospective comparison of a lower target  $SpO_2$  range (85% to 89%) with a higher more conventional target  $SpO_2$  range (91% to 95%) until the infant was 36 weeks or no longer received ventilatory support or oxygen.<sup>2</sup>

**Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u> <u>Saturation</u>	<u>Higher</u> <u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) <sup>δ</sup>	849±186	852±193	858±186	844±192
Gestational age (weeks) <sup>δ</sup>	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10 <sup>th</sup> %) <sup>ε</sup>	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male <sup>ε</sup>	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White <sup>ε</sup>	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black <sup>ε</sup>	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic <sup>ε</sup>	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown <sup>ε</sup>	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation <sup>ε</sup>	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any <sup>ε</sup>	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section <sup>ε</sup>	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only <sup>ε</sup>	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married <sup>ε</sup>	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents <sup>ε</sup>	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < highschool	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

**Comment [CGS1]:** We ask that table fit on one page in print version and this looks questionable. Recommend shorten number of rows in print version to focus on what you consider the more important variables (eg would remove English as primary language, whether both parents at home (or marriage status...) etc.) Recommend include retain table with all variables in web appendix and in text can refer to this for more details re baseline data.

Also would note in footnote that data are mean ± SD or n (%) (or just % depending on space in the print version...) (and then can remove the details after each entry.)

degree <sup>€</sup>				
Income < \$30,000/year <sup>€</sup>	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language <sup>€</sup>	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP <sup>€</sup>	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD <sup>¶</sup> <sup>€</sup>	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL <sup>€</sup>	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC <sup>€</sup>	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis <sup>€</sup>	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids <sup>€</sup>	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) <sup>δ</sup>	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

<sup>δ</sup> Mean ± SD

<sup>€</sup> no./total no.(%)

<sup>¶</sup> At 36 weeks postmenstrual age

\*p<0.05, \*\* p<0.01, \*\*\*p<0.001 (Comparison for groups within each intervention arm)

Comparisons adjusted for stratification by center and gestational age and for familial clustering

Comment [CG52]: Per our format for table 1.  
Also probably useful to specify that this is for  
comparison between the two groups.

**Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT**

<u>24 0/7-25 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level $\geq$ 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07
<u>26 0/7-27 6/7 weeks</u>	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level $\geq$ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31

Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

\*no./total no. (%)

\*\* Adjusted Relative Risk ( 95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)



**Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS**

<u>24 0/7-25 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22
<u>26 0/7-27 6/7 weeks</u>	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97

NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level $\geq$ 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral palsy	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78

\*no./total no. (%)

\*\* Adjusted Relative Risk ( 95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small

N)

**Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms**

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets

	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

\*ARR ( Adjusted relative risk)

\*\* (adjusted mean ± standard error)

\*\*\*(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

**Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups**

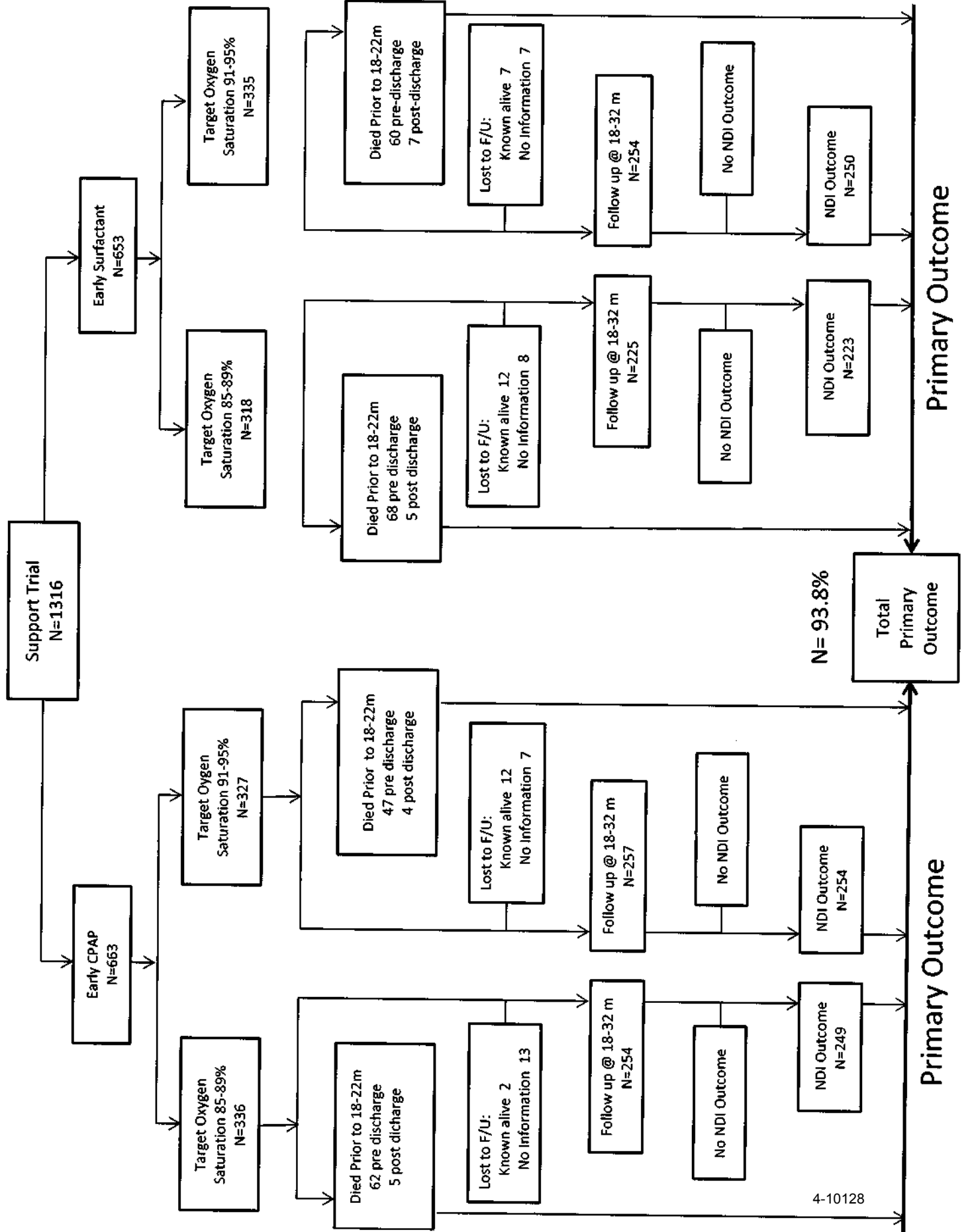
<b>Reason for Eye surgery</b>	<b>Lower N=31</b>	<b>Higher N=67</b>	<b>Total N=98</b>
Retinopathy of Prematurity	26 (83%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)

## References

1. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.

2. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.

Consort Diagram for SUPPORT



## Neurodevelopmental Outcome of the Early CPAP and Pulse Oximetry Trial

Comment [vex 1]: Alternative if we can use the SUPPORT abbreviation in the title

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Word count: 2668

Text: MeSH terms:

Cerebral palsy  
Infant, Newborn  
Infant, Low Birth Weight  
Infant, Extremely Low Birth Weight  
Infant, Premature  
Infant, Extremely Low Gestational Age  
Infant mortality  
Intellectual disability  
Intensive care, neonatal  
Neurodevelopmental outcome  
Oximetry  
Randomized controlled trial  
Continuous Positive Airway Pressure  
Intubation, intratracheal  
Pulmonary surfactants/therapeutic use  
Oxygen inhalation therapy/methods  
Oxygen administration & dosage  
Retinopathy of prematurity, epidemiology  
Child development  
Developmental disabilities, epidemiology  
Psychomotor disorders, epidemiology  
Follow-up studies



## ABSTRACT

**BACKGROUND:** Early results of the SUPPORT trial showed no significant difference in the outcome of death or BPD between infants receiving early CPAP versus early surfactant, and showed lower rates of severe retinopathy but higher mortality with lower (versus higher) oxygen saturation targets. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI).

**METHODS:** Infants born at 24 0/7 through 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP with a limited ventilation strategy versus early surfactant administration and to lower (85-89%) versus higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months corrected age.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants; 93.6% (990/1058) of survivors were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of infants in the CPAP group vs. 29.9% (183/613) in the surfactant group (RR 0.93, 95% CI 0.78 to 1.1, p=0.38); and in 30.2% (185/612) of the lower oxygen saturation group versus 27.5% (171/622) of the higher oxygen saturation groups (RR 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality was greater in the lower oxygen saturation group (18.2% versus 22.1%; RR 1.25, 95% CI 1.004 to 1.55, p=0.046).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

Word Count: 249

## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have not demonstrated significant reductions in mortality and morbidity or improved developmental outcomes with any of these treatments.<sup>13-17</sup> Likewise, we previously reported results of the multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants (24 through 27 weeks gestation), demonstrating that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth, as compared with early intubation and surfactant administration, did not reduce rates of death or BPD or other major morbidities at 36 weeks postmenstrual age.<sup>18</sup>

Comment [CGS2]: OK?

Comment [yev 3]: OK

Although for many preterm oxygen supplementation is necessary for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between infants randomized to a lower (85-89%) versus higher (91-95%) oxygen saturation target. However, the risk of retinopathy of prematurity among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

Comment [CGS4]: OK as shortened? (else can add back other morbidities, but need to reword slightly for clarity)

Comment [yev 5]: OK

We now report results of our longer term follow-up of the infants in SUPPORT, assessing whether 1) early, non-invasive CPAP with a limited ventilation strategy, compared to early surfactant administration and 2)

Comment [CGS6]: OK?

Comment [yev 7]: OK

lower, compared to higher, oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age(CA).

## METHODS

### Study Design

SUPPORT was a randomized controlled trial including 1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, who were enrolled at delivery. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation.<sup>18</sup> Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygen saturation target group) using specially designed blinded oximeters.<sup>24</sup> Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18,24</sup> The trial was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

**Comment [CGS8]:** Note we generally aim to avoid abbreviations that would not be familiar to most readers

**Comment [rev 9]:** OK

**Comment [CGS10]:** Suggest review the details of the limited vent strategy and re the oximeter blinding strategy, in supp web appendix (so readers don't need to go to prior publications to review this..) and then refer to Supp Web appendix for details

**Comment [rev 11]:** OK: Will put in Supplement web appendix

### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability. Cognitive function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>26</sup> Moderate to severe cerebral palsy was defined as a nonprogressive disorder having abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture which was associated with a GMFCS  $\geq 2$ .<sup>27,28</sup> Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification, and visual impairment, defined as vision < 20/200), were based upon examination and parental report.

Certified research staff collected demographic and neonatal outcome data using standard NRR definitions. Demographic and outcome data collected included gestational age, birthweight, sex, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage or periventricular leukomalacia, late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Socioeconomic data were updated during the 18-22 month visit; these data were used if data from the neonatal period were not available.

### Outcome

The pre-specified, primary composite outcome for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score < 70, GMFCS  $\geq$  2, moderate or severe CP, or hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality and NDI among survivors. Exploratory secondary outcomes included the individual components of NDI and levels of cognitive delay. Outcomes were also compared for higher and lower gestational age strata

Comment [CGS12]: Clarify if prespecified

Comment [yav 13]: Comparison by gestational age strata was not prespecified

#### Statistical Analysis

The sample size calculations were based on Neonatal Research Network data for infants born in the year 2000; details have been previously reported.<sup>18,24</sup> While the sample size for the study was estimated based on hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in the composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Comment [CGS14]: OK?

Comment [yav 15]: OK

Data were entered on standard forms and were transmitted to RTI International, the Data Coordinating Center for the Neonatal Research Network, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson

regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator used to calculate the frequency of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Comment [CGS16]: OK?

Comment [yew 17]: OK

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted, where missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes<sup>29</sup>. Two-sided p values of < 0.05 were considered significant for all analyses; no adjustments were made for multiple comparisons.

Comment [CGS18]: OK to delete the sentence that followed given comments of the stat reviewer?

Comment [yew 19]: OK

## RESULTS

The primary composite outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children missing a neurodevelopmental assessment, 33 were known to be alive. A neurodevelopmental assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. The presence or absence of NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months corrected age, mothers of the 68 children who were not assessed were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

Demographic and clinical characteristics of the follow-up population are summarized in Table 1 and Appendix

S1. Almost all mothers received antenatal corticosteroids. At follow up there were more small for gestational age children and children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had necrotizing enterocolitis and less likely to have been exposed to postnatal corticosteroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room; 65% received surfactant with limited ventilation.

Comment [CGS20]: OK?

Comment [yav 21]: OK

#### Primary outcome

The frequency of the composite outcome of death or NDI did not significantly differ between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months corrected age (Table 2 a and b). Results from the sensitivity analysis using multiple imputations were virtually identical to the analysis of the non-missing cases. (Results not shown). There were no significant differences in the primary outcome between treatment groups in subgroup analyses stratified by gestational age at birth (Appendix A). The mortality rate was not significantly different between the CPAP and Surfactant arms but was significantly higher in the lower versus higher oxygen saturation target group. There was no significant interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all  $p$  values  $> 0.7$ ).

Other outcomes: The incidences of individual components of NDI [cognitive impairment (BSID-III cognitive composite score < 70), gross motor function level  $\geq$  2, moderate/severe cerebral palsy, hearing impairment, and blindness] among survivors were not significantly different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Tables 2 and 3). Neither were there differences between treatment arms when stratified by gestational age (See Appendix). However, in the lower gestational age stratum, mortality was higher in the Surfactant treatment arm compared to the CPAP arm. Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were greater in the higher versus lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye, or other vision impairment did not significantly differ between groups at 18 to 22 months corrected age. (Table 4) There were no significant differences between the CPAP and Surfactant arms or between the lower and higher oxygen saturation target groups in rates of the composite outcome of death or individual NDI components (results not shown), mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (See Appendix). Sixty percent (583/977) of children evaluated at 18-22 months corrected age had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq$  85) evaluations.

**Comment [CGS22]:** Correct as edited? Else clarify

**Comment [rev 23]:** No were no differences between treatment arms within each of the two GA strata.

**Comment [CGS24]:** As raised by reviewer (and acknowledged in your discussion), available data re visual outcomes are relatively crude. If you have more info re the vis outcomes (as queried by reviewer), recommend include in supp appendix

**Comment [rev 25]:** We do not have additional visual outcome data.

**Comment [rev 26]:**

**Comment [rev 27]:** This was the composite of death or individual components of NDI rather than the composite of death or NDI. This table was included in the original CPAP paper (Table 3) but in the interest of brevity eliminated from the combined resubmission. We could add this if needed to the Appendix.

## DISCUSSION

In this large multicenter trial of very high risk, extremely premature infants, we found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP versus early intubation and surfactant administration or between those randomized to the lower versus higher oxygen saturation target groups. Consistent with our earlier results, the mortality rate did not differ significantly between infants randomized to CPAP versus

**Comment [CGS28]:** OK? (and if yes, insert cross refs)

**Comment [rev 28]:** Added at end of sentence



surfactant, and remained significantly higher in the lower compared to the higher oxygen saturation target group.<sup>18,24</sup> There were no significant differences between the early CPAP versus surfactant group, or between the higher versus lower oxygen saturation groups, in the frequencies among survivors of NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq$  2), hearing impairment, and bilateral blindness.

Recent trials have raised concerns about using lower oxygen saturation targets because of the possibility of increased mortality in extremely premature infants.<sup>21,30</sup> In SUPPORT, death during initial hospitalization was increased among neonates randomized to the lower oxygen-saturation target as well as in the most immature gestational age stratum of the surfactant administration group. As previously reported, the causes of death did not differ significantly between the lower and higher oxygen saturation groups.<sup>24</sup> Although significant differences in mortality in both intervention arms persisted at 18 to 22 months corrected age, these differences reflected the higher mortality which occurred before hospital discharge. Additional information concerning neurodevelopmental outcome and mortality will be available in 2014 when the results of five individual trials which randomized infants to higher versus lower oxygen saturation targets, including SUPPORT, are combined in a meta-analysis.<sup>31</sup>

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>32,33</sup> In this study, infants in the lower oxygen saturation target arm who survived to discharge had a lower incidence of severe retinopathy of prematurity (8.6% vs. 17.9% in the higher saturation group).<sup>24</sup> Although eye surgery was significantly less frequent in the lower oxygen saturation target group, there were no significant differences between saturation groups in unilateral and bilateral blindness, nystagmus, strabismus or the use of corrective lenses.

We did not collect detailed data on visual function at the 18 to 22 months visit.

**Comment [CGS30]:** This additional subgroup analysis might better to belong in a separate short para addressing the CPAP findings and then noting this one subgroup finding.  
It is important also to acknowledge the large number of comparisons you performed and the need to interpret subgroup findings with caution

**Comment [CGS31]:** I think it is important to acknowledge explicitly that the vast majority of deaths had occurred as of the time of the earlier publication (on review of that there were 130 deaths in the lower sat group by hosp discharge vs 107 in higher sat group; at this 18-22 mo f/u, there were 140 and 111, respectively; thus the "continuing" lower mortality is driven by the fact that most deaths occur early.. AS raised by reviewer 2, I think useful to clarify in results the number of death occurring before versus after hospital discharge, and then to include brief comment here re this (espec in view of statistician's comment re acknowledging the marginal p value (the point that this confirmed an earlier finding must also take into account that the numbers did not change much from the earlier time point..))

**Comment [CGS32]:** OK?  
**Comment [rev 33]:** OK

**Comment [CGS34]:** OK?  
**Comment [rev 35]:** OK

The strengths of this study include the large initial sample size, providing sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the high percentage of survivors who had comprehensive, standardized neurodevelopmental evaluation at 18-22

months corrected age. Antenatal consent, which is associated with enrollment bias, may limit generalizability

<sup>34,35</sup> In this study, the incidence of NDI in extremely premature infants is substantially lower than that

previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment,

whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization

may account for the lower incidence of NDI reported here.<sup>36</sup> Although Bayley scores in this study were higher

than previously reported for extremely premature infants, there were no significant differences between

treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected

age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be

followed at school age to evaluate longer-term neurodevelopmental outcome. In comparing several secondary

outcomes between treatment groups for both arms of this factorial design trial, no adjustments were made

for multiple comparisons; appropriate caution should be used in interpreting the reported results.

Neurodevelopmental outcome differences may have been blunted by there being less difference in oxygen

saturation between the higher and lower saturation target groups.<sup>24</sup> Although a large proportion of the Early

CPAP intervention arm ultimately required intubation for respiratory care, the purpose of SUPPORT was not to

compare the outcome of CPAP versus intubation per se, but rather to determine whether an initially less

invasive respiratory strategy would improve neurodevelopmental outcome.<sup>18</sup>

In summary, there were no significant differences in the composite outcome of death or NDI at 18-22 months

corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or

early intubation with surfactant administration and to either lower or higher oxygen saturation targets. Thus,

**Comment [CGS36]:** As space allows, suggest reiterate some limitations noted earlier that would still apply to the f/u results—eg issue of crossover from CPAP to intubation (given pre-birth randomization) and (as raised by editorialist for prior paper) that O2 sats actually ran higher than planned, and less difference between groups than planned...

**Comment [rev 37]:** Done

early CPAP with a limited ventilation strategy can thus be considered an alternative to early surfactant even in infants as immature as 24 weeks. Lower mortality and comparable rates of neurodevelopmental impairment and major adverse visual outcomes at 18-22 months corrected age in the higher oxygen saturation group argue against lower oxygen saturation targets in these extremely preterm infants.

**Comment [CGS38]:** Would be inclined just to note this conclusion without re-emphasizing this subgroup comparison which you will have discussed above..

**Comment [yev 39]:** OK

Word Count: 2692

Figure: Consort Diagram for SUPPORT

Table 1: Demographic and neonatal characteristics of follow-up cohorts

Table 2: Primary outcome (Death or NDI) and component outcomes: CPAP vs. Surfactant

Table 3: Primary outcome (Death or NDI) and component outcomes: Lower vs. Higher Oxygen Saturation

Target groups

Table 4: Visual outcome: Lower vs. Higher Oxygen Saturation Target groups

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPIcure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Lupton AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Ulado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.

23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
27. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
28. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8-14.
29. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
30. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
31. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
32. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
33. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
34. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
35. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
36. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;in press.

**Table 1: Demographic and Clinical Characteristics of the Follow-up Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower</u> <u>Saturation</u>	<u>Higher</u> <u>Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams) <sup>δ</sup>	849±186	852±193	858±186	844±192
Gestational age (weeks) <sup>δ</sup>	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
SGA (birthweight < 10 <sup>th</sup> %) <sup>ε</sup>	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male <sup>ε</sup>	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Multiple gestation <sup>ε</sup>	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any <sup>ε</sup>	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section <sup>ε</sup>	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Severe ROP <sup>ε</sup>	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD <sup>ε¶</sup>	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL <sup>ε</sup>	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC <sup>ε</sup>	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis <sup>ε</sup>	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids <sup>ε</sup>	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months)	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

<sup>δ</sup> Mean ± SD

<sup>ε</sup> no./total no.(%)

<sup>¶</sup> At 36 weeks postmenstrual age; Comparisons adjusted for stratification by center and gestational age and for familial clustering

\*p<0.05, \*\* p<0.01, \*\*\*p<0.001 (Comparison for groups within each intervention arm)

See web appendix, Table S1 for additional cohort demographics

**Comment [OGS40]:** We ask that table fit on one page in print version and this looks questionable. Recommend shorten number of rows in print version to focus on what you consider the more important variables (eg would remove English as primary language, whether both parents at home (or marriage status...) etc...) Recommend include retain table with all variables in web appendix and in text can refer to this for more details re baseline data..

Also would note in footnote that data are mean ± SD or n (%) (or just % depending on space in the print version...) (and then can remove the details after each entry..)

**Comment [rev 41]:** Table shortened; complete demographic table now in Appendix. Mean ± SD and n/total n (%) now in footnotes. Comparison clarified in footnote.

**Comment [OGS42]:** Per our format for table 1.. Also probably useful to specify that this is for comparison between the two groups

**Table 2: Rates and Relative Risks of Death or NDI in the CPAP versus Surfactant Groups**

	<u>CPAP*</u>	<u>Surfactant*</u>	<u>ARR**</u>	<u>p</u>
Death or NDI	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

\*no./total no. (%)

\*\* Adjusted Relative Risk ( 95% CI)

**Comment [CGS43]:** Won't work to have a and b portion of table. Either this needs to be 2 separate tables (as I partially edited to include OR, if does not look too unwieldy, could consider combining by having 7 columns - ie rates in each pair of treatments and their ARR (95% CI) and delete column of p values (can include as you wish in an expanded version in supplementary web appendix

**Comment [CGS44]:** As in above table, just note in footnote that you are reporting no/total no (%) so don't need to list for each entry

**Comment [yew 45]:** Tables separated



**Table 3: Rates and Relative Risks of Death or NDI in the Lower versus Higher Oxygen Saturation Groups**

	<u>Lower*</u>	<u>Higher*</u>	<u>ARR**</u>	<u>P</u>
Death or NDI	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

**Comment [CGS46]:** As in above table, just note in footnote that you are reporting no/total no (%) so don't need to list for each entry

NOTE that if these table numbers change, need to change call outs in text accordingly..

\*no./total no. (%)

\*\* Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and gestational age group)

and familial clustering (except blindness was not adjusted for study center due to small N)

**Table 4: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower*	Higher*	ARR**	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes¶	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes¶	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes¶	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings¶	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Blind in at least one eye¶	5/479 (1.0)	8/511 (1.6)	0.67 (0.22, 2.02)	0.48
Eye surgery€	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002

\*no./total no. (%)

\*\* Adjusted Relative Risk (95% CI)

¶versus normal

€ See web appendix for reasons for surgery

**From:** [Gantz, Marie](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Das, Abhik](#)  
**Subject:** RE: WINFROP and SUPPORT  
**Date:** Friday, September 07, 2012 3:27:20 PM

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Hi Rose,

When you sent the document to Richard, it was sent with the recommendation that his analysis be combined with the ROP analysis I am working on, but after further discussions, we thought it would be a better fit with the growth secondary. I saw emails from Neil, Wally and Abhik that they approved of combining it with the growth secondary, but I wasn't sure if the decision had been made final or if it had been communicated to Richard.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, September 07, 2012 2:04 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik  
**Subject:** RE: WINFROP and SUPPORT

Marie

This was sent to Richard – is this what you mean??

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Friday, September 07, 2012 11:55 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** RE: WINFROP and SUPPORT

Rose,

Have you let Richard Ehrenkranz know about the recommendation to combine his WINROP analysis with the growth secondary? I told him I would follow up with him this week, but I didn't know where we currently stood.

Thanks,  
Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-251-0255

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**From:** Das, Abhik  
**Sent:** Friday, August 31, 2012 9:10 AM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wacarlo@uab.edu](mailto:wacarlo@uab.edu)  
**Cc:** Gantz, Marie  
**Subject:** RE: WINFROP and SUPPORT

Agree as well.

Thanks

Abhik

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Friday, August 31, 2012 9:02 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wacarlo@uab.edu](mailto:wacarlo@uab.edu)  
**Cc:** Gantz, Marie; Das, Abhik  
**Subject:** RE: WINFROP and SUPPORT

I agree. I am ok without a call if we all agree.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
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FAX: 205 934 3100  
Cell: 205 (b)(6)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, August 31, 2012 7:57 AM

**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu))

**Cc:** [mgantz@rti.org](mailto:mgantz@rti.org); Abhik Das ([adas@rti.org](mailto:adas@rti.org))

**Subject:** WINFROP and SUPPORT

Hi Marie spoke with Richard Ehrenkranz about potentially combining his SUPPORT secondary proposal to use the WINROP algorithm along with the SUPPORT growth data. Marie felt that this may better be done with the growth secondary study- would you be ok with this??

Do we need another call?

Thanks k

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

CDBPM, NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** [Vaucher, Yvonne](#)  
**To:** [Finer, Neil](#)  
**Cc:** [Gantz, Marie](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: PAS 2013  
**Date:** Saturday, September 01, 2012 12:51:54 AM

---

Thanks all. Marie, let's star with the same analyses as with the SUPORT paper.

Yvonne

Sent from my iPad

On Aug 28, 2012, at 2:10 PM, "Finer, Neil" <nfiner@ucsd.edu> wrote:

> Many thanks  
> Neil  
>  
> On 8/28/12 1:36 PM, "Gantz, Marie" <mgantz@rti.org> wrote:  
>  
>> Will do. Thanks.  
>>  
>> Marie  
>>  
>> Marie Gantz, Ph.D.  
>> Senior Research Statistician  
>> RTI International  
>> mgantz@rti.org  
>> 828-254-6255  
>>  
>>  
>> -----Original Message-----  
>> From: Finer, Neil [<mailto:nfiner@ucsd.edu>]  
>> Sent: Tuesday, August 28, 2012 2:23 PM  
>> To: Das, Abhik; Gantz, Marie  
>> Cc: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
>> Subject: Re: PAS 2013  
>>  
>> Please make sure Wade is involved with this Neil  
>>  
>> From: <Das>, Abhik Das <adas@rti.org<<mailto:adas@rti.org>>>  
>> Date: Tuesday, August 28, 2012 11:20 AM  
>> To: Marie Gantz <mgantz@rti.org<<mailto:mgantz@rti.org>>>  
>> Cc: Yvonne Vaucher <yvaucher@ucsd.edu<<mailto:yvaucher@ucsd.edu>>>, UCSD  
>> Pediatrics <nfiner@ucsd.edu<<mailto:nfiner@ucsd.edu>>>, Rosemary Higgins  
>> <higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>>  
>> Subject: PAS 2013  
>>  
>> Marie:  
>>  
>> I am assigning you to work with Yvonne on her proposal entitled 'Compare  
>> early childhood neurodevelopmental outcome of 24-25 week gestation ELBW  
>> children enrolled vs. those not-enrolled in SUPPORT Trial'.  
>>  
>> Thanks  
>>

>> Abhik  
>>  
>>  
>> Abhik Das,Ph.D.  
>> Senior Research Statistician  
>> RTI International  
>> 6110 Executive Blvd., Suite 902  
>> Rockville, MD 20852-3903  
>> e-mail: [adas@rti.org](mailto:adas@rti.org)<<mailto:adas@rti.org>>  
>> Phone: 301-770-8214  
>> Fax: 301-230-4646  
>

**From:** [Vaucher, Yvonne](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Finer, Neil](#)  
**Subject:** Re: Support FU paper  
**Date:** Saturday, September 01, 2012 12:14:16 AM

---

I hope to have the paper ready by the end of the week.

Yvonne

Sent from my iPad

On Aug 31, 2012, at 6:36 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

- > How close are we to resubmission?
- > Thanks
- > Rose



**From:** [Vaucher, Yvonne](mailto:Yvaucher@ucsds.edu)  
**To:** [Gantz, Marie](mailto:mgantz@rti.org)  
**Cc:** [Myriam Peralta, M.D.](mailto:MPeralta@peds.uab.edu); [Das, Abhik](mailto:Das, Abhik); [Wally Carlo, M.D.](mailto:WCarlo@uab.edu); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins, Rosemary (NIH/NICHD) [E]); [Finer, Neil; wacarlo@uab.edu](mailto:Finer, Neil; wacarlo@uab.edu); [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer, Stephanie (NIH/NICHD) [E])  
**Subject:** Re: New England Journal of Medicine 12-08506  
**Date:** Friday, August 31, 2012 11:12:30 PM

---

Thanks Marie.

We need to fit the tables on one portrait page. They are presently landscape to fit in all the information. The editor had some suggestions which seem ok to me. Do you have any other recommendations before I reformat the tables?

Sent from my iPad

On Aug 31, 2012, at 3:39 PM, "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)<<mailto:mgantz@rti.org>>> wrote:

My suggested edits and responses to the reviewer are attached, as well as an additional table I produced to address the issue about differences between SES variables at discharge and FU.

Also, I have attached some output I sent Myriam in November about the reasons for eye surgery and a version I just created with the information additionally broken out by SpO2 target group. The issue is that there are differences between eye surgery reported at FU and ROP surgery reported on the SUPP10. I just wanted to let everyone see this in case you think we need to delve into it further, since we are including a table of eye surgery reasons in the appendix. I've made one correction to the current eye surgery reason table in the attached version of the tables. Reasons for eye surgery in this table are from the FU data only (form NF04).

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)<<mailto:mgantz@rti.org>>  
828-254-6255

From: Myriam Peralta, M.D. [<mailto:MPeralta@peds.uab.edu>]  
Sent: Friday, August 24, 2012 6:55 PM  
To: 'Vaucher, Yvonne'; Das, Abhik; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarlo@uab.edu](mailto:wacarlo@uab.edu)<<mailto:wacarlo@uab.edu>>  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 12-08506

Hi Yvonne I added some information to table 3 regarding blindness in at least one eye and I added a table in the Appendix with reasons for the eye surgery. Let me know what do you think. I will try to add a comment regarding this in the paper but will try to limit as much as possible over the weekend and send it to you by Monday thanks.

---

From: Vaucher, Yvonne [<mailto:yvaucher@ucsds.edu>]  
Sent: Friday, August 24, 2012 2:57 PM  
To: Das, Abhik; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarlo@uab.edu](mailto:wacarlo@uab.edu)<<mailto:wacarlo@uab.edu>>; Myriam Peralta, M.D.; Vaucher, Yvonne  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 12-08506

All,

The editor addressed many of the reviewer's questions in their comments and rewrites which I either OK'd or

commented on additionally. I will write the point by point letter with the resubmission.

Editors comments: each addressed in adjacent comments included in revised version included in previous email.

Reviewer 1

1. Rewritten by the editor
2. Rewritten per editor's suggestion
3. < 20/200. Correct as is
4. Done
5. Myriam's input needed
6. Will do when reformatting tables
- 7.

Reviewer 2: (The page numbers in my draft may be different and the reviewers questions were somewhat unclear )

P 6. I will check with Wade about when FUP consent was obtained. Wade is out today.

p.6 Use of later SES variable is not available in the neonatal period: Marie's input needed

p.6. Explanation of components of NDI needed as not all readers will be familiar with the assessment. Unchanged by the editor ( if this is what the reviewer is referring to)

p.7 Is this question in reference to the multiple imputation analyses? Marie's input needed

p.10 We can add this to the figure or to the tables (easier to add to the tables)

8. p.11 Myriam's input needed

Statistical reviewer 1:

Multiple testing issuediscussed at length by Abhik/Marie and the group. Sentence eliminated re number of significant p values and Wally's sentence advising caution in interpretation added in discussion. Marie's input needed

Again: Please read for what can be shortened by about 100 words.

Yvonne

From: Das, Abhik [mailto:adas@rti.org]  
Sent: Friday, August 24, 2012 8:01 AM  
To: Vaucher, Yvonne; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu<mailto:wacarlo@uab.edu>; Myriam Peralta, M.D.  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 12-08506

Yvonne:

Don't you need a point by point response to the reviewers in a cover letter? I did not see that in these attachments.

Thanks

Abhik

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Thursday, August 23, 2012 5:44 PM

To: Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu<mailto:wacarlo@uab.edu>; Myriam Peralta, M.D.; Vaucher, Yvonne  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 12-08506

All,

I have attached 1)NEJM Editor letter with reviewer comments, 2) Original NEJM edited manuscript 3) NEJM edited manuscript with my responses to the editor and reviewers 4) Tables in paper and appendix separately as they are in landscape format 5)Consort diagram

- Title Word/space count (70) is now < 75 but still open to suggestions about wording. I do think "neurodevelopmental" should be included in the title rather than just "outcome" as the latter is too general
  - Authors are corrected (Brenda added)
  - Abstract word count is 249 (limit 250)
  - Paper word count (2807) now exceeds 2700 word limit.
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  - I have highlighted text changes which I have made in response to the editor/reviewers and left comments in place
  - Figure needs to be professionally redone for spacing, etc in PDF format including title and legend on same page in portrait layout. We are working on this.
  - Tables need to a major reformat to portrait rather than landscape (I am working on this)
  - Appendix needs to be completed. Acknowledgements moved to Appendix
- All: Please reread for content and see what you think we can cut to get down to the required 2700 maximum word count. We need to cut 1007 words.
- Myriam: Please address Reviewer 1 comment #5 and Reviewer 2 comment on p. 11.
- Marie: Please review statistical rewrites and answer question posed by Reviewer 2 on p 6 concerning SES variables and on page 7 re survival of LTFU
- Neil/Wally: Do we need more detailed explanation in the Appendix re oxygen saturation methodology?

I would like to resubmit the paper by September 6th.

I will be OOT hiking in the high sierras breathing rarified air, and thus out of email contact, until September 3rd.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

<PaperSUPPORTResubmissionwcgscmtsNEJM081012YEVRRevision082012without TablesEdits acceptedwc\_MG.docx>  
<MG Responses to reviewers 20120831.doc>  
<T6 With FU vs LTFU (no FU SES) - 31AUG12.doc>  
<Eye surgery reasons - 07NOV11.doc>  
<Eye surgery reasons by oxim - 31AUG12.doc>  
<All Tables 1\_2\_3\_Appendices A\_B\_LandscapeEditorcomments082312\_fromMP20120824\_MG.docx>  
<All Tables 1\_2\_3\_Appendices A\_B\_LandscapeEditorcomments082312\_fromMP20120824\_MG.docx>

**From:** [Finer, Neil](#)  
**To:** [Gantz, Marie](#); [Myriam Peralta, M.D.](#); [Vaucher, Yvonne](#); [Das, Abhik](#); [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHHD\) \[E\]](#); [wacarolo@uab.edu](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHHD\) \[E\]](#)  
**Subject:** Re: New England Journal of Medicine 12-08506  
**Date:** Friday, August 31, 2012 7:08:34 PM

---

Thanks Marie

I will need time to review all of this

Hopefully we can resubmit early next week

Neil

From: <Gantz>, Marie Gantz <[mgantz@rti.org](mailto:mgantz@rti.org)<<mailto:mgantz@rti.org>>>  
Date: Friday, August 31, 2012 3:39 PM  
To: "Myriam Peralta, M.D." <[MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)<<mailto:MPeralta@peds.uab.edu>>>, Yvonne Vaucher <[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)<<mailto:yvaucher@ucsd.edu>>>, Abhik Das <[adas@rti.org](mailto:adas@rti.org)<<mailto:adas@rti.org>>>, Wally Carlo <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)<<mailto:wcarlo@peds.uab.edu>>>, Rosemary Higgins <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>>, UCSD Pediatrics <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)<<mailto:nfiner@ucsd.edu>>>, "wacarolo@uab.edu" <<mailto:wacarolo@uab.edu>>>  
Cc: Stephanie Archer <[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)<<mailto:archerst@mail.nih.gov>>>  
Subject: RE: New England Journal of Medicine 12-08506

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Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
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---

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wacarlo@uab.edu<<mailto:wacarlo@uab.edu>>; Myriam Peralta, M.D.; Vaucher, Yvonne  
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All,

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Editors comments: each addressed in adjacent comments included in revised version included in previous email.

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Sent: Friday, August 24, 2012 8:01 AM

To: Vaucher, Yvonne; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu<<mailto:wacarlo@uab.edu>>; Myriam Peralta, M.D.

Cc: Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: New England Journal of Medicine 12-08506

Yvonne:

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Thanks

Abhik

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Thursday, August 23, 2012 5:44 PM  
To: Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu<mailto:wacarlo@uab.edu>; Myriam Peralta, M.D.; Vaucher, Yvonne  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 12-08506

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- Marie: Please review statistical rewrites and answer question posed by Reviewer 2 on p 6 concerning SES variables and on page 7 re survival of LTFU
- Neil/Wally: Do we need more detailed explanation in the Appendix re oxygen saturation methodology?

I would like to resubmit the paper by September 6th

I will be (b)(6) and thus out of email contact, until September 3rd.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**From:** [Finer, Neil](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally Carlo \(wacarolo@uab.edu\)](#)  
**Cc:** [mgantz@rti.org](#); [Abhik Das \(adas@rti.org\)](#)  
**Subject:** RE: WINFROP and SUPPORT  
**Date:** Friday, August 31, 2012 9:25:38 AM

---

I am OK with this approach

Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, August 31, 2012 5:57 AM  
**To:** Finer, Neil; Wally Carlo ([wacarolo@uab.edu](mailto:wacarolo@uab.edu))  
**Cc:** [mgantz@rti.org](mailto:mgantz@rti.org); [Abhik Das \(adas@rti.org\)](mailto:adas@rti.org)  
**Subject:** WINFROP and SUPPORT

Hi Marie spoke with Richard Ehrenkranz about potentially combining his SUPPORT secondary proposal to use the WINROP algorithm along with the SUPPORT growth data. Marie felt that this may better be done with the growth secondary study- would you be ok with this??

Do we need another call?

Thanks k

Rose

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

**From:** [Wrage, Lisa Ann](#)  
**To:** [Luc Brion; Das, Abhik](#)  
**Cc:** [\(b\)\(6\)@gmail.com](#); [Gantz, Marie](#); [Pablo Sanchez](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT pre-post comparison  
**Date:** Thursday, August 30, 2012 3:45:22 PM

---

Great, that was quick and helpful. I'll get back to you as other questions come up.

Lisa

---

**From:** [Luc Brion \[mailto:Luc.Brion@UTSouthwestern.edu\]](mailto:Luc.Brion@UTSouthwestern.edu)  
**Sent:** Thursday, August 30, 2012 3:43 PM  
**To:** [Wrage, Lisa Ann](#); [Das, Abhik](#)  
**Cc:** [\(b\)\(6\)@gmail.com](#); [Gantz, Marie](#); [Pablo Sanchez](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT pre-post comparison

Lisa:

Thanks for your email.

I would classify as

- 1) 'retinal detachment' either partial or complete retinal detachment (stage 4 or 5 ROP)
- 2) retinal ablation as 'surgery'.

If you have any additional question please let me know.

Luc

Luc P. Brion, MD  
Professor of Pediatrics  
Director, Fellowship Training Program in Neonatal-Perinatal Medicine  
University of Texas Southwestern Medical School Program  
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](mailto:luc.brion@utsouthwestern.edu)

+++++CONFIDENTIALITY NOTICE+++++

All information included in this Communication, including attachments, is strictly confidential and intended solely for use by the addressee(s) identified above, and may contain privileged, confidential, proprietary and/or trade secret information entitled to protection and/or exempt from disclosure under applicable law. If you are not the intended recipient, please take notice that any use, distribution, or copying of this Communication is unauthorized and may be unlawful. If you have received this Communication in error, please notify the sender and delete this Communication from your computer. Please note that any views or opinions presented in this email are solely those of the author and do not necessarily represent those of UT Southwestern. University of Texas Southwestern Medical Center 5323 Harry Hines Blvd., Dallas TX 75390  
[www.utsouthwestern.edu](http://www.utsouthwestern.edu) ( <http://www.utsouthwestern.edu/> )

---

**From:** [Wrage, Lisa Ann \[mailto:wrage@rti.org\]](mailto:wrage@rti.org)  
**Sent:** Thursday, August 30, 2012 2:41 PM  
**To:** [Luc Brion](#); [Das, Abhik](#)  
**Cc:** [doctorlevan@gmail.com](mailto:doctorlevan@gmail.com); [Gantz, Marie](#); [Pablo Sanchez](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT pre-post comparison

RE: severe ROP definition:

I believe so, I just need clarification as to:

- 1) for 'retinal detachment' should I use partial or complete retinal detachment (stage 4 or 5 ROP)  
\*or\* just complete retinal detachment (stage 5 ROP), and



2) is it correct to classify retinal ablation as 'surgery'.

Thank you for the short list of secondary outcomes, very helpful.  
Lisa

---

**From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]  
**Sent:** Thursday, August 30, 2012 3:36 PM  
**To:** Das, Abhik; Wrage, Lisa Ann  
**Cc:** (b)(6)@gmail.com; Gantz, Marie; Pablo Sanchez; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT pre-post comparison

Lisa and Abhik:

I just spoke with Jackie:

Can we define severe ROP as in either eye ROP surgery, retinal detachment, or Avastin injection/anti-VEGF.

Primary outcomes:

- a. **The use of intubation in DR**
- b. The incidence of composite of death or BPD at 36 weeks (O<sub>2</sub> requirement at 36 weeks of postmenstrual age).
- c. The incidence of composite of severe ROP or death before discharge

Here is the subset of most important secondary outcome variables:

- BPD (defined by oxygen requirement at 36 weeks)
- **Mortality rate before discharge**
- **Severe ROP**
- **Surfactant administration**
- Pneumothorax
- Pulmonary hemorrhage
- Use of postnatal steroids for BPD
- Duration of ventilation among survivors;
- Duration of oxygen supplementation among survivors
- Severe intraventricular hemorrhage (grade III or IV)
- Necrotizing enterocolitis (stage 2 or greater)
- Length of stay

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[www.utsouthwestern.edu](http://www.utsouthwestern.edu) ( <http://www.utsouthwestern.edu/> )

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**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Thursday, August 30, 2012 2:22 PM  
**To:** Wrage, Lisa Ann; Luc Brion  
**Cc:** (b)(6)@gmail.com; Gantz, Marie  
**Subject:** RE: SUPPORT pre-post comparison

Luc:

Perhaps you can also weigh in on the questions raised by Lisa and Jackie can chime in later as her communications improve? The main issue to settle at first seems to be creating consistent ROP definitions across time period because of changes to the GDB forms over time.

Thanks

Abhik

---

**From:** Wrage, Lisa Ann  
**Sent:** Thursday, August 30, 2012 3:19 PM  
**To:** 'Luc Brion'  
**Cc:** (b)(6)@gmail.com; Das, Abhik; Gantz, Marie  
**Subject:** RE: SUPPORT pre-post comparison

Ok – thanks for the info. I will hold off temporarily as I don't think that will be too efficient. There are some other things I can do while I am waiting on her reply to my questions. I'm not sure where she is, but it sounds like she's been dealing with Isaac or another similarly bad storm. I will hope for the best for her that her power/internet service comes back soon!

Lisa

---

**From:** Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
**Sent:** Thursday, August 30, 2012 3:03 PM  
**To:** Wrage, Lisa Ann  
**Cc:** (b)(6)@gmail.com  
**Subject:** RE: SUPPORT pre-post comparison

Lisa:

FYI, the best way to reach Jackie at this point is texting her on her cell phone.

Her internet access is limited because of a prior storm in the area.

Luc

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Thursday, August 30, 2012 1:32 PM  
**To:** Luc Brion  
**Subject:** RE: SUPPORT pre-post comparison

Thanks!

---

**From:** Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
**Sent:** Thursday, August 30, 2012 2:30 PM  
**To:** Wrage, Lisa Ann  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; (b)(6)@gmail.com; Das, Abhik; Pablo Sanchez  
**Subject:** RE: SUPPORT pre-post comparison

Lisa:

As you requested, I attach the abstract and the PowerPoint presentation from Jackie's PAS presentation in 2012.

Best regards,  
Luc

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**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; (b)(6)@gmail.com; Das, Abhik; Pablo Sanchez  
**Subject:** RE: SUPPORT pre-post comparison

Absolutely, thanks for the reply.

Lisa

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Could you please include me in your emails on this abstract, since I am the PI on this study.

Thanks a lot and best regards,

Luc

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**Sent:** Thursday, August 30, 2012 1:03 PM  
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**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Wrage, Lisa Ann; Luc Brion; (b)(6)@gmail.com  
**Subject:** RE: SUPPORT pre-post comparison

Abhik: her e-mail is (b)(6)@gmail.com and her cell is (b)(6) -I will speak with luc about this--thanks--pablo

---

**From:** Das, Abhik [adas@rti.org]  
**Sent:** Thursday, August 30, 2012 12:45 PM  
**To:** Pablo Sanchez

**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Wrage, Lisa Ann  
**Subject:** RE: SUPPORT pre-post comparison

Pablo:

We don't seem to have the right email address for Jackie. Can you please add her to this email chain?

Thanks a lot

Abhik

---

**From:** Das, Abhik  
**Sent:** Thursday, August 30, 2012 1:44 PM  
**To:** Wrage, Lisa Ann; 'JACLYN LEVAN'  
**Cc:** 'Pablo.Sanchez@UTSouthwestern.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie  
**Subject:** RE: SUPPORT pre-post comparison

Jackie and Pablo:

As Lisa alludes, we have a tight PAS timeline (this is not the only analysis for PAS that she or any other RTI statistician is involved in) and this is a complicated analysis. So, please let us know if you receive this email and engage with Lisa on her questions so that we can move this forward.

Thanks

Abhik

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**From:** Wrage, Lisa Ann  
**Sent:** Thursday, August 30, 2012 1:39 PM  
**To:** Das, Abhik; 'JACLYN LEVAN'  
**Cc:** 'Pablo.Sanchez@UTSouthwestern.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** RE: SUPPORT pre-post comparison

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Also, due to tight timelines for the abstracts we generally do a subset of the requested analyses – if you could prioritize or

otherwise let me know what specifically would be crucial for the abstract that would be helpful. And I see that you have already done some similar analyses for a single center, it could potentially be helpful to me to see those abstracts as well, if you could share.

I am looking forward to continuing to work on this with you. Feel free to contact me with any questions you may have.  
Thank you,  
Lisa

Lisa Wrage, MPH  
Research Statistician  
Statistics & Epidemiology  
RTI International  
[wrage@rti.org](mailto:wrage@rti.org)  
919-220-2653

---

**From:** Das, Abhik  
**Sent:** Tuesday, August 28, 2012 2:26 PM  
**To:** JACLYN LEVAN  
**Cc:** Wrage, Lisa Ann; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT pre-post comparison

Hello Jackie:

I am assigning Lisa Wrage from RTI as the statistician for this study. Please work with her on the analysis.

Thanks

Abhik

**Abhik Das, Ph.D.**  
**Senior Research Statistician**

---

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**e-mail: [adas@rti.org](mailto:adas@rti.org)**  
**Phone: 301-770-8214**  
**Fax: 301-230-4646**

---

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**From:** Luc Brion  
**To:** Wrage, Lisa Ann  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; (b)(6)@gmail.com; Das, Abhik; Pablo Sanchez  
**Subject:** RE: SUPPORT pre-post comparison  
**Date:** Thursday, August 30, 2012 2:31:23 PM  
**Attachments:** PAS Presentation rev 042812.ppt  
PAS 2012 - Abstract Submission Site 111611.pdf

---

Lisa:

As you requested, I attach the abstract and the PowerPoint presentation from Jackie's PAS presentation in 2012.

Best regards,

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Absolutely, thanks for the reply.

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---

UT Southwestern Medical Center  
The future of medicine, today.

# **Impact of Initiating the NICHD SUPPORT Trial on Management and Outcomes of Gestational Age-Matched Non-Participants**

**Jaclyn LeVan, DO, Myra Wyckoff, MD,  
Mambarath Jaleel, MD, Pablo Sánchez, MD,  
Chul Ahn, PhD, Jeannette Burchfield, RNC,  
Lucy Christie, RNC, and Luc Brion, MD**

**University of Texas Southwestern at Dallas, TX  
Division of Neonatal-Perinatal Medicine**



**All the authors have documented that they have no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.**

# Background

**Patients enrolled in randomized trials may have different outcomes compared with non-participants. This can result from:**

- **Bias**
- **Trial Effect:**
  - **Placebo effect**
  - **Hawthorne effect**
  - **Treatment effect**
  - **Protocol effect**
  - **Care effect.**

# **The NICHD Neonatal Research Network SUPPORT Trial**

- **Infants < 28 wks gestational age (GA) randomized to**
  - **High or low target oxygen saturation range: blinded**
  - **Intubation and surfactant or Continuous Positive Airway Pressure (CPAP) 5 cm H<sub>2</sub>O initiated in delivery room: un-blinded**
- **Rich et al showed evidence for bias but not for trial effect.**

# **Does Initiation of a Randomized Trial Affect Care of Non-Participants?**

- To our knowledge no study has assessed whether observation of short term un-blinded outcomes in a randomized trial affects patient care in non-enrolled patients.**
- This study was designed to assess whether initiation of the SUPPORT trial affected delivery room (DR) management in non-enrolled patients in the absence of any changes in standard of care or initiation of new protocol.**

# Primary Hypothesis

**Initiation of the SUPPORT Trial will result in a 33% relative risk reduction in delivery room intubation rate among non-participants at Parkland Hospital**

- **In eligible, non-enrolled 24-27<sup>6/7</sup> week GA infants**
- **In non-eligible 28-34<sup>6/7</sup> weeks GA infants.**



# Design/Methods

- **Retrospective before-and-after cohort study**
- **Inclusion criteria**
  - **Inborn infants <35 weeks born**
    - **01/2003-06/2005 (Before SUPPORT)**
    - **07/2005-02/2009 (During SUPPORT)**
    - **03/2009-06/2010 (After SUPPORT)**
- **Exclusion criteria**
  - **Infants in SUPPORT trial**
  - **Infants who received comfort care**
  - **Major congenital anomalies**

# Primary Outcome

- **Frequency of intubation in delivery room (DR) adjusted for baseline variables.**
- **Variables were selected based on published data and data from our own unit.**

# Statistics

- **Sample size (power 80%, alpha 0.05):**
  - **24-27 wk: 97 patients per epoch to detect a reduction in intubation from 60% to 40%**
  - **28-34 wk: 1100 patients to detect a reduction in intubation from 10 to 6.7%**
- **Primary outcome:**
  - **Stepwise logistic regression**
- **Secondary outcomes:**
  - **ANOVA and Scheffe**
  - **Chi-square (Fisher exact test; Bonferroni)**
  - **Significant p value indicated as \***
  - **Serial time analysis: 15-month subepochs**

# Results for 24-27 <sup>6/7</sup> Week Infants

<b>EPOCH</b>	<b>1 N=161</b>	<b>2 N=135</b>	<b>3 N=76</b>	<b>P</b>
<b>Intubation in DR</b>	136 (85)	82 (61)*	46 (61)*	<0.001
<b>CPAP in DR</b>	48 (30)	76 (56)*	48 (63)*	<0.001
<b>Intubation in NICU &lt; 4 hrs of age</b>	7 (4)	15 (11)	10 (13)**	0.033
<b>Total Intubation</b>	141 (88)	97 (72)*	56 (73)**	0.002
<b>Surfactant</b>	121 (75)	80 (59)**	50 (66)	0.001
<b>Pneumothorax</b>	11 (7)	13 (10)	14 (18)**	0.022

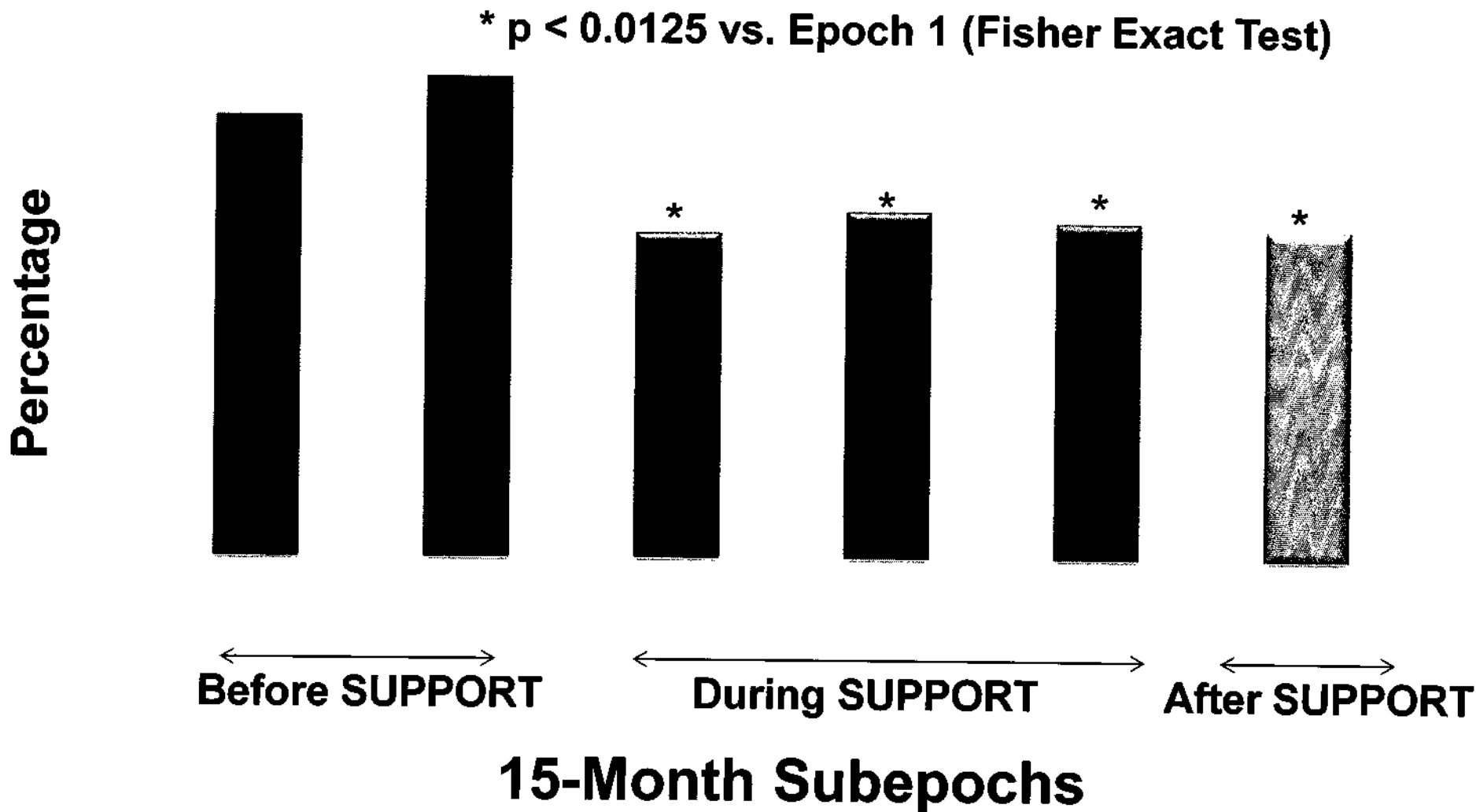
\*  $p \leq 0.001$ , \*\*  $p < 0.025$  vs. Epoch 1

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\*  $p \leq 0.001$ , \*\*  $p < 0.025$  vs. Epoch 1

# DR Intubation Rate Significantly Decreased over Time in 24-27<sup>6/7</sup> Week Infants



# Baseline Characteristics

## 28-34<sup>6/7</sup> Week Infants

<b>EPOCH</b>	<b>1</b> <b>N=951</b>	<b>2</b> <b>N=1657</b>	<b>3</b> <b>N=549</b>
<b>GA (weeks)</b>	32.1±1.8	32.2±1.8	32.4±1.8*
<b>Birth weight (gm)</b>	1824±468	1904±486**	1932±472**
<b>Large for GA</b>	103 (11)	239 (14)	64 (12)
<b>Small for GA</b>	101 (11)	139 (8)	49 (9)
<b>Gender (Female)</b>	422 (46)	716 (44)	247 (46)
<b>Multiple Birth</b>	182 (19)	333 (20)	122 (22)

\* P = 0.003 vs. Epoch 1; \*\* p < 0.001 vs. Epoch 1

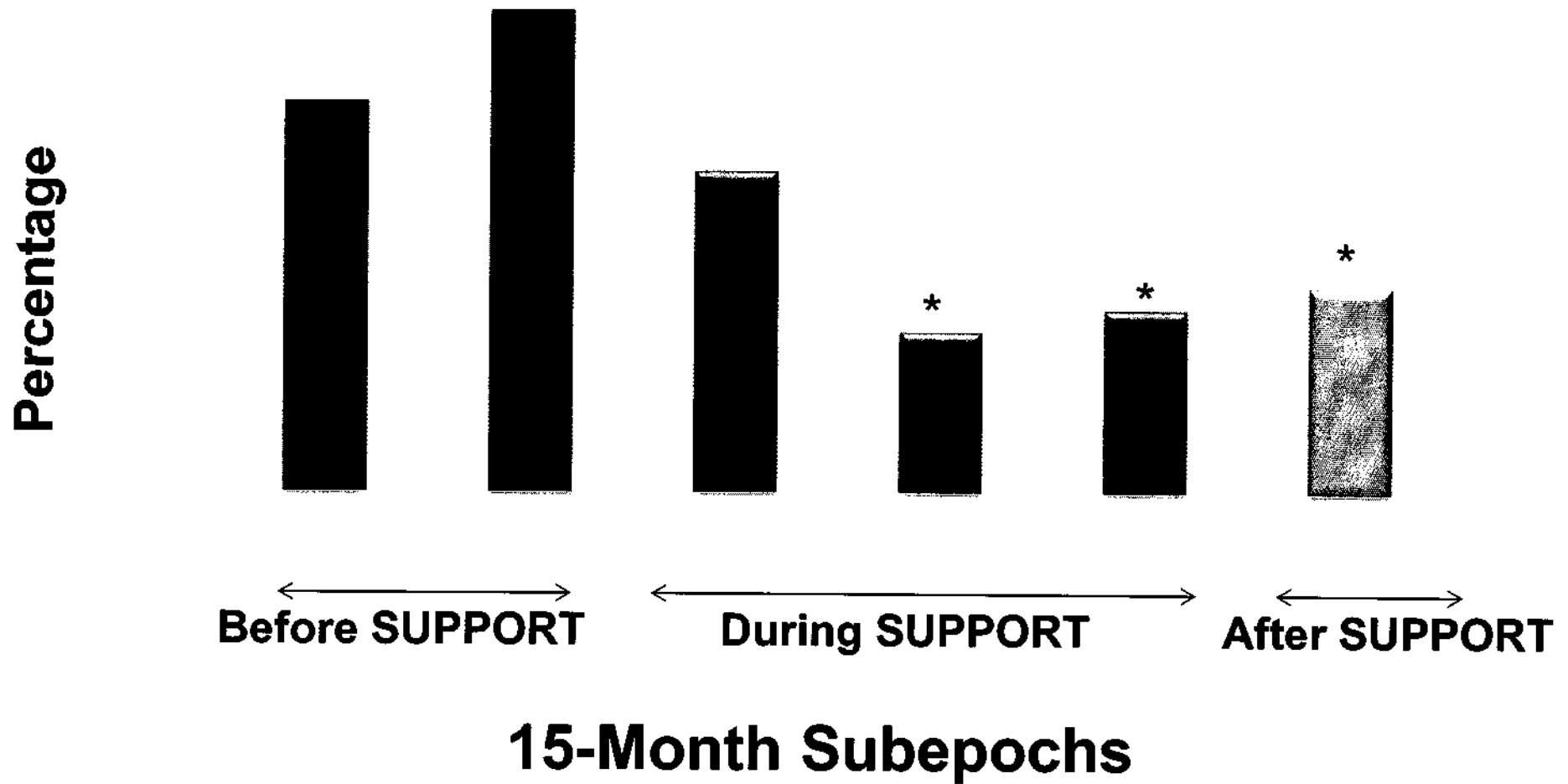
# Results for 28-34<sup>6/7</sup> Week Infants

<b>EPOCH</b>	<b>1 N=951</b>	<b>2 N=1657</b>	<b>3 N=549</b>	<b>P</b>
<b>Intubation in DR</b>	177 (19)	162 (10)*	47 (9)*	<0.001
<b>CPAP in DR</b>	314 (33)	588 (36)	194 (35)	0.41
<b>Intubation in NICU &lt;4 hrs</b>	43 (5)	82 (5)	28 (5)	0.84
<b>Total Intubation</b>	220 (23)	242 (15)*	75 (14)*	<0.001
<b>Surfactant</b>	105 (11)	131 (8)**	50 (9)	<0.001
<b>Pneumothorax</b>	29 (3)	40 (2)	12 (2)	0.33

\* p < 0.001, \*\* p < 0.025 vs. Epoch 1



# DR Intubation Rate Significantly Decreased over Time in 28-34<sup>6/7</sup> Week Infants



# **Stepwise Logistic Regression Assessing Factors Associated with DR Intubation Among All Infants**

	<b>P value</b>	<b>OR</b>	<b>CI</b>
<b>Epoch 2 vs. Epoch 1</b>	<b>&lt;0.001</b>	<b>0.36</b>	<b>(0.28, 0.47)</b>
<b>Epoch 3 vs. Epoch 1</b>	<b>&lt;0.001</b>	<b>0.31</b>	<b>(0.21, 0.45)</b>
<b>Birth Weight Z score</b>	<b>0.003</b>	<b>0.85</b>	<b>(0.77, 0.95)</b>
<b>GA (per week)</b>	<b>&lt;0.001</b>	<b>0.64</b>	<b>(0.61, 0.67)</b>
<b>Gestational Hypertension</b>	<b>0.001</b>	<b>0.60</b>	<b>(0.45, 0.80)</b>
<b>Abruption</b>	<b>0.017</b>	<b>2.20</b>	<b>(1.15, 4.22)</b>
<b>Bag-mask ventilation</b>	<b>&lt;0.001</b>	<b>9.33</b>	<b>(6.98, 12.49)</b>

# Summary

- **Initiation of the SUPPORT trial at Parkland Hospital was associated with**
  - **Reduction in the rates of**
    - **DR intubation and**
    - **Intubation within 4 hours of life in preterm infants < 35 weeks**
  - **Increase in the use of CPAP in the DR in infants < 28 weeks.**
- **These changes persisted after the end of recruitment to the SUPPORT trial.**

# Conclusion

- **The decrease in DR intubation in non-enrolled patients happened despite the absence of**
  - **A change in standard of care**
  - **Initiation of a new protocol**
  - **Any previously described trial effect.**
- **Our data suggest that observation of short term un-blinded outcomes in a randomized trial may affect patient care in non-enrolled patients.**
- **This could be a new type of trial effect.**

# Acknowledgements

- **Luc P. Brion, MD**
- **Pablo Sánchez, MD**
- **Myra Wyckoff, MD**
- **Roy Heyne, MD**
- **Mambarath Jaleel, MD**
- **Lina Chalak, MD**
- **Chul Ahn, PhD**
- **Lucy Christie, RN**
- **Jeannette Burchfield, RN**

**Thank you**

# SUPPORT Trial: Intubation vs. CPAP

- **Primary Outcome:**
  - No significant difference in rates of the composite primary outcome of death or BPD.
- **Secondary Outcomes in CPAP group:**
  - More infants alive and off mechanical ventilation by day 7
  - Fewer days of ventilation
  - Less frequent use of postnatal steroids for BPD
  - No change in the frequency of pneumothorax

# **SUPPORT Trial**

## **Participants vs. Non-Participants**

- **Rich, et al. Pediatrics 2010, 2012.**
  - **Higher antenatal consultation**
  - **Higher proportion of antenatal steroids**
  - **Significantly lower rates of death, severe IVH/PVL, and BPD in univariate comparison but not after taking baseline variables into account**
  - **Enrollment bias from consent**
  - **No evidence for trial effect**



# SUPPORT vs. NON-SUPPORT at Parkland

	<b>SUPPORT N=69</b>	<b>NON-SUPPORT N= 135</b>	<b>P Value</b>
<b>GA</b>	<b>25.5 ± 0.96</b>	<b>25.9 ± 1.1</b>	<b>0.007</b>
<b>Birth Weight</b>	<b>864.7 ± 164.5</b>	<b>905.5 ± 238.4</b>	<b>0.16</b>
<b>Gender (Male)</b>	<b>39 %</b>	<b>47%</b>	<b>0.78</b>
<b>Small for GA</b>	<b>1.4%</b>	<b>10.6%</b>	<b>0.02</b>
<b>Ethnicity</b>			<b>0.09</b>
<b>Hispanic</b>	<b>76%</b>	<b>58%</b>	
<b>Non-Hispanic</b>	<b>24%</b>	<b>42%</b>	
<b>PIH</b>	<b>18%</b>	<b>20%</b>	<b>0.75</b>
<b>Antenatal Steroids</b>	<b>65%</b>	<b>39%</b>	<b>0.001</b>
<b>Abruption</b>	<b>3%</b>	<b>8%</b>	<b>0.14</b>

# **Post-hoc Analysis of Pneumothorax**

- **The majority of pneumothoraces occurred in patients who were intubated in the delivery room and received surfactant within the first 2 hours of life.**
- **The increase in frequency during the 3<sup>rd</sup> epoch was associated with high mean airway pressure during weaning off high-frequency oscillation.**

# **Pneumothoraces in 24 – 27 <sup>6/7</sup> Week Infants**

<b>EPOCH</b>	<b>1</b>	<b>2</b>	<b>3</b>
<b>Number</b>	<b>7</b>	<b>10</b>	<b>10</b>
<b>DR intubation</b>	<b>6</b>	<b>9</b>	<b>8</b>
<b>Surfactant (n; median time)</b>	<b>6;73</b>	<b>8;68</b>	<b>10;68</b>
<b>PIE</b>	<b>1</b>	<b>2</b>	<b>5</b>
<b>On SIMV</b>	<b>6</b>	<b>5</b>	<b>4</b>
<b>HFOV</b>	<b>0</b>	<b>5</b>	<b>5</b>
<b>CPAP</b>	<b>1</b>	<b>0</b>	<b>1</b>

# Pneumothoraces in 24 – 27<sup>6/7</sup> Week Infants

<b>EPOCH</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>P</b>
<b>Number</b>	<b>7(5%)</b>	<b>10(10%)</b>	<b>10(16%)</b>	<b>0.05</b>
<b>SIMV</b>				
<b>MAP (cm)</b>	<b>7.4 ± 1.3</b>	<b>8.2 ± 0.8</b>	<b>8.3 ± 0.6</b>	<b>0.38</b>
<b>HFOV</b>				
<b>MAP (cm)</b>	<b>None</b>	<b>11.4 ± 0.9</b>	<b>14.2 ± 2.7</b>	<b>0.06</b>
<b>Amplitude</b>	<b>None</b>	<b>24.4 ± 1.5</b>	<b>22.0 ± 3.7</b>	<b>0.22</b>
<b>FiO2</b>	<b>None</b>	<b>0.96 ± 0.09</b>	<b>0.73 ± 0.38</b>	<b>0.22</b>
<b>ΔP:MAP&lt;2</b>	<b>None</b>	<b>0 (0)</b>	<b>4 (80)</b>	<b>0.048</b>

# **Factors Associated with Pneumothorax in Infants < 35 wk GA (Excluding PDA ligation)**

	<b>P value</b>	<b>OR</b>	<b>CI</b>
<b>Epoch 3 vs. Epoch 1</b>	<0.001	3.70	(1.7, 7.9)
<b>Epoch 2 vs. Epoch 1</b>	0.21	1.62	(0.8,3.4)
<b>GA (per week)</b>	0.02	0.86	(0.75, 0.98)

## **Not significant:**

- Intubation in the DR**
- CPAP in the DR**
- Time of surfactant administration**

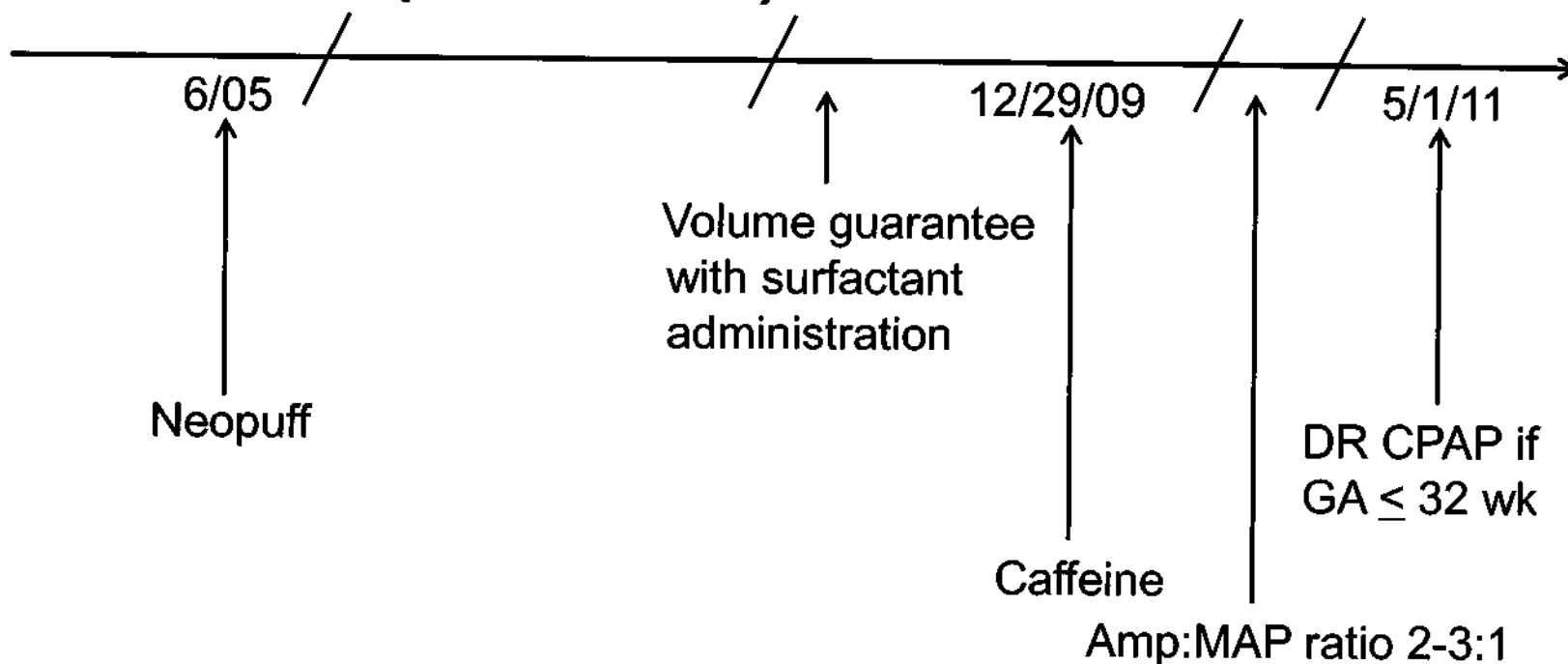
# Very Low Birth Weight Infants

<b>EPOCH</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>P</b>
<b>Number</b>	<b>419</b>	<b>578</b>	<b>180</b>	<b>159</b>	
<b>DR Intubation</b>	<b>57%</b>	<b>36%*</b>	<b>43%*</b>	<b>41%*</b>	<b>&lt;0.0001</b>
<b>Surfactant</b>	<b>48%</b>	<b>37%*</b>	<b>46%</b>	<b>49%</b>	<b>0.001</b>
<b>First Surfactant</b>				<b>*</b>	<b>0.003</b>
<b>16-30 min</b>	<b>1%</b>	<b>0.5%</b>	<b>0%</b>	<b>0%</b>	
<b>31-60 min</b>	<b>36%</b>	<b>32%</b>	<b>28%</b>	<b>44%</b>	
<b>61-120 min</b>	<b>51%</b>	<b>48%</b>	<b>50%</b>	<b>21%</b>	
<b>&gt;120 min</b>	<b>12%</b>	<b>20%</b>	<b>23%</b>	<b>35%</b>	
<b>Pneumothorax</b>	<b>4.3%</b>	<b>6.2%</b>	<b>10.6%*</b>	<b>1.9%</b>	<b>0.003</b>

**\* p < 0.005 vs. Epoch 1**

# Timeline

<b>EPOCH 1</b>	<b>EPOCH 2</b>	<b>EPOCH 3</b>	<b>EPOCH 4</b>
<b>01/03-06/05</b>	<b>07/05-02/09</b>	<b>03/09-06/10</b>	<b>01/11-03/12</b>
	<b>(SUPPORT)</b>		





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**Responsible Author:** Jaclyn M LeVan, D.O.  
**Presenting Author:** Jaclyn M LeVan, D.O.  
**Contact Person:** Jaclyn M LeVan, D.O.

Filename: 751138

### 2012 PAS Annual Meeting

**Subspecialty:** Neonatology - General  
**Theme:** Neonatal - Patient-Oriented Research

**Contact Author:** Jaclyn M LeVan, D.O.  
**Department/Institution/Address:** Department of Pediatrics, University of Texas Southwestern Dallas, 5323 Harry Hines Blvd, Dallas, TX, 75390, United States  
**Phone:** 817-360-7552 **Fax:** 214-648-2481 **E-mail:** jaclyn.levan@phhs.org

**Responsible Author:** Jaclyn M LeVan, D.O.  
**Department/Institution/Address:** Department of Pediatrics, University of Texas Southwestern Dallas, 5323 Harry Hines Blvd, Dallas, TX, 75390, United States  
**Phone:** 817-360-7552 **Fax:** [Redacted]  
**Responsible Author E-mail:** jaclyn.levan@phhs.org  
**Responsible Author Declaration:** As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

**Presenting Author:** Jaclyn M LeVan, D.O.  
**Department/Institution/Address:** Department of Pediatrics, University of Texas Southwestern Dallas, 5323 Harry Hines Blvd, Dallas, TX, 75390, United States  
**Phone:** 817-360-7552 **Fax:** [Redacted]  
**Presenting Author E-mail:** jaclyn.levan@phhs.org

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**Pediatric Hospital Medicine:** No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012  
**Research Type:** Clinical  
**Presentation Sabbath Conflict on:** N/A  
**APA Special Interest Groups, Committees or Regions:** None

#### AWARDS APPLIED FOR:

No awards selected

#### SPONSOR INFORMATION

**Sponsoring Member for PAS/ASPR abstract:**

**Sponsor Name:** Luc P Brion, MD  
**Email:** luc.brion@utsouthwestern.edu

**Is the Sponsor an Author?** Yes

**Sponsoring Societies:**

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- American Pediatric Society
- American Society of Pediatric Nephrology
- Society for Pediatric Research

**Title:** IMPACT OF INITIATING THE NICHD NEONATAL RESEARCH NETWORK SUPPORT TRIAL ON MANAGEMENT AND OUTCOMES OF GESTATIONAL AGE-MATCHED NON-PARTICIPANTS

Jaclyn M LeVan, D.O.<sup>1</sup>, Myra H Wyckoff, M.D.<sup>1</sup>, Mamborath A Jaleel, M.D.<sup>1</sup>, Pablo J Sanchez, M.D.<sup>1</sup>, Chul Ahn, PhD<sup>1</sup>, Jeanette Burchfield, RNC<sup>1</sup>, Lucy Christie, RNC<sup>1</sup> and Luc P Brion, M.D.<sup>1</sup>, <sup>1</sup>Department of Pediatrics, University of Texas Southwestern Dallas, Dallas, TX, United States.

**Background:** We hypothesized that being involved in a randomized trial can affect the management of non-participants both during and after trial recruitment, presumably reflecting observations of outcomes among trial participants. The SUPPORT trial randomized



infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks (wk) gestational age (GA) to delivery room (DR) CPAP vs. intubation and early surfactant administration. Preliminary data on short-term respiratory outcomes showed that DR intubation rate in non-participants decreased and DR CPAP rate increased during the first 2.5 years of trial recruitment at our institution.

**Objective:** To compare rates of DR intubation in non-participants before, during and after SUPPORT trial

**Design/Methods:** This was a retrospective cohort study using our prospective neonatal databases. We included 24<sup>0/7</sup>-27<sup>6/7</sup> wk GA infants who were not enrolled in the trial (Group 1) and those 28<sup>0/7</sup>-34<sup>6/7</sup> wk (Group 2), born during 3 epochs [before (01/03-06/05), during (07/05-02/09), and after SUPPORT trial (3/09-6/10)]. In our center, surfactant is given for significant respiratory distress syndrome (RDS) based on chest radiograph and O<sub>2</sub> requirement.

**Results:** The frequency of DR intubation in both groups significantly decreased during epochs 2 & 3. In Group 1, the rates of early NICU intubation (< 4 hrs of age) and of pneumothorax increased in epoch 3; in multivariate analysis pneumothorax was associated with epoch and with surfactant for RDS. The rate of death or BPD (O<sub>2</sub> requirement at 28 days) was significantly associated with need for respiratory support (DR intubation, DR CPAP, surfactant for RDS), with low GA and low weight for GA, but not with epoch.

**Group 1: 24 0/7- 27 6/7 wk**

	Epoch 1	Epoch 2	Epoch 3	P value
N	180	230	78	
DR Intubation	78%	55%	50%	<0.0001
DR CPAP	27%	51%	52%	<0.0001
Surfactant	59%	56%	64%	0.03
Early NICU Intubation	4%	9%	13%	0.02
Pneumothorax	7%	10%	18%	0.02
Death or BPD	52%	45%	57%	0.26

**Group 2: 28 0/7 -34 6/7 wk**

	Epoch 1	Epoch 2	Epoch 3	P value
N	1012	1755	588	
DR Intubation	19%	11%	10%	<0.0001
DR CPAP	32%	35%	34%	0.26
Surfactant	11%	8%	9%	0.05
Early NICU Intubation	5%	5%	6%	0.63
Pneumothorax	3%	3%	2%	0.32
Death or BPD	3%	2%	3%	0.44

**Conclusions:** After initiation of the SUPPORT trial at our institution, there was a significant decrease in the DR intubation rate in preterm infants not enrolled in the trial, without any change in the rate of death or BPD.

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**From:** Pablo Sanchez  
**To:** Das, Abhik; Wrage, Lisa Ann; JACLYN LEVAN  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie  
**Subject:** RE: SUPPORT pre-post comparison  
**Date:** Thursday, August 30, 2012 1:51:00 PM

---

Hi Abik--Jackie was a fellow and left--I will get her new email, but Luc is coordinating the study and I will speak with him so we can move forward--thanks!--pablo

---

**From:** Das, Abhik [adas@rti.org]  
**Sent:** Thursday, August 30, 2012 12:43 PM  
**To:** Wrage, Lisa Ann; JACLYN LEVAN  
**Cc:** Pablo Sanchez; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie  
**Subject:** RE: SUPPORT pre-post comparison

Jackie and Pablo:

As Lisa alludes, we have a tight PAS timeline (this is not the only analysis for PAS that she or any other RTI statistician is involved in) and this is a complicated analysis. So, please let us know if you receive this email and engage with Lisa on her questions so that we can move this forward.

Thanks

Abhik

---

**From:** Wrage, Lisa Ann  
**Sent:** Thursday, August 30, 2012 1:39 PM  
**To:** Das, Abhik; 'JACLYN LEVAN'  
**Cc:** 'Pablo.Sanchez@UTSouthwestern.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** RE: SUPPORT pre-post comparison

Hi Jackie,

I've tried to send an introductory email a few times, for some reason it has been bounced back to me as undeliverable to your email address. This time I am just replying to all to see if that, for some reason, makes a difference.

I have had a chance to read over your outline and I have started looking at the data that we will need for the analysis. I have a question about one of your primary outcomes: severe ROP or death. Specifically I want to make sure that I am using the data available for the pre-SUPPORT and post-SUPPORT groups to define severe ROP as you want it defined (retinal detachment or ROP surgery). It looks like for the pre-SUPPORT group I will have information as to highest stage of ROP reached in either eye (and stage 4 or 5 = partial or complete retinal detachment) and I have information on whether retinal ablation or surgery was performed in either eye (do you consider 'retinal ablation' to be 'surgery' for your definition of severe ROP?). For the post-SUPPORT group I will have whether or not severe ROP was determined in either eye (with severe ROP defined as ROP surgery, retinal detachment, or Avastin injection/anti-VEGF), will this be sufficient to use for this group?

Otherwise for this group I will have whether or not they had retinal ablation, surgery, or other therapies, but I won't have specifics on if they had stage 4 or 5 ROP.

Also, due to tight timelines for the abstracts we generally do a subset of the requested analyses – if you could prioritize or otherwise let me know what specifically would be crucial for the abstract that would be helpful. And I see that you have already done some similar analyses for a single center, it could potentially be helpful to me to see those abstracts as well, if you could share.

I am looking forward to continuing to work on this with you. Feel free to contact me with any questions you may have.  
Thank you,  
Lisa

Lisa Wrage, MPH  
Research Statistician  
Statistics & Epidemiology  
RTI International  
[wrage@rti.org](mailto:wrage@rti.org)  
919-220-2653

---

**From:** Das, Abhik  
**Sent:** Tuesday, August 28, 2012 2:26 PM  
**To:** JACLYN LEVAN  
**Cc:** Wrage, Lisa Ann; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT pre-post comparison

Hello Jackie:

I am assigning Lisa Wrage from RTI as the statistician for this study. Please work with her on the analysis.

Thanks

Abhik

**Abhik Das, Ph.D.**  
**Senior Research Statistician**

---

**RTI International**  
**6110 Executive Blvd., Suite 902**  
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**Phone: 301-770-8214**  
**Fax: 301-230-4646**

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**From:** Das, Abhik  
**To:** Pablo.Sanchez@UTSouthwestern.edu  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Wrage, Lisa Ann  
**Subject:** RE: SUPPORT pre-post comparison  
**Date:** Thursday, August 30, 2012 1:45:47 PM  
**Importance:** High

---

Pablo:

We don't seem to have the right email address for Jackie. Can you please add her to this email chain?

Thanks a lot

Abhik

---

**From:** Das, Abhik  
**Sent:** Thursday, August 30, 2012 1:44 PM  
**To:** Wrage, Lisa Ann; 'JACLYN LEVAN'  
**Cc:** 'Pablo.Sanchez@UTSouthwestern.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Gantz, Marie  
**Subject:** RE: SUPPORT pre-post comparison

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Thank you,

Lisa

Lisa Wrage, MPH  
Research Statistician  
Statistics & Epidemiology  
RTI International  
[wrage@rti.org](mailto:wrage@rti.org)  
919-220-2653

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**Sent:** Tuesday, August 28, 2012 2:26 PM  
**To:** JACLYN LEVAN  
**Cc:** Wrage, Lisa Ann; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT pre-post comparison

Hello Jackie:

I am assigning Lisa Wrage from RTI as the statistician for this study. Please work with her on the analysis.

Thanks

Abhik

**Abhik Das, Ph.D.**  
**Senior Research Statistician**

---

**RTI International**  
**6110 Executive Blvd., Suite 902**  
**Rockville, MD 20852-3903**  
**e-mail: [adas@rti.org](mailto:adas@rti.org)**  
**Phone: 301-770-8214**  
**Fax: 301-230-4646**

**From:** Das, Abhik  
**To:** JACLYN LEVAN  
**Cc:** [Wrage, Lisa Ann](#); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT pre-post comparison  
**Date:** Tuesday, August 28, 2012 2:27:13 PM  
**Attachments:** [Revised Jackie LeVan Protocol 12-22-11 rev.docx](#)

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**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** pre and post SUPPORT  
**Date:** Tuesday, August 28, 2012 2:19:18 PM

---

Rose:

Do you have Jackie's latest submission?

Thanks

Abhik

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**Senior Research Statistician**  
**RTI International**  
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Phone: 301-770-8214  
Fax: 301-230-4646

**From:** [Myriam Peralta, M.D.](#)  
**To:** "[Vaucher, Yvonne](#)"; [Das, Abhik](#); [Wally Carlo, M.D.](#); [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wcarlo@uab.edu](mailto:wcarlo@uab.edu)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Friday, August 24, 2012 6:57:08 PM  
**Attachments:** [All Tables 1 2 3 Appendices A B LandscapeEditorcomments082312.docx](#)

---

Hi Yvonne I added some information to table 3 regarding blindness in at least one eye and I added a table in the Appendix with reasons for the eye surgery. Let me know what do you think. I will try to add a comment regarding this in the paper but will try to limit as much as possible over the weekend and send it to you by Monday thanks.

---

**From:** Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
**Sent:** Friday, August 24, 2012 2:57 PM  
**To:** [Das, Abhik](#); [Wally Carlo, M.D.](#); [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wcarlo@uab.edu](mailto:wcarlo@uab.edu); [Myriam Peralta, M.D.](#); [Vaucher, Yvonne](#)  
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**To:** [Vaucher, Yvonne](#); [Das, Abhik](#); [Wally Carlo, M.D.](#); [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [wacarolo@uab.edu](#); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Friday, August 24, 2012 4:12:04 PM

---

Great

Let's wait for Marie's edits

Neil

---

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**To:** Das, Abhik; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarolo@uab.edu](#); Myriam Peralta, M.D.; Vaucher, Yvonne  
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**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Thursday, August 23, 2012 8:58:16 PM  
**Attachments:** [PaperSUPPORTResubmissionwcgscommentsNEJM081012YEVRevision082012without TablesEdits acceptedwc.docx](#)

---

Hi Everyone:

I am including minor tracked changes.

Wally

---

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**To:** Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarlo@uab.edu](#); Myriam Peralta, M.D.; Vaucher, Yvonne  
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**Date:** Thursday, August 23, 2012 5:44:37 PM  
**Attachments:** All Tables 1 2 3 Appendices A B LandscapeEditorcomments082312.docx  
PaperSUPPORTResubmissionwrcscommentsNEJM081012YEVRevision082012without TablesEdits accepted.docx  
EditorLetterNEJMwithReviewerComments\_08\_10\_12.docx  
OriginalNEJMSUPPORTResubmissionmanuscript witheditorialcomments081012.docx  
Consort Figure CombinedFinal071212.doc

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-Tables need to a major reformat to portrait rather than landscape (I am working on this)

-Appendix needs to be completed. Acknowledgements moved to Appendix

**-All:** Please reread for content and see what you think we can cut to get down to the required 2700 maximum word count. We need to cut 1007 words.

**-Myriam:** Please address Reviewer 1 comment #5 and Reviewer 2 comment on p. 11.

**-Marie:** Please review statistical rewrites and answer question posed by Reviewer 2 on p 6 concerning SES variables and on page 7 re survival of LTFU

**-Neil/Wally:** Do we need more detailed explanation in the Appendix re oxygen saturation methodology?

I would like to resubmit the paper by September 6<sup>th</sup>.

I will be OOT hiking in the high sierras breathing rarified air, and thus out of email contact, until September 3<sup>rd</sup>.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine

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**Clinical Professor of Pediatrics  
UCSD School of Medicine**

**tele: 619-543-3759  
FAX: 619-543-3812**

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To: Finer, Neil  
Subject: New England Journal of Medicine 12-08506

Dear Dr. Finer:

I am writing about your manuscript, "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)". Your combined manuscript was evaluated by 2 external reviewers, a statistical reviewer, and the editors. While your new manuscript nicely combines key findings of the 2 manuscripts, some further revisions taking into account the reviewer comments (below) and editorial comments (see attached manuscript) are requested before it could be accepted for publication.

As you have already substantially revised your initial submission(s), I wanted to try to consolidate further the revision process. Thus I am attaching at this time a partially edited version of your manuscript, in which I have inserted (in text and tables) editorial comments/queries and reference to some reviewer comments. These comments are best seen by viewing the print or web version in Word. (I apologize in advance for assorted typos in these comments.) In general, the suggested changes should be incorporated, unless there are places where I have inadvertently changed your meaning.

Remember that the final version of your manuscript should not exceed 2700 words (text) and there should be no more than 5 tables or figures. The abstract should not exceed 250 words. We are also asking that you shorten the title, which should be no more than 75 characters (including spaces).

When you send in your revised manuscript, please provide a point-by-point response to the reviewers' comments in a covering letter. There is no need to provide a point-by-point response to my inserted comments, but I would ask that you let me know (in the associated comment box) anywhere you did not agree with suggested changes (and why).

Please return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. Please include a word count for the text. Any changes in authorship must be made in writing, signed by all authors.

To submit your revision, log into <http://mc.manuscriptcentral.com/nejm> and enter "For Authors." Click on "Manuscripts Awaiting Revision." Proceed to the bottom of the screen, where your article will be listed. Under "Actions," click on "Create a Revision."

If your article contains supplementary material, please review the attached checklist before submitting your revision.

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. If not already done, please ask all authors to sign and fax back the enclosed form as soon as possible to (781) 207-6529. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The Universal Disclosure form is also attached. If not already done, each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to [editorial@nejm.org](mailto:editorial@nejm.org) or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them. Please be aware that in the event of publication, each author's submitted disclosure form will be posted on the web (with any dollar amounts redacted).

Please note that if your Journal submission is accepted for publication and subsequently selected as a CME activity, the Accreditation Council for Continuing Medical Education (ACCME) requires that financial disclosure (statement of any author's relevant financial relationships or attestation of no relevant financial relationships) appear with the article. At that time, we will ask you, as the corresponding author, to draft a disclosure statement for your manuscript based on the information in the submitted disclosure forms. Please ask your co-authors to send you copies of their completed disclosure forms for your reference.

If not already done, we also ask that you make clear in your cover letter who designed the study, who gathered the data, who analyzed the data, who vouches for the data and the analysis, who wrote the paper, and who decided to publish the paper. Please state as well if there were any agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. (see the editorial in the September 13, 2001, issue of the Journal). If your manuscript includes subgroup analyses, please report them in accordance with the Journal's guidelines as outlined in the attached Special Report (Wang et al., November 22, 2007).

When you submit your revision, we request that you include a copy of the initial protocol for your trial, all amendments, and a copy of the final protocol. Please also send a copy of your study's statistical analysis plan. In the event that your manuscript is accepted for publication, please be aware that the Journal may post these documents as supplementary material along with the manuscript.

In addition, please indicate who wrote the first draft of your manuscript. If it was not one of the authors, please name the person or persons and indicate who paid them. If any writing assistance other than copy editing was provided, please name the person or persons and indicate who paid them.

We ask that all manuscripts include full, accurate, and up-to-date reporting of adverse events. In general, this should be in the form of a table containing descriptions of all serious adverse events and all other common or important adverse events. The abstract should contain a statement regarding adverse events.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

If you have not done so already, please provide the editors with copies of other manuscripts by you or your coauthors addressing similar or related research questions that are in preparation or under consideration at other journals.

If you have any questions about compliance with these policies, please contact the editorial office for clarification.

We look forward to receiving your revised manuscript, and would ask that you return it no later than August 31, 2012. If this is not possible, please let us know when we can expect it.

Thank you again for your work. Please do not hesitate to contact me if you have any questions.

Sincerely,

Caren G. Solomon, MD  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Reviewer: 1

<b>Comments for the Author</b>

This neurodevelopmental outcome study is a follow up of 18-22 month old children who were in the SUPPORT study published in the NEJM in 2010. The study data showed

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**Reviewer: 2**

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**From:** [Vaucher, Yvonne](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Thursday, August 23, 2012 12:49:19 PM

---

Rose could you please send a revised title page with Brenda listed in the appropriate places?

Thanks!

yvonne

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, August 21, 2012 12:29 PM  
**To:** Vaucher, Yvonne; Finer, Neil  
**Subject:** FW: New England Journal of Medicine 12-08506

Just in case you need this for the resubmission-

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
and Perinatology Branch CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

**From:** Ripley, Julie [<mailto:jripley@nejm.org>]  
**Sent:** Wednesday, August 15, 2012 1:33 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'nfiner@ucsd.edu'  
**Subject:** RE: New England Journal of Medicine 12-08506

Hi Rose,

I spoke with my manager and we will not need any paperwork to add this author since this was basically an administrative error. We will need a new title page for the manuscript, however, with her included. You can send this to me and I will add it to the manuscript.

Once I've received the revised title page, I will add her in our system.

Thanks!  
Julie

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, August 13, 2012 4:26 PM  
**To:** Ripley, Julie; [pandrhiggins@aol.com](mailto:pandrhiggins@aol.com)  
**Subject:** RE: New England Journal of Medicine 12-08506

Hi

Dr. Anna Dusick died. Dr. Brenda Poindexter's name was inadvertently left off of the author line when the two papers were merged. She was originally listed on Dr. Peralta's submission 12-01618.

Thanks so much for your help

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
and Perinatology Branch CDBPM, NIH

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301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

From: [onbehalfof+jripley+nejm.org@manuscriptcentral.com](mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com)

[<mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com>] On Behalf Of [jripley@nejm.org](mailto:jripley@nejm.org)

Sent: Monday, August 13, 2012 4:19 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; [pandrhiggins@aol.com](mailto:pandrhiggins@aol.com)

Subject: New England Journal of Medicine 12-08506

Re: 12-08506 - Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Dear Dr. Higgins:

Thank you for calling earlier today. I was told one of the authors of this manuscript is now deceased. Which author is it?

I will also ask my manager if we need change of author forms to "add" the author that was forgotten when the manuscripts merged. What is the name of that author?

Sincerely,

Julie Ripley

Editorial Assistant

New England Journal of Medicine

10 Shattuck Street

Boston, MA 02115

(617) 734-9800

Fax: (617) 739-9864

<http://www.nejm.org>

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**From:** Ehrenkranz, Richard  
**To:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** RE: Ehrenkranz SUPPORT ROP PAS abstract  
**Date:** Thursday, August 23, 2012 11:34:31 AM

---

Marie:

I am on clinical service next week, but Tuesday afternoon after about 3 pm should work.

Richard

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, August 23, 2012 10:37 AM  
**To:** Ehrenkranz, Richard; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** RE: Ehrenkranz SUPPORT ROP PAS abstract

Can we talk next week? I am available any time on Tuesday, and I have sporadic meetings on the other days of the week, but if you let me know some times that work for you I will send you an invitation.

Thanks,  
Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]  
**Sent:** Tuesday, August 21, 2012 4:00 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Gantz, Marie  
**Subject:** RE: Ehrenkranz SUPPORT ROP PAS abstract

Rose:

I would be pleased to work with Marie and include this analysis the paper on which she is working.

Marie: Please let me know how to proceed.

Richard

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
PO Box 208064  
New Haven, CT 06520-8064

tele: 203-688-2320

fax: 203-688-5426

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

**Sent:** Tuesday, August 21, 2012 2:27 PM

**To:** Ehrenkranz, Richard

**Cc:** Abhik Das ([adas@rti.org](mailto:adas@rti.org)); [mgantz@rti.org](mailto:mgantz@rti.org)

**Subject:** Ehrenkranz SUPPORT ROP PAS abstract

Richard

Here is the review from the PAS abstract submission – the SUPPORT subcommittee would like to combine this with another paper that Marie Gantz is currently working on.

Let us know how you wish to proceed.

Thanks

Rose

**From:** Susan Hintz  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Fwd: PAS abstract priority  
**Date:** Wednesday, August 22, 2012 5:51:31 PM  
**Attachments:** Rank table.docx  
**Importance:** High

---

Hi Rose

See below for my rankings -

Thanks

Susan

Begin forwarded message:

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Date:** August 21, 2012 6:20:35 AM PDT  
**To:** "Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)" <Barbara.Stoll@oz.ped.emory.edu>, "mcw3@po.cwru.edu" <mcw3@po.cwru.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Truog, William (MD)" <wtruog@cmh.edu>, "Pablo Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "Betty Vohr (bvohr@wihri.org)" <bvohr@wihri.org>, "srhintz@stanford.edu" <srhintz@stanford.edu>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "dwallace@rti.org" <dwallace@rti.org>, "RAP32@columbia.edu" <RAP32@columbia.edu>  
**Cc:** "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>  
**Subject:** PAS abstract priority

Hi

In follow up to last week's discussion, please rank order the attached abstract table using 1-10 with 1 being the highest priority and 10 being the lowest priority. Return to me by Friday August 24.

Thanks

rose

Author	Title	
Autmizguine, Julie; Smith PB; Cohen-Wolkowicz, Michael; Cotten CM; Goldberg RN; Stoll BJ; Benjamin DK Jr.	Antifungal Susceptibility and Clinical Outcome in Neonatal Candidiasis	6
Heyne RJ	BSIDIII Motor Scores vs. Palisano GMFCS Analysis	7
De Jesus L; Sood BG; Shankaran S; Das A; Bell EF; Stoll BJ; Laptook AR; Walsh MC; Hale EC; Newman N; Bara R; Higgins RD for the	Cardio-respiratory Effects of Antenatal Magnesium for Fetal Neuroprotection in the Extremely Preterm Infants	8



Eunice Kennedy Shriver National Institute of Health and Human Development Neonatal Research Network		
DeMauro SB; D'Agostino JA; Kirpalani H	Outcomes of Extremely Low Birth Weight Infants with Tracheostomies	1
Mirza, Hussain; Oh W; Vohr BR; Laptook Ar; Stonestreet B; the GDB Subcommittee	Indomethacin Prophylaxis for Intraventricular Hemorrhage (IVH) in Extremely Low Birth Weight (ELBW) Infants: Effects of Timing of Administration	10
Patel, Ravi M.; Stoll BJ; Hale EC; and the GDB Subcommittee	Cause and Timing of Mortality in Extremely Preterm Infants	5
Poindexter BB; Hintz SR; Ehrenkranz RA	Have We Caught Up? Growth and Neurodevelopment Outcomes in ELBW Infants	2
Salas AA; Ambalavanan N; Das A; Carlo WA	Gestational age or birth weight: which one is the best indicator of baseline risk in preterm infants?	9
Truog W; Nelin L	Inhaled Nitric Oxide Usage in Preterm Infants in the NICHD Neonatal Research Network Generic Database: Changing Use Pattern and Any Evidence of Efficacy?	3
Vaucher YE; Hintz SR; Rich W	Compare early childhood neurodevelopmental outcome of 24-25 week gestation ELBW children enrolled vs. those not-enrolled in SUPPORT Trial	4

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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6100 Executive Blvd., Room 4B03  
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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)

Author	Title	
Autmizguine, Julie; Smith PB; Cohen-Wolkowicz, Michael; Cotten CM; Goldberg RN; Stoll BJ; Benjamin DK Jr.	Antifungal Susceptibility and Clinical Outcome in Neonatal Candidiasis	
Heyne RJ	BSIDIII Motor Scores vs. Palisano GMFCS Analysis	
De Jesus L; Sood BG; Shankaran S; Das A; Bell EF; Stoll BJ; Laptook AR; Walsh MC; Hale EC; Newman N; Bara R; Higgins RD for the Eunice Kennedy Shriver National Institute of Health and Human Development Neonatal Research Network	Cardio-respiratory Effects of Antenatal Magnesium for Fetal Neuroprotection in the Extremely Preterm Infants	
DeMauro SB; D'Agostino JA; Kirpalani H	Outcomes of Extremely Low Birth Weight Infants with Tracheostomies	
Mirza, Hussain; Oh W; Vohr BR; Laptook Ar; Stonestreet B; the GDB Subcommittee	Indomethacin Prophylaxis for Intraventricular Hemorrhage (IVH) in Extremely Low Birth Weight (ELBW) Infants: Effects of Timing of Administration	
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Vaucher YE; Hintz SR; Rich W	Compare early childhood neurodevelopmental outcome of 24-25 week gestation ELBW children enrolled vs. those not-enrolled in SUPPORT Trial	

**From:** [Kennedy, Kathleen A](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT FU paper question  
**Date:** Tuesday, August 21, 2012 11:59:57 AM

---

That's correct. We didn't do SUPPORT at LBJ.

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:** Tuesday, August 21, 2012 8:16 AM  
**To:** Kennedy, Kathleen A; Tyson, Jon E  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** SUPPORT FU paper question

Jon or Kathleen –

Did SUPORT recruitment occur at LBJ Hospital? My recall is no, but I want to be absolutely sure.

This is how the listing from your site appears:

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jimenez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

Let me know today

Thanks

Rose

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

**From:** Patricia Evans  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\*URGENT REQUEST\*\*\*\*\*  
**Date:** Tuesday, August 21, 2012 11:25:14 AM

---

Rose,

I just resent my email from last week. Please let me know if you need something different.

All the best,

Patricia

On Aug 21, 2012 8:13 AM, "Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

Patricia-

We still need you copyright form for the SUPPORT FU paper. If you are unable to either sign, scan and send back OR sign and fax, please have someone at UT Houston sign for you.

We need these to resubmit the paper.

Thanks for your help!  
Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

CDBPM, NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

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301-496-3790 (FAX)

higginsr@mail.nih.gov

**From:** Evans, Patricia W  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Smith, Nancy M  
**Subject:** FW: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 21, 2012 11:25:01 AM  
**Attachments:** ICMJE-Disc-100524f11.pdf

---

Rose,

I hope this is what you need. Please let me know if it isn't.

Patricia Wilder Evans, MD  
832 (b)(6) Cell  
Patricia.W.Evans@uth.tmc.edu

---

**From:** Evans, Patricia W  
**Sent:** Wednesday, August 15, 2012 5:55 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

See attached. Please let me know if you need anything else. I am not checking my UT email frequently, so if you need to reach me immediately, please text my cell number or send email to my personal account--

(b)(6)@gmail.com<mailto:(b)(6)@gmail.com>.

Hope you're doing well. All the best,

Patricia Wilder Evans, MD  
832 (b)(6) Cell  
Patricia.W.Evans@uth.tmc.edu<mailto:Patricia.W.Evans@uth.tmc.edu>

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 3:45 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHHospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Evans, Patricia W; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Tyson, Jón E; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

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Rose



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

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#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.





## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) 2. Surname (Last Name) 3. Effective Date (07-August-2008)  
 Patricia Evans 15-August-2012
4. Are you the corresponding author?  Yes  No Corresponding Author's Name  
Neil Finer
5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Evans

2



## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



## ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

SAVE



## ICMJE Form for Disclosure of Potential Conflicts of Interest

---

### Evaluation and Feedback

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.

**From:** Roy Heyne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 20, 2012 12:09:10 PM

---

Just faxed to you. Sorry didn't get in by Friday, I was (b)(6)

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 3:46 PM  
**To:** mperalta@ped.s.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@ped.s.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo Sanchez; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the "TO" line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

---

**UT Southwestern Medical Center**  
**The future of medicine, today.**

**From:** McGowan, Elisabeth C  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 20, 2012 9:30:51 AM  
**Attachments:** DOC082012-08202012092247.pdf  
ICMJE-Disc-100524.pdf

---

Rose,

Great news ! Thanks for your hard work on this. Attached are completed forms.

liz

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; McGowan, Elisabeth C; richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
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THE NEW ENGLAND JOURNAL OF MEDICINE  
10 SHATTUCK STREET, BOSTON, MA 02115 U.S.A.  
781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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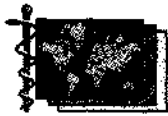
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If author was a U.S. Government employee at the time the article was written, please check below.

AGREED TO THIS DAY OF 08, 20, 2012

PRINTED NAME Elisabeth C. McGowan, MD

SIGNATURE  MD



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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name)  
Elisabeth
2. Surname (Last Name)  
McGowan
3. Effective Date (07-August-2008)  
20-August-2012
4. Are you the corresponding author?  Yes  No  
Corresponding Author's Name  
Neil Finer, MD
5. Manuscript Title  
Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD Neonatal Research Network		X
						ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD Neonatal Research Network		X
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD



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Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

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 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
						X
						ADD
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
						X
						ADD
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
						X
						ADD
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
						X
						ADD
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
						X
						ADD
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

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\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

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Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):



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**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** NEJM disclosure and copyright forms  
**Date:** Saturday, August 18, 2012 10:23:17 PM  
**Attachments:** 20120815124919314.pdf  
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---

Here are my forms.  
Ricki

Ricki F. Goldstein MD  
Professor of Pediatrics  
Director, High-Risk Infant Follow-up Program and  
Special Infant Care Clinic  
Division of Neonatology  
Box 2739, Duke University Medical Center  
Durham, NC 27710  
Office: 919-681-3501  
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Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

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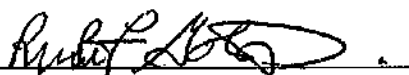
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#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

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#### 4. Other relationships.

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### Section 1. Identifying Information

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 3. Effective Date (07-August-2008) 18-August-2012

4. Are you the corresponding author?  Yes  No  
 Corresponding Author's Name  
 Neil Finer

5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD	Follow-up evaluations	X
						ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD	F/U PI meeting	X
						ADD

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.



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### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
2. Consultancy	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Glaxo Smith Kline	Drug study	X
						ADD
5. Grants/grants pending	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Duke Endowment	Medical Home	X
						ADD

\* This means money that your institution received for your efforts.

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**Date:** Friday, August 17, 2012 4:47:25 PM  
**Attachments:** Scan001.pdf  
[CMIE-Disc-100524.pdf]

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Rosemary,  
Documents are attached. I hope that all is going well with you and the network.  
Warm Regards,  
Mike

**Michael Acarregui, MD, MBA**

Chief Medical Officer  
Providence Health & Services Alaska  
3200 Providence Dr  
Anchorage, AK 99508  
(907) 212-6020

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 12:48 PM  
**To:** Acarregui, Mike  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

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

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org);

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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edwardbell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu

**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

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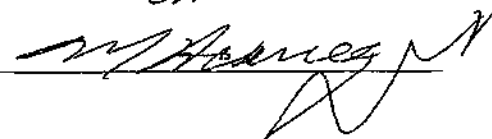
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SIGNATURE 



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Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

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#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.





## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) Michael  
 2. Surname (Last Name) Acarregui  
 3. Effective Date (07-August-2008) 17-August-2012
4. Are you the corresponding author?  Yes  No  
 Corresponding Author's Name  
 Neil Finer, MD
5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	University of Iowa		X ADD
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3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	University of Iowa		X ADD
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6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Acarregui

2



## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

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Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	University of Iowa		X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

SAVE



## ICMJE Form for Disclosure of Potential Conflicts of Interest

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### Evaluation and Feedback

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.

**From:** Phelps, Dale  
**To:** "Kennedy, Kathleen A."; Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Friday, August 17, 2012 3:47:47 PM  
**Attachments:** ROP Natural History Study Manuscript (for subcommittee).DLP.edits.docx

---

Comments/edits on the ROP Observational Paper

Hi Kathleen,

I've put in my edits and questions in 'track changes', and incorporated several comments from the other reviewers that have come in. I can't promise I got them all, but I tried to combine.

I hope these are helpful. This is moving forward very well.

Dale

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Friday, July 27, 2012 6:53 AM  
**To:** Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
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*edits from Dale Phelps 8/17/2012*

**Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

Kathleen A Kennedy, Lisa A Wrage, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Michelle Walsh, Abbot Laptok, Roger Faix, Brad Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, Wade Rich, Dale L Phelps

**Abbreviations:**

GA – gestational age  
PMA – postmenstrual age  
ROP – retinopathy of prematurity  
SUPPORT – Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

**Keywords**

retinopathy of prematurity, screening, extremely preterm infants

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**Acknowledgments:**

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

**What This Study Adds**

Our data are consistent with the timing of examinations do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, did not replicate challenge the accepted observation notion that the onset of ROP is better correlated with postmenstrual than chronological age within this limited gestational age range.

**Comment [01]:** I agree with W. Carlo that it is better to state this in the positive. I also put in 'timing' because we are silent on the part of the guidelines that say WHO to exam. DLP

**Comment [02]:** This latter finding is sufficiently limited that we will probably be asked to remove it from 'What this study adds'. DLP

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines for timing of first and repeat examinations are based on infants born in 1986-1997. Since earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended, it is important to determine if these guidelines are still valid.

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Results:** 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had an ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP post study treatment criteria), defined as in zone I: stage 3 alone or plus disease with ROP, or in in-zone II, plus disease with or stage 2 or 3 ROP, with plus disease in zone II, rather than CRYO-ROP threshold ROP. While Type 1 ROP is usually used as treatment criteria, Type 2 ROP is at a somewhat less severe point in the course of ROP and bears close follow up (Type 2 ROP is stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II). Therefore we also looked at the age of onset of Type 2 ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up

**Comment [03]:** See corrected reference #8 so that we are quoting the original primary publication. DLP

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**Comment [04]:** W.Carlo's paper reported severe ROP among survivors. The wording in his methods says "...". DLP

**Comment [05]:** I disagree with W.Carlo about removing this caution. It is important to have in the abstract since many people never go beyond the abstract, or if out of the country, may not have access to the full paper. DLP

**Comment [06]:** Kathleen, do you what to say "...until after discharge from the newborn intensive care unit."? - probably too many words. :) DLP

**Comment [07]:** Reference 7 is from 2007, 5 years ago. We may have requests from a reviewer for more recent data, perhaps adding (not replacing) this reference. I skimmed through the NRR publications since 2007 and have put some possibilities on the bibliography page for you to consider. DLP

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**Comment [08]:** Kathleen, what you are describing is Type 1 and Type 2 ROP -- these were not the treatment criteria used during the ETROP study, but rather were clinical applications of the findings of the ETROP study described in a secondary analysis, but published together in the primary outcome paper in 2003. DLP

**Comment [09]:** I've added a section here on Type 2 ROP to assist the rest of the paper to flow more readily.



can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants, inborn at 24-27<sup>0/7</sup> weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines are still were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

#### Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0/7</sup> - 27<sup>6/7</sup> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: death; Severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab); vs No Severe ROP (full vascularization to the ora serrata, or vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up was curtailed ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth (in-weeks + days (using the best obstetrical estimate) plus the chronological age in weeks + days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

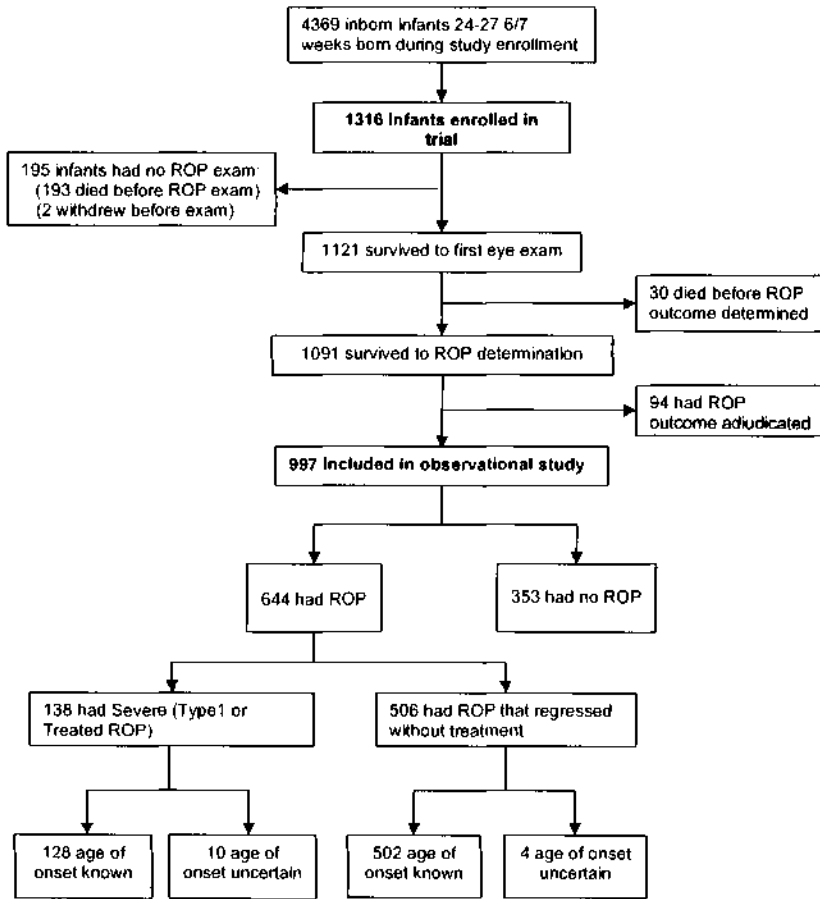
#### Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). 94 of these ROP outcomes, 94 were adjudicated. Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. Sixty five percent 65% (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

**Comment [O10]:** Edit to accommodate W. Carlo's addition and to get a leading number of the sentence. DLP

**Comment [O11]:** Because you will need a legend for each figure, I have offered a draft on the same page with the Figure title. DLP  
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**Figure 1. Flow diagram of patient enrollment. CONSORT diagram showing the flow of subjects included in the original study and meeting criteria for the current analysis.**



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup> [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

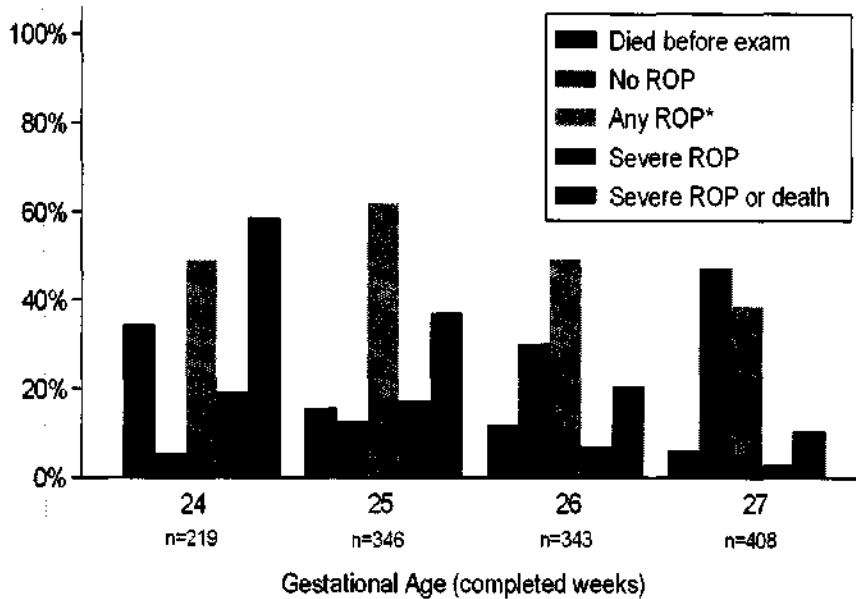
<sup>1</sup> includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

**Comment [O12]:** Watch instructions to authors. Some journals require you not to use superscript numbers because they get confused with references. They suggest using letters or symbols (depends on journal). DLP

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth.** Rates of study events are shown (completed weeks) among all 1316 infants in SUPPORT Trial, and plotted by completed weeks. ("24 completed weeks" = infants of 24<sup>0/7</sup> to 24<sup>6/7</sup> weeks gestation).



\*Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/treated) ROP

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a longer duration of supplemental oxygen than infants without ROP.

39 +/- 32 days for no ROP  
 69 +/- 37 days for ROP less than threshold  
 88 +/- 29 days for ROP Type I  
 Maybe 'no ROP' vs 'any ROP' is not significant by a t-test. However:  
 These data are almost always skewed and are shown using medians, and a different test is used.  
 Usually it is a test of 'no ROP' vs severe ROP  
 It looks to me like you'd want to think about the statistical test that looks at the trend over the 3 categories... Please discuss. ---DLP

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 Comment [O13]: I hope I got this definition correct. ! DLP  
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Comment [O14]: OK, at least 4 of us note that this does not seem consistent with the data in Table 2. I think this must be an error....  
 We all want to see p values for Table 2. And even if the p value for days on oxygen is >0.05, you'll have to restate it so that it does not say "infants with ROP did not have a longer duration"...

**Table 2. Risk factors for ROP.**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
n	353	644	138
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [n (%)]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

<sup>2</sup> missing data

**Comment [O15]:** Neil Finer has some interesting questions about kids about late surgery and inexplicable acceleration of their ROP. I don't know if the data are here to determine that. We do have surgery for PDA (would be early) and NEC, but I don't think we have hernia repairs, or other surgeries. What do you think? DLP

**Comment [O16]:** shouldn't this be median and interquartile or something similar? I'll bet the data are very skewed. DLP

**Comment [O17]:** W. Carlo suggests removing denominators, but I favor keeping them. DLP

**Comment [O18]:** see comment about superscripts in Table 1 DLP

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		Min <sup>a</sup>	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. Ages in weeks + days were converted to decimal weeks for analysis and as shown in the table.

<sup>a</sup> min = minimum age that event was observed

<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

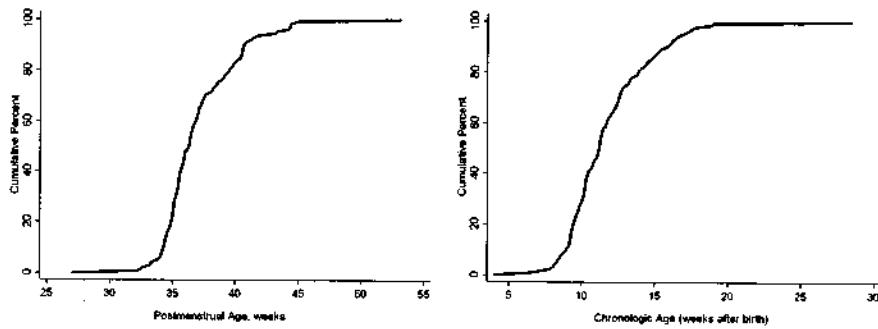
**Comment [O19]:** Interesting point per W. Carlo that we don't define what we mean by 'any ROP'. Can we please ask RTI what definition they used and then add to the Methods section and/or the foot notes here. DLP

**Comment [O20]:** see note about superscripts in Table 1

**Comment [O21]:** If you are going to use min for the minimum age an event was observed, would it be consistent to use 'max' instead of '100%'? Just asking, I have no opinion. DLP

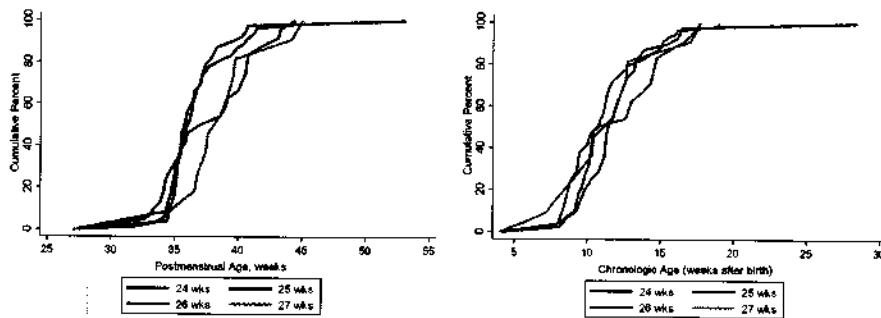
**Comment [O22]:** It's awkward that this is the first appearance of "Type 2" in the paper.

**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**

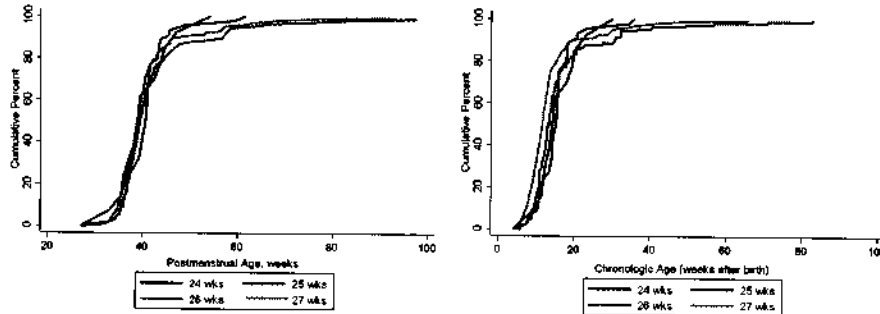


Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

**Comment [023]:** This is a tantalizing sentence and B.Yoder asks if they has any ROP in zone III, or were they just immature vessels in Zone III? A nice question. DLP

**Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth**

**No ROP**

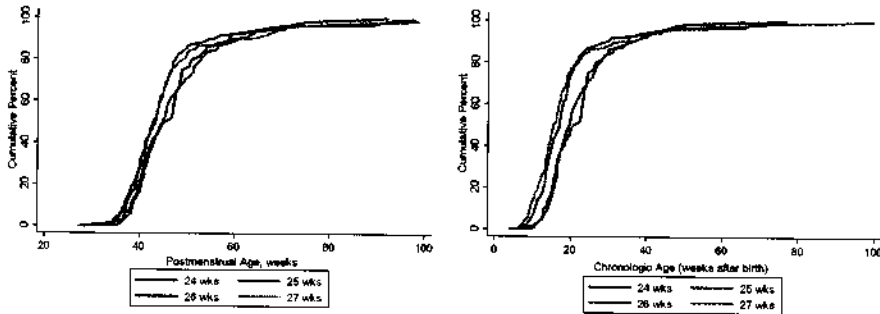


**Comment [024]:** CAREFUL !!! I THINK THE TITLE ON THE GRAPH IS ERRONEOUS DALE

We have not used "mature vessels" in the paper up to this point, and I strongly suspect that this graph is not showing mature vessels: that is vessels all the way across Zone III and to the ora serrata. Instead, I'm pretty sure these figures are for when infants reached 'final favorable outcome' of two sequential examinations in zone III with no ROP or no stage 3 ROP or vessels reached the ora serrata. DLP

Also, you may wish to say "Never ROP" instead of "No ROP"

**Mild/Moderate ROP**



In general, retinal vessels reached final status ~~matured~~ several weeks later in infants with mild or moderate ROP as compared to infants who never had with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower

**Comment [025]:** I am pretty certain that this is reworded to be correct now, but we have to have confirmation from RTI how they counted and plotted these data. DLP

acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

**Comment [026]:** There was one suggestion to drop this table and put the numbers in the text. However, the division of data is complex to grasp intuitively at first and the Table is extremely clear and helpful. I would leave it.  
For example, it was not just one infant who needed treatment after back transfer, there were 5, but only one of those was still an inpatient at the back-transfer center -- and the other 4 who had been discharged from the back-transfer center were probably at even higher risk for lost-to-follow up! DLP

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)

**Comment [027]:** What is 'mature' here? Is it only to the ora serrata? or does it also include infants who have been in Zone III for 2 sequential examinations? We have to be clear on this.



Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home**

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

## Discussion

In prior ROP natural history studies,<sup>32</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>12</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and ~~stratified analyzed~~ categorized to compare to rather than gestational age, it is also possible that the lowest birth weight stratum (<750g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological age and severe ROP did not occur before 6 weeks. This

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**Comment [028]:** Would 'converged' be a better description than 'overlapped'? just a thought. DLP

**Comment [029]:** There was no stratification in CRYO-ROP prior to randomization. DLP

distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented and only inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT Trial inclusion criteria also limit the did not allow us to generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP, or to infants over 27 weeks gestation.

Comment [030]: I like the way W.Carlo added this.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>14+4</sup>

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## Conclusion

Current screening guidelines, published in 2006,<sup>11</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

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In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

## References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Pediatrics* 1988; 81: 697-706.

- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 1998; 338: 1572-1576.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 402: 233-250.
- The Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003;121:1684-1696.
- <sup>9</sup> Good WV, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
- <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tomqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
- <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.
- <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
- <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
- <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.

Possibly one of these might be a more up-to-date alternatives for reference #7 on survival rates of ELGA or ELBW infants. — I picked by title, I have not verified that the content is appropriate. DLP

Stoll BJ; Hansen NI; Bell EF; Shankaran S; Laptook AR; Walsh MC; Hale EC; Newman NS; Schibler K; Carlo WA; Tyson JE; Poindexter BB; Finer NN; Ehrenkranz RA; Duara S; Sánchez PJ; O'Shea TM; Goldberg RN; Van Meurs KP; Faix RG; Phelps DL; Frantz ID; 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 Sep;126(3):443-56. Epub 2010 Aug 23. PMID: 20732945; PMCID: 2982806.

Carlo WA; McDonald SA; Tyson JE; Stoll BJ; Ehrenkranz RA; Shankaran S; Goldberg RN; Das A; Schendel D; Thorsen P; Skogstrand K; Hougaard DM; Oh W; Laptook AR; Duara S; Fanaroff AA; Donovan EF; Korones SB; Stevenson DK; Papile L; Finer NN; O'Shea TM; Poindexter BB; Wright LL; Ambalavanan N; Higgins RD. Cytokines and Neurodevelopmental Outcomes in Extremely Low Birth Weight Infants. *J Pediatr*. 2011 Dec;159(6):919-25.e3. Epub 2011 Jul 27. PMID22147379. PMCID3215787.

?? 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; the Generic Database Subcommittee; for the Eunice Kennedy Shriver National Institute of Child Health; Human Development Neonatal Research Network. Approach to Infants Born at 22 to 24 Weeks' Gestation: Relationship to Outcomes of More-Mature Infants. *Pediatrics*. 2012 May 28. [Epub ahead of print]. PMID: 22641761.

**From:** [Finer, Neil](#)  
**To:** [Wally Carlo, M.D.](#); [Walsh, Michele](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: PAS SUPPORT SUBMISSIONS  
**Date:** Friday, August 17, 2012 2:54:47 PM

---

Rose Will you be scheduling another call?  
Neil

From: "<Wally Carlo>", Wally Carlo <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)<<mailto:wcarlo@peds.uab.edu>>>  
Date: Friday, August 17, 2012 8:48 AM  
To: Michele Walsh <[Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)>>, UCSD Pediatrics <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)<<mailto:nfiner@ucsd.edu>>>  
Cc: Rosemary Higgins <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>>  
Subject: RE: PAS SUPPORT SUBMISSIONS

Hi Michele:

We should discuss this on our next call.

Thanks so much for considering the feedback.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
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Phone: 205 934 4680  
FAX: 205 934 3100  
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From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
Sent: Friday, August 17, 2012 10:08 AM  
To: Wally Carlo, M.D.; Finer, Neil  
Subject: FW: PAS SUPPORT SUBMISSIONS

Hello:

Please see my rebuttal below on Further explorations of causes of mortality in the SUPPORT trial. This is an exploratory look at the data to generate Hypotheses to test in future studies. I am aware of the work that has been Done previously, but feel this can be explored further.

I am happy to talk more. I am sorry I could not be on the call

But had no cell service at (b)(6)

Best,

Michele Walsh, MD

Chief, Division of Neonatology

216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Walsh, Michele  
Sent: Friday, August 17, 2012 11:06 AM  
To: 'Higgins, Rosemary (NIH/NICHD) [E]'  
Subject: RE: PAS SUPPORT SUBMISSIONS

Support committee:

I would like to offer a rebuttal to the comments about power.

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1. Rather I wish to look by pt and look for clusters of causes of mortality.
2. Explore effect modification by SGA status.

I would propose that Marie, run an analysis of effect modification in SGA Vs AGA pts- if there is no effect modification on mortality, then Will withdraw the abstract.

Michele Walsh, MD

Chief, Division of Neonatology

216.844.3759

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---

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Thursday, August 09, 2012 8:15 AM  
To: Walsh, Michele  
Subject: RE: PAS SUPPORT SUBMISSIONS

Michele

SUPPORT subcommittee recommended the following:

Walsh – reject due to low power but propose to NEOPROM group as a study when the information on 5000 infants are available

DiFiore – major revision

Ehrenkranz – reject, but combine with a previously approved study from Marie + W

Also – you inositol proposal had a high level of enthusiasm but was rejected due to low power – they suggest a prospective look in the phase 3 trial.

I have attached the reviews, but they are unedited and have NOT yet gone to the PAS abstract review committee – call is next week on Wednesday

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
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From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
Sent: Wednesday, August 08, 2012 3:30 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: PAS SUPPORT SUBMISSIONS

Hi Rose: What were the committee decisions on these?

Michele Walsh, MD

Chief, Division of Neonatology

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---

From: Higgins, Rosemary (NIH/NICHD) [E][mailto:higginsr@mail.nih.gov]  
<mailto:%5bmailto:higginsr@mail.nih.gov%5d>  
Sent: Monday, July 09, 2012 12:40 PM  
To: Finer, Neil; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; mew3@cwru.edu<mailto:mew3@cwru.edu>; 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'<mailto:'ROGER.FAIX@HSC.UTAH.EDU'>; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; 'dwallace@rti.org'<mailto:'dwallace@rti.org'>; mgantz@rti.org<mailto:mgantz@rti.org>; wrich@ucsd.edu<mailto:wrich@ucsd.edu>; nancy newman; 'Bradley.Yoder@hsc.utah.edu'<mailto:'Bradley.Yoder@hsc.utah.edu'>  
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Gabrio, Jenna'; Cunningham, Meg; 'Zaterka-Baxter, Kristin'  
Subject: PAS SUPPORT SUBMISSIONS

Hi  
Here are 3 SUPPORT PAS abstract submissions. Jenna will set up a call to discuss.

Thanks  
Rose

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Pregnancy and Perinatology Branch

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

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: PAS SUPPORT SUBMISSIONS  
**Date:** Friday, August 17, 2012 11:06:11 AM

---

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*Chief, Division of Neonatology  
216.844.3759*

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---

**From:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Wednesday, August 08, 2012 3:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: PAS SUPPORT SUBMISSIONS

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*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, July 09, 2012 12:40 PM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; [mcw3@cwru.edu](mailto:mcw3@cwru.edu); 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; [dwallace@rti.org](mailto:dwallace@rti.org); [mgantz@rti.org](mailto:mgantz@rti.org); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); nancy newman; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Gabrio, Jenna'; Cunningham, Meg; 'Zaterka-Baxter, Kristin'  
**Subject:** PAS SUPPORT SUBMISSIONS

Hi

Here are 3 SUPPORT PAS abstract submissions. Jenna will set up a call to discuss.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
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**From:** Newman, Nancy S  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Date:** Thursday, August 16, 2012 10:50:35 AM  
**Attachments:** Copyright\_Transfer\_12\_08506\_SUPPORT.pdf  
ICMJE-Disc-100524\_SUPPORT.pdf

---

Hi Rose- attached are the NEJM papers for the SUPPORT paper. Thanks.

*Nancy*

Nancy Newman, BA, RN  
Case Western Reserve University  
Rainbow Babies and Children's Hospital  
[nxs5@case.edu](mailto:nxs5@case.edu)

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781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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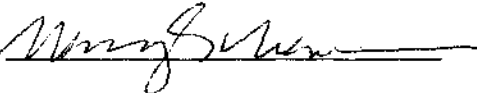
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4. Are you the corresponding author?  Yes  No  
Corresponding Author's Name  
Dr. Neil Finer
5. Manuscript Title  
Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
12-08506

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- Yes, the following relationships/conditions/circumstances are present (explain below):

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**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Wednesday, August 15, 2012 6:57:18 PM  
**Attachments:** ICMJE-Disc-100524[1].pdf

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(b)(6)@gmail.com<mailto:account-(b)(6)@gmail.com>.

Hope you're doing well. All the best,

Patricia Wilder Evans, MD  
832 (b)(6) Cell  
Patricia.W.Evans@uth.tmc.edu<mailto:Patricia.W.Evans@uth.tmc.edu>

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 3:45 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Evans, Patricia W; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Tyson, Jon E; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

In the meantime, I need everyone listed in the "TO" line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose





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Neil Finer
5. Manuscript Title  
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1. Grant	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Evans

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7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

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						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
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13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

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**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Wednesday, August 15, 2012 1:13:11 PM  
**Attachments:** NEJM Form-Gantz.pdf  
ICMJE-Disc-100524-Gantz.pdf

---

Rose, here are my forms.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarolo@uab.edu); Walsh, Michele (Michele.Walsh@UHHospitals.org); Gantz, Marie; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Das, Abhik; Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpointindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
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**Importance:** High

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**email and send it back to me by Friday August 17.  
We will submit all of them centrally to NEJM. This is  
also under embargo, so is not to be released as the  
publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

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10 SHATTUCK STREET, BOSTON, MA 02115 U.S.A.  
781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF 8, 15, 2012

PRINTED NAME Marie G. Gantz

SIGNATURE Marie G. Gantz





## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

**The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.**

#### **1. Identifying information.**

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### **2. The work under consideration for publication.**

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### **3. Relevant financial activities outside the submitted work.**

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### **4. Other relationships.**

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



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### Section 1. Identifying Information

1. Given Name (First Name) 2. Surname (Last Name) 3. Effective Date (07-August-2008)  
 Marie Gantz 15-August-2012
4. Are you the corresponding author?  Yes  No Corresponding Author's Name  
Dr. Neil Finer
5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NIH	Cooperative agreement to support RTI's role as Data Coordinating Center of the Neonatal Research Network	X
						ADD

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work					
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments
13. Other (err on the side of full disclosure)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	American Academy of Pediatrics	Travel/accommodations to give a presentation on statistical methods at the 36th Southeastern Conference on Perinatal Research of the American Academy of Pediatrics in Key Largo, FL
13. Other (err on the side of full disclosure)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Mead Johnson Nutrition	Honorarium for giving a presentation on statistical methods at the 36th Southeastern Conference on Perinatal Research of the American Academy of Pediatrics in Key Largo, FL

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):



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---

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Show All Table Rows

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**From:** Dr. Frank  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Wednesday, August 15, 2012 12:18:26 PM  
**Attachments:** NEJM\_Form[1].pdf  
ICMJE-Disc-100524f11.pdf

---

Dear Rose,

Attached are the requested signed and completed forms.  
Congratulations. My Best, Dee Wilson

(b)(6)@aol.com

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

From: Higgins, Rosemary (NIH/NICHD) [E] (NIH/NICHD) [E]  
<higginsr@mail.nih.gov>  
To: mperalta <mperalta@peds.uab.edu>; Yvonne Vaucher  
<yvaucher@ucsd.edu>; nfiner <nfiner@ucsd.edu>; Wally Carlo  
(wacarilo@uab.edu) <wacarilo@uab.edu>; Walsh, Michele  
(Michele.Walsh@UHhospitals.org)  
(Michele.Walsh@UHhospitals.org) <Michele.Walsh@UHhospitals.org>;  
mgantz <mgantz@rti.org>; Abbot Laptook <Alaptook@wihri.org>; Brad Yoder  
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Patricia.W.Evans <Patricia.W.Evans@uth.tmc.edu>; golds005  
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<michael-acarregui@uiowa.edu>; Adams-Chapman, Ira <iadamsc@emory.edu>;  
(apappas@med.wayne.edu) <apappas@med.wayne.edu>; srhinz  
<srhinz@stanford.edu>; (EMcGowan@tufts-nemc.org)  
<EMcGowan@tufts-nemc.org>; richard.ehrenkranz  
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unm.edu (JaFuller@salud.unm.edu) <JaFuller@salud.unm.edu>; moshea  
<moshea@wfubmc.edu>; Gary Myers (gary\_myers@URMC.Rochester.edu)  
<gary\_myers@URMC.Rochester.edu>; bpoindex <bpoindex@iupui.edu>  
Cc: Archer, Stephanie (NIH/NICHD) [E] (NIH/NICHD) [E]  
<archerst@mail.nih.gov>; Pablo.Sanchez  
<Pablo.Sanchez@UTSouthwestern.edu>; Kennedy, Kathleen A  
<Kathleen.A.Kennedy@uth.tmc.edu>; Jon.E.Tyson  
<Jon.E.Tyson@uth.tmc.edu>; goldb008 <goldb008@mc.duke.edu>; cotte010  
<cotte010@mc.duke.edu>; Ed Bell (edward-bell@uiowa.edu)  
<edward-bell@uiowa.edu>; Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)  
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<sshankar@med.wayne.edu>; Krisa Van Meurs (vanmeurs@stanford.edu)  
<vanmeurs@stanford.edu>; dstevenson <dstevenson@stanford.edu>; 'Duara,  
Shahnaz' (SDuara@med.miami.edu) (SDuara@med.miami.edu)  
<SDuara@med.miami.edu>; Kristi Watterberg (kwatterberg@salud.unm.edu)

<kwatterberg@salud.unm.edu>; dale\_phelps  
<dale\_phelps@urmc.rochester.edu>; carl\_dangio  
<carl\_dangio@urmc.rochester.edu>  
Sent: Mon, Aug 13, 2012 4:45 pm  
Subject: **\*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\***

Hi We have good news from the New England Journal – They say ...changes are requested before it can be accepted..... Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision. In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized. I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there. Rose

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781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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PRINTED NAME Deanne Wilson-Costello

SIGNATURE Deanne Wilson-Costello



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Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

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#### **3. Relevant financial activities outside the submitted work.**

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

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For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### **4. Other relationships.**

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 Deanne Wilson-Costello 15-August-2012

4. Are you the corresponding author?  Yes  No Corresponding Author's Name  
Neil Finer

5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Wilson-Costello

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## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

No other relationships/conditions/circumstances that present a potential conflict of interest

Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

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### Evaluation and Feedback

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**From:** Phelps, Dale  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Wednesday, August 15, 2012 10:14:32 AM

---

Marie,

Thank you, I don't think I told you that this was very helpful. I do think we have two outliers, and I'll discuss it with Abhik and Rose whether we'll just do general education on the issue, or in addition especially contact those two centers. I do not know who they are, and probably don't need to.

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Friday, August 10, 2012 2:40 PM  
**To:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Dale,

The attached document is the previous output I had sent you on the 23 who did not meet criteria for surgery, but I have added the percent of infants enrolled at center who had ROP surgery without meeting criteria. Let me know if that answers your question.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Sunday, July 22, 2012 7:27 PM  
**To:** Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi Marie,

I have carefully reviewed each of these cases and they're an interesting mix\*(see attached).

Although the cases were 'spread over 11 centers', there were two centers that had 5 cases, and the other 9 centers had only 1 or 2 cases. In order to know if there is a problem here, we need to be able to appreciate if the two centers with 5 cases each (your coded centers E and upper case i) were high enrollers overall. Also, while some centers had "only" 1 or 2 cases, some center enrolled less than 10 subjects.

I know we want to keep things coded, but in order to get the full grasp, I need more. Perhaps you could express it as a percentage of enrollees (which would approximate things, but would not reveal a percentages of survivors who got exams) ?

Dale

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**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Friday, May 25, 2012 11:15 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Rose and Dale,

SUPP10 data for the 23 infants who did not meet criteria for surgery are attached. I've coded the center and infant IDs, but you can see that the 23 infants were spread across 11 centers. Note that there were a couple of cases where "Threshold (New Type 1)" was coded as "Y" on the SUPP10, but the other individual variables (zone, stage and plus disease) did not back that up. I know that when we were doing the original analysis, we queried cases where there were similar disagreements in the data, but I think we must have only queried cases where the ROP final outcome was based on threshold ROP rather than on surgery (these 23 cases were all classified based on surgery). Let me know if you have any questions.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, May 25, 2012 9:53 AM  
**To:** Das, Abhik  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Yes – maybe some of them had other issues and we need to know. We also need to know if this is only a few sites or spread across the network.

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](mailto:higginsr@mail.nih.gov)

---

**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Friday, May 25, 2012 9:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Rose:

I was surprised to see that as well. We can pull all the data from the SUPP10 forms for each of these babies for you to review. Is that what you had in mind?

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, May 25, 2012 9:49 AM  
**To:** Das, Abhik  
**Subject:** FW: ROP data from SUPPORT TRIAL FOR DSMC

Abhik

I am a little concerned that we had 23 infants who got ROP surgery, but didn't meet the criteria- we should look at these cases in a little more detail (as well as see if this is site dependent)>

Is it possible to get the SUPP 10 forms on each of these infants – this will help to try to figure out why they had surgery and didn't reach the usual "Threshold" definition??

We need this to be able to explain this to the DSMC.

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](mailto:higginsr@mail.nih.gov)

---

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Thursday, May 24, 2012 5:15 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik

**Subject: RE: ROP data from SUPPORT TRIAL FOR DSMC**

Hi Marie,

There are quite a few more cases of treatment before documented criteria for treatment than I had expected.

As we go back to the DSMC with this, I think it would be important to be able to better explain it.

Also, just to confirm with you. Infants who might have had ROP disease worse than Type 1 would also be considered treated appropriately. Did you exclude any infants because they had stage 4a or 4b or stage 5?

If it is going to take a lot of time, please discuss it with Dr. Das first. He and Dr. Higgins and I can discuss whether to go forward.

I do think it will be important to understand and be able to account for at least some of them -- and the fuller clinical ROP picture is likely to do that.

Therefore, I would like to request that you provide the more detailed data.

I also volunteer to individually review the ROP printouts from the subgroups listed below: (there is a nice de-identified format that was used for INS-2 that you could use that gives me basically two pages per infant -- one for each eye)

5 who met criteria for surgery, but were not recorded as having had surgery (123-127=5)  
23 who did receive surgery, but did not meet criteria for surgery

Thanks!

Dale

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

**Sent:** Thursday, May 24, 2012 1:39 PM

**To:** Phelps, Dale

**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik

**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Dale, do you still need the more detailed data you requested?

Marie

Marie Gantz, Ph.D.

Senior Research Statistician

RTI International

[mgantz@rti.org](mailto:mgantz@rti.org)

828-251-6255

---

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]

**Sent:** Thursday, May 24, 2012 4:18 PM

**To:** Gantz, Marie

**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik



**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Thank you Marie,

The answers provide very interesting data for discussion.

We will have some work to do with the Ophthalmologists in the inositol Study.

Particularly: treating in zone II without evidence of plus disease.

One the cases below not meeting criteria is unlikely enough that it is probably a keying error, but I would not want to go back at this point in time to do a query.

Dale

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Thursday, May 24, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi all, I included answers to Rose's questions below, based on my preliminary look at the SUPPORT data. I will send more complete answers to Dale's questions when I have them.

Marie

Mario Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery 127 (based on Wally's paper, this looks like 132) MG: 132 includes infants with severe ROP as defined in the paper who did not have surgery recorded.

Can you tell us how many had each of these categories:

1. type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);

MG: 22 met these criteria in at least one eye

2. zone I, stage 3 ROP without plus disease;

MG: An additional 6 met these criteria in at least one eye (there were a total of 11 but 5 also met criteria for type I ROP in #1)

**3. zone II, stage 2 or 3 ROP with plus disease.**

MG: An additional 76 met these criteria in at least one eye (there were a total of 80 but 4 also met criteria in #1 or #2)

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

MG: There were 23 who did not meet criteria in #1-3 but who did have surgery:

1 had zone II stage 2 with plus disease missing

2 had zone II stage 2 no plus disease

18 had zone II stage 3 no plus disease

1 had zone III stage 3 no plus disease

1 had missing zone and stage but plus disease

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](mailto:higginsr@mail.nih.gov)**

**From:** Adams-Chapman, Ira  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Wednesday, August 15, 2012 10:05:23 AM  
**Attachments:** ICMJE-Disc-100524[2].AdamsChapman.pdf  
20120815100647787[1].pdf

---

Hi Rose,  
Attached are my two forms.  
Thanks,  
Ira

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Tuesday, August 14, 2012 9:59 AM  
**To:** 'mperalta@peds.uab.edu'; 'Yvonne Vaucher'; 'nfiner@ucsd.edu'; 'Wally Carlo (wacarlo@uab.edu)'; 'Walsh, Michele (Michele.Walsh@UHhospitals.org)'; 'mgantz@rti.org'; 'Abbot Laptook'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; 'Roger Faix (Roger.Faix@hsc.utah.edu)'; 'Abhik Das (adas@rti.org)'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Wade RIch'; 'nxs5@case.edu'; 'Betty Vohr (bvohr@wihri.org)'; 'Kimberly Yolton (kimberly.yolton@cchmc.org)'; 'Roy Heyne (Roy.Heyne@utsouthwestern.edu)'; '(b)(6)@aol.com'; 'Patricia.W.Evans@uth.tmc.edu'; 'gold005@mc.duke.edu'; 'Acarregui, Michael'; 'Adams-Chapman, Ira'; ' (apappas@med.wayne.edu)'; 'srhintz@stanford.edu'; ' (EMcGowan@tufts-nemc.org)'; 'richard.ehrenkranz@yale.edu'; 'Anna Bodnar (abodnar@utah.gov)'; 'cbauer@peds.med.miami.edu'; 'JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)'; 'moshea@wfubmc.edu'; 'Gary Myers (gary\_myers@URMC.Rochester.edu)'; 'bpoindex@iupui.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Kennedy, Kathleen A'; 'Jon.E.Tyson@uth.tmc.edu'; 'goldb008@mc.duke.edu'; 'cotte010@mc.duke.edu'; 'Ed Bell (edward-bell@uiowa.edu)'; 'Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)'; 'Seetha Shankaran'; 'Krisa Van Meurs (vanmeurs@stanford.edu)'; 'dstevenson@stanford.edu'; 'Duara, Shahnaz' (SDuara@med.miami.edu); 'Kristi Watterberg (kwatterberg@salud.unm.edu)'; 'dale\_phelps@urmc.rochester.edu'; 'carl\_dangio@urmc.rochester.edu'  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Hi all  
The corresponding author if Dr. Neil Finer (it is on one form but not the other)

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](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh,

Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpointex@iupui.edu

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edwardbell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu

**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

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#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



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1. Given Name (First Name) **Ira**      2. Surname (Last Name) **Adams-Chapman**      3. Effective Date (07-August-2008) **13-August-2012**

4. Are you the corresponding author?     Yes     No      Corresponding Author's Name  
**Neil Finer**

5. Manuscript Title  
**Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

6. Manuscript Identifying Number (if you know it)  
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						ADD
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						ADD

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### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

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						ADD
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						ADD
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Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF 8 / 13 / 2012 ( )

PRINTED NAME Ira Adams - Chapman, MD

SIGNATURE 

**From:** [Myriam Peralta, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Date:** Tuesday, August 14, 2012 6:27:02 PM  
**Attachments:** [ICMJE-Disc-100524.pdf](#)  
[0199\\_001.pdf](#)

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Here are my forms Rose, I had sent my comments to Yvonne and we will keep trying to get the review done asap thanks.



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) **Ada Myriam**      2. Surname (Last Name) **Peralta-Carcelen**      3. Effective Date (07-August-2008) **14-August-2012**
4. Are you the corresponding author?     Yes     No      Corresponding Author's Name  
**Neil Finer, MD**
5. Manuscript Title  
**Neurodevelopmental Outcome at 18-22 moths of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial**
6. Manuscript Identifying Number (if you know it)  
**12-08506**

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Peralta-Carcelen

2



## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

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Hide All Table Rows Checked 'No'

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Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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PRINTED NAME Myriam Peralta-Carcelen

SIGNATURE Myriam Peralta-Carcelen

**From:** Roger Faix  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 4:43:22 PM  
**Attachments:** ICMJE-Disc-100524.pdf  
NEJM Form.pdf

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Attached are the completed ICMJE form and copyright assignment forms. Let me know if you require anything further!

Roger

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 2:45 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Bradley Yoder; Roger Faix; Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the "TO" line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

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Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

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PRINTED NAME Roger G. Faix, M.D.

SIGNATURE Roger G. Faix, M.D.



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### Instructions

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Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

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Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



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## ICMJE Form for Disclosure of Potential Conflicts of Interest

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1. Given Name (First Name)  
Roger
2. Surname (Last Name)  
Faix
3. Effective Date (07-August-2008)  
14-August-2012
4. Are you the corresponding author?  Yes  No Corresponding Author's Name  
Finer N.
5. Manuscript Title  
Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
12-08506

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X



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The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.

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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Ikaria Corporation	Selection board for fellowship grants	X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



## ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>ADD</b>
						<b>X</b>
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>ADD</b>
						<b>X</b>
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>ADD</b>
						<b>X</b>
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>ADD</b>
						<b>X</b>
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>ADD</b>
						<b>X</b>
13. Other (err on the side of full disclosure)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Biosynexus, Inc.	Chair of DSMB for RCT of a staphylococcal immune globulin in VLBW NICU infants	<b>ADD</b>
						<b>X</b>

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

**Hide All Table Rows Checked 'No'**

**SAVE**





**INTERNATIONAL COMMITTEE *of***  
**MEDICAL JOURNAL EDITORS**

## **ICMJE Form for Disclosure of Potential Conflicts of Interest**

---

### **Evaluation and Feedback**

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.

**From:** Gantz, Marie  
**To:** Kennedy, Kathleen A; Wrage, Lisa Ann; dale\_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; alaptook@WHIRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Tuesday, August 14, 2012 3:07:24 PM  
**Attachments:** ROP Natural History Study Manuscript (for subcommittee)\_MG.doc

---

Very interesting paper. I did have some questions about the interpretation of the relationship between GA and age of onset of ROP. Specific comments/questions are in the attached version.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-4825

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Friday, July 27, 2012 9:53 AM  
**To:** Wrage, Lisa Ann; dale\_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WHIRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

**From:** [Schibler, Kurt](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 2:21:19 PM  
**Attachments:** [NEJM 2012 08 14 Schibler.pdf](#)  
[ICMJE-Disc-100524.pdf](#)

---

Hi Rose,  
Here are my forms for the NEJM for the SUPPORT FU paper.  
Thanks,  
Kurt

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Tuesday, August 14, 2012 10:00 AM  
**To:** 'Imperalta@peds.uab.edu'; 'Yvonne Vaucher'; 'finer@ucsd.edu'; 'Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu))'; 'Walsh, Michele ([Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org))'; 'mgantz@rti.org'; 'Abbot Laptook'; 'Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu))'; 'Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu))'; 'Abhik Das ([adas@rti.org](mailto:adas@rti.org))'; 'Schibler, Kurt'; 'Wade RIch'; 'nxs5@case.edu'; 'Betty Vohr ([bvohr@wihri.org](mailto:bvohr@wihri.org))'; 'Yolton, Kimberly (Kim)'; 'Roy Heyne ([Roy.Heyne@utsouthwestern.edu](mailto:Roy.Heyne@utsouthwestern.edu))'; '(b)(6)@aol.com'; 'Patricia.W.Evans@uth.tmc.edu'; 'gold005@mc.duke.edu'; 'Acarregui, Michael'; 'Adams-Chapman, Ira'; ' (apappas@med.wayne.edu)'; 'srhintz@stanford.edu'; ' (EMcGowan@tufts-nemc.org)'; 'richard.ehrenkranz@yale.edu'; 'Anna Bodnar ([abodnar@utah.gov](mailto:abodnar@utah.gov))'; 'cbauer@peds.med.miami.edu'; 'JaFuller@salud.unm.edu' ([JaFuller@salud.unm.edu](mailto:JaFuller@salud.unm.edu)); 'moshea@wfubmc.edu'; 'Gary Myers ([gary\\_myers@URMC.Rochester.edu](mailto:gary_myers@URMC.Rochester.edu))'; 'bpointex@iupui.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Kennedy, Kathleen A'; 'Jon.E.Tyson@uth.tmc.edu'; 'goldb008@mc.duke.edu'; 'cotte010@mc.duke.edu'; 'Ed Bell ([edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu))'; 'Barbara Stoll ([Barbara.Stoll@oz.ped.emory.edu](mailto:Barbara.Stoll@oz.ped.emory.edu))'; 'Seetha Shankaran'; 'Krisa Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu))'; 'dstevenson@stanford.edu'; 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); 'Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu))'; 'dale\_phelps@urmc.rochester.edu'; 'carl\_dangio@urmc.rochester.edu'  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Hi all  
The corresponding author if Dr. Neil Finer (it is on one form but not the other)

Thanks  
Rose

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]

**Sent:** Monday, August 13, 2012 4:46 PM

**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu

**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

**AUTHORS: PLEASE RETURN THIS FORM TO:**

**COPYRIGHT TRANSFER ADMINISTRATION  
THE NEW ENGLAND JOURNAL OF MEDICINE  
10 SHATTUCK STREET, BOSTON, MA 02115 U.S.A.  
781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF 8, 14, 2012

( )

PRINTED NAME KURT SCHIBLER

SIGNATURE [Handwritten Signature]



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) Kurt  
 2. Surname (Last Name) Schibler  
 3. Effective Date (07-August-2008) 14-August-2012
4. Are you the corresponding author?  Yes  No  
 Corresponding Author's Name  
 Neil Finer, MD
5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD	HD27853	X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD	HD27853	X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD	HD27853	X

Schibler

2



## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X





## ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

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## **ICMJE Form for Disclosure of Potential Conflicts of Interest**

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### **Evaluation and Feedback**

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 1:40:18 PM

---

faxing

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, August 14, 2012 1:20 PM  
**To:** Walsh, Michele  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

We need the copyright form also – do I need to resend??

Thanks

Rose

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

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Tuesday, August 14, 2012 1:18 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele; mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); Costello, Frank; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edwardbell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_pheips@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

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I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

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**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 1:18:25 PM  
**Attachments:** ICMJE-Disc-100524-Finer.pdf

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*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

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#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.





# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) **Michele**      2. Surname (Last Name) **Walsh**      3. Effective Date (07-August-2008) **14-August-2012**
4. Are you the corresponding author?     Yes     No      Corresponding Author's Name  
**Finer, Neil**
5. Manuscript Title  
**Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**
6. Manuscript Identifying Number (if you know it)  
**12-08506**

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Walsh

2



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## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

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Hide All Table Rows Checked 'No'

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---

### Evaluation and Feedback

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**From:** Michael O'Shea  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 1:15:04 PM  
**Attachments:** ICMJE-Disc-100524-OShea.pdf  
NEJM\_form\_-\_OShea.pdf

---

Rose,  
Here are the two completed forms for me.  
Thank you  
Mike

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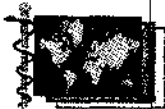
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6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
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7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X





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12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

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THE NEW ENGLAND JOURNAL OF MEDICINE  
10 SHATTUCK STREET, BOSTON, MA 02115 U.S.A.  
781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF AUGUST 14, 2012 ( )

PRINTED NAME THOMAS MICHAEL D. O'SHEA, JR

SIGNATURE T. Michael O'Shea

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 1:02:10 PM

---

No attachment

Michele Walsh, MD  
Chief, Division of Neonatology  
216.844.3759

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, August 14, 2012 10:00 AM  
**To:** 'Imperalta@peds.uab.edu'; 'Yvonne Vaucher'; 'nfiner@ucsd.edu'; 'Wally Carlo (wacarlo@uab.edu)'; Walsh, Michele; 'mgantz@rti.org'; 'Abbot Laptok'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; 'Roger Faix (Roger.Faix@hsc.utah.edu)'; 'Abhik Das (adas@rti.org)'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Wade RIch'; 'nxs5@case.edu'; 'Betty Vohr (bvohr@wihri.org)'; 'Kimberly Yolton (kimberly.yolton@cchmc.org)'; 'Roy Heyne (Roy.Heyne@utsouthwestern.edu)'; Costello, Frank; 'Patricia.W.Evans@uth.tmc.edu'; 'goldb005@mc.duke.edu'; 'Acarregui, Michael'; 'Adams-Chapman, Ira'; ' (apappas@med.wayne.edu)'; 'srhintz@stanford.edu'; ' (EMcGowan@tufts-nemc.org)'; 'richard.ehrenkranz@yale.edu'; 'Anna Bodnar (abodnar@utah.gov)'; 'cbauer@peds.med.miami.edu'; 'JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)'; 'moshea@wfubmc.edu'; 'Gary Myers (gary\_myers@URMC.Rochester.edu)'; 'bpoindex@iupui.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Kennedy, Kathleen A'; 'Jon.E.Tyson@uth.tmc.edu'; 'goldb008@mc.duke.edu'; 'cotte010@mc.duke.edu'; 'Ed Bell (edward-bell@uiowa.edu)'; 'Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)'; 'Seetha Shankaran'; 'Krisa Van Meurs (vanmeurs@stanford.edu)'; 'dstevenson@stanford.edu'; 'Duara, Shahnaz' (SDuara@med.miami.edu)'; 'Kristi Watterberg (kwatterberg@salud.unm.edu)'; 'dale\_phelps@urmc.rochester.edu'; 'carl\_dangio@urmc.rochester.edu'  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Hi all

The corresponding author if Dr. Neil Finer (it is on one form but not the other)

Thanks  
Rose

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpointex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

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#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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1. Given Name (First Name) **Janell**      2. Surname (Last Name) **Fuller**      3. Effective Date (07-August-2008) **14-August-2012**

4. Are you the corresponding author?     Yes     No      Corresponding Author's Name  
**Neil Finer, MD**

5. Manuscript Title  
**Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

6. Manuscript Identifying Number (if you know it)  
**12-08506**

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The Work Under Consideration for Publication						
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1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD/NRN		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD/NRN		X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
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6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Fuller





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7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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Relevant financial activities outside the submitted work						
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						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

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\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Hide All Table Rows Checked 'No'

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781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF 8 / 14 / 2012

PRINTED NAME: Janell Fuller, MD

SIGNATURE: 

**From:** Michael O'Shea  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 12:18:19 PM

---

Thank you, Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, August 14, 2012 9:59 AM  
**To:** Michael O'Shea  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

The corresponding author is Neil Finer

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Michael O'Shea [mailto:moshea@wakehealth.edu]  
**Sent:** Tuesday, August 14, 2012 8:55 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Rose,

The form asks for the corresponding author. Is this Yvonne or Myriam?

Thank you,

Mike

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** [mperalta@peds.uab.edu](mailto:mperalta@peds.uab.edu); Yvonne Vaucher; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)); Walsh, Michele ([Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)); [mgantz@rti.org](mailto:mgantz@rti.org); Abbot Laptook; Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)); Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Abhik Das ([adas@rti.org](mailto:adas@rti.org)); Kurt Schibler ([kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)); Wade RIch; [nxs5@case.edu](mailto:nxs5@case.edu); Betty Vohr ([bvohr@wihri.org](mailto:bvohr@wihri.org)); Kimberly Yolton ([kimberly.yolton@cchmc.org](mailto:kimberly.yolton@cchmc.org)); Roy Heyne ([Roy.Heyne@utsouthwestern.edu](mailto:Roy.Heyne@utsouthwestern.edu));

(b)(6) @aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Michael O'Shea; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu;

carl\_dangio@urmc.rochester.edu

**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

**From:** Myers, Gary  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 11:02:48 AM  
**Attachments:** SUPPORT trial NICHD COI NEJM 13-aug 12 ICMJE-Disc-100524.pdf  
SUPPORT NEJM Copyright release 8-14-12.pdf

---

Hi Rose

Attached are my COI & copyright transfer. This is very good news.

Gary

Gary J Myers, MD  
Professor of Neurology, Pediatrics and Environmental Medicine  
Department of Neurology, Child Neurology Box 631  
University of Rochester Medical Center  
601 Elmwood Avenue  
Rochester, NY 14642  
585-275-2971  
[gary\\_myers@urmc.rochester.edu](mailto:gary_myers@urmc.rochester.edu)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Myers, Gary; bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Phelps, Dale; D'Angio, Carl  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

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**the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose



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Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

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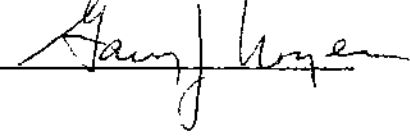
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 Corresponding Author's Name  
 Dr. Neil Finer
5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
 12-08506

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1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NIH	5 U01-HD40521-02-NICHD 1 PI Dr. D Phelps	X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD



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6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
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Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
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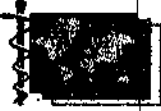
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**Date:** Tuesday, August 14, 2012 10:17:21 AM  
**Attachments:** ICMJE-Disc-100524AD.pdf  
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 2. Surname (Last Name) Das  
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5. Manuscript Title Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

6. Manuscript Identifying Number (if you know it) 12-08506

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Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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SIGNATURE Abhis Das

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**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 10:16:33 AM  
**Attachments:** Copyright-NEJM-Finer-SUPPORT FU 14Aug12.pdf

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Stephanie:  
Sorry. Is this okay?  
Richard

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**From:** Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]  
**Sent:** Tuesday, August 14, 2012 10:05 AM  
**To:** Ehrenkranz, Richard  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Hi Richard,

Can you please also send the attached copyright form too?

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](mailto:archerst@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, August 13, 2012 5:21 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

---

**From:** Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]  
**Sent:** Monday, August 13, 2012 05:19 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Rose:

That's great news. Here is my ICMJE Disclosure.

Richard

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
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New Haven, CT 06520-8064  
tele: 203-688-2320  
fax: 203-688-5426

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**Sent:** Monday, August 13, 2012 4:46 PM

**To:** mperalta@ped.s.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); Ehrenkranz, Richard; Anna Bodnar (abodnar@utah.gov); cbauer@ped.s.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu

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Rose

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781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF August 14, 2012

PRINTED NAME Richard A Ehrenkranz, MD

SIGNATURE Richard A Ehrenkranz



**From:** Phelps, Dale  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 10:12:15 AM

---

Just confirming... If we are on the CC line, we do not do these forms. (only the "To:" line)  
Dale

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, August 14, 2012 7:00 AM  
**To:** 'mperalta@peds.uab.edu'; 'Yvonne Vaucher'; 'nfiner@ucsd.edu'; 'Wally Carlo (wacarlo@uab.edu)'; 'Walsh, Michele (Michele.Walsh@UHhospitals.org)'; 'mgantz@rti.org'; 'Abbot Laptook'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; 'Roger Faix (Roger.Faix@hsc.utah.edu)'; 'Abhik Das (adas@rti.org)'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Wade RIch'; 'nxs5@case.edu'; 'Betty Vohr (bvohr@wihri.org)'; 'Kimberly Yolton (kimberly.yolton@cchmc.org)'; 'Roy Heyne (Roy.Heyne@utsouthwestern.edu)'; '(b)(6)@aol.com'; 'Patricia.W.Evans@uth.tmc.edu'; 'golds005@mc.duke.edu'; 'Acarregui, Michael'; 'Adams-Chapman, Ira'; ' (apappas@med.wayne.edu)'; 'srhintz@stanford.edu'; ' (EMcGowan@tufts-nemc.org)'; 'richard.ehrenkranz@yale.edu'; 'Anna Bodnar (abodnar@utah.gov)'; 'cbauer@peds.med.miami.edu'; 'JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)'; 'moshea@wfubmc.edu'; 'Myers, Gary'; 'bpoindex@iupui.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Kennedy, Kathleen A'; 'Jon.E.Tyson@uth.tmc.edu'; 'goldb008@mc.duke.edu'; 'cotte010@mc.duke.edu'; 'Ed Bell (edward-bell@uiowa.edu)'; 'Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu)'; 'Seetha Shankaran'; 'Krisa Van Meurs (vanmeurs@stanford.edu)'; 'dstevenson@stanford.edu'; 'Duara, Shahnaz' (SDuara@med.miami.edu); 'Kristi Watterberg (kwatterberg@salud.unm.edu)'; Phelps, Dale; D'Angio, Carl  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Hi all

The corresponding author if Dr. Neil Finer (it is on one form but not the other)

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:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; Betty Vohr (bvohr@wihri.org);

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I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

**From:** [Yolton, Kimberly \(Kim\)](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 10:04:50 AM  
**Attachments:** [NEJM form Yolton signed.pdf](#)  
[ICMJE-Disc-100524 KYolton.pdf](#)

---

Thanks Rose.

-Kim

Kimberly Yolton, PhD  
Associate Professor of Pediatrics  
Division of General and Community Pediatrics  
Cincinnati Children's Hospital Medical Center  
513-636-2815  
[Kimberly.yolton@cchmc.org](mailto:Kimberly.yolton@cchmc.org)

---

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**Sent:** Tuesday, August 14, 2012 10:00 AM  
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PRINTED NAME Kimberly Yolton, PhD

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Rev. 10/09



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#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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Kimberly
2. Surname (Last Name)  
Yolton
3. Effective Date (07-August-2008)  
13-August-2012
4. Are you the corresponding author?  Yes  No  
Corresponding Author's Name  
Neil Finer
5. Manuscript Title  
Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
6. Manuscript Identifying Number (if you know it)  
12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Cincinnati Children's Hospital		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X





## ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>ADD</b>
						<b>X</b>
						<b>ADD</b>
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>X</b>
						<b>ADD</b>
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>X</b>
						<b>ADD</b>
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>X</b>
						<b>ADD</b>
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>X</b>
						<b>ADD</b>
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>X</b>
						<b>ADD</b>
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			<b>X</b>
						<b>ADD</b>

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### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):



**ICMJE** INTERNATIONAL COMMITTEE *of*  
MEDICAL JOURNAL EDITORS

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**Hide All Table Rows Checked 'No'**

**SAVE**

### Evaluation and Feedback

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.

**From:** [Laptook, Abbot](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 9:20:09 AM  
**Attachments:** [ICMJE-Disc-100524.pdf](#)  
[SupportCopyright.PDF](#)

---

Rose

Completed forms are attached. Tx, AL

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHHospitals.org); mgantz@rti.org; Laptook, Abbot; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Vohr, Betty; Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpointex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

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<br><hr><font face='Verdana' color='Gray' size='1'><br>This e-mail and any files transmitted with it are confidential and intended solely for the use of the individual<br>or entity to whom they are addressed. If you are not the intended recipient, you are hereby notified<br>that any disclosure, copying, distribution or taking of any action in reliance on the information contained in<br>this e-mail is prohibited. If you have received this e-mail in error, please notify sender by reply e-mail and<br>delete this message and any attachment(s) immediately. Thank you for your consideration in this matter <br></font>



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



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### Section 1. Identifying Information

1. Given Name (First Name) **Abbot**      2. Surname (Last Name) **Laptook**      3. Effective Date (07-August-2008) **14-August-2012**

4. Are you the corresponding author?     Yes     No      Corresponding Author's Name  
**Dr Neil Finer**

5. Manuscript Title  
**Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

6. Manuscript Identifying Number (if you know it)  
**12-08506**

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD Neonatal Research Network		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD Neonatal Research Network		X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD



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The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



## ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

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### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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# ICMJE

INTERNATIONAL COMMITTEE of  
MEDICAL JOURNAL EDITORS

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At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

**Hide All Table Rows Checked 'No'**

**SAVE**

### Evaluation and Feedback

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THE NEW ENGLAND JOURNAL OF MEDICINE  
10 SHATTUCK STREET, BOSTON, MA 02115 U.S.A.  
781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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( )

PRINTED NAME Abbet Koftack

SIGNATURE Abbet Koftack

**From:** Dr. Athina Pappas  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Tuesday, August 14, 2012 5:12:11 AM  
**Attachments:** Pappas Copyright Form.docx  
Pappas ICMJE-Disc-100524.pdf

---

Copyright forms attached.

Thanks,  
Athina

*Athina Pappas, MD*

Assistant Professor of Pediatrics

Associate Neonatologist, Children's Hospital of Michigan and Hutzel Women's Hospital

Director, Developmental Assessment Clinic Children's Hospital of Michigan

Wayne State University School of Medicine

Phone: 313-745-5638 Fax: 313-745-5867

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Monday, August 13, 2012 3:46 PM

**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu

**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the "TO"**

**line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

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Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) Athina  
 2. Surname (Last Name) Pappas  
 3. Effective Date (07-August-2008) 14-August-2012

4. Are you the corresponding author?  Yes  No  
 Corresponding Author's Name  
 Neil Finer

5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

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						ADD
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1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

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Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

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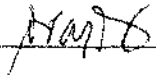
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"Gary Myers ([gary\\_myers@URMC.Rochester.edu](mailto:gary_myers@URMC.Rochester.edu)<[mailto:gary\\_myers@URMC.Rochester.edu](mailto:gary_myers@URMC.Rochester.edu)>)"  
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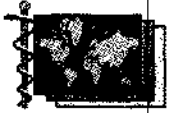
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Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

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I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose



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#### 4. Other relationships.

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						X
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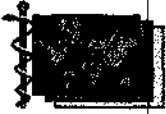
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						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
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5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
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						X
						ADD
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
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Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF Aug, 13, 2012

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**From:** Susan Hintz  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 13, 2012 5:45:30 PM  
**Importance:** High

---

Hi Rose

Do you have the "short description" of the title so I can be consistent?

Thanks

S

On Aug 13, 2012, at 1:45 PM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the "TO" line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

<NEJM-inst-for-ICMJE-form-2-10.pdf><ICMJE-Disc-100524.pdf><NEJM Form.pdf>

**From:** Roy Heyne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 13, 2012 5:22:25 PM

---

Rose, whom should we list as the corresponding author?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 3:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade RIch; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo Sanchez; Kennedy, Kathleen A; Joh.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edwardbell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Importance:** High

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Rose

---

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**From:** Ehrenkranz, Richard  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 13, 2012 5:20:01 PM  
**Attachments:** ICMJE-Disclosure-Finer FU-13Aug12.pdf

---

Rose:

That's great news. Here is my ICMJE Disclosure.

Richard

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
PO Box 208064  
New Haven, CT 06520-8064  
tele: 203-688-2320  
fax: 203-688-5426

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**Sent:** Monday, August 13, 2012 4:46 PM  
**To:** mperalta@peds.uab.edu; Yvonne Vaucher; nfiner@ucsd.edu; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHHospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Wade Rich; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhinz@stanford.edu; (EMcGowan@tufts-nemc.org); Ehrenkranz, Richard; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
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Rose



## ICMJE Form for Disclosure of Potential Conflicts of Interest

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### Instructions

**The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.**

#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



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### Section 1. Identifying Information

1. Given Name (First Name) Richard  
 2. Surname (Last Name) Ehrenkranz  
 3. Effective Date (07-August-2008) 13-August-2012

4. Are you the corresponding author?  Yes  No Corresponding Author's Name  
 Neil N. Finan

5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NIH/NICHD		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Ehrenkranz





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## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

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- Yes, the following relationships/conditions/circumstances are present (explain below):

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Hide All Table Rows Checked 'No'

SAVE



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**From:** [Wally Carlo, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 13, 2012 5:04:23 PM  
**Attachments:** [ICMJE-Disc-100524.pdf](#)  
[20120813155953.pdf](#)

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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  
L7GF Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Kennedy, Kathleen A; [Jon.E.Tyson@uth.tmc.edu](mailto:Jon.E.Tyson@uth.tmc.edu); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Ed Bell ([edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)); Barbara Stoll ([Barbara.Stoll@oz.ped.emory.edu](mailto:Barbara.Stoll@oz.ped.emory.edu)); Seetha Shankaran ; Krisa Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); [dstevenson@stanford.edu](mailto:dstevenson@stanford.edu); 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); [carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu)  
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781.207.6529 FAX**

Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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AGREED TO THIS DAY OF 8/13/2012 ( )

PRINTED NAME: Waldemar A. Carlo

SIGNATURE [Signature]



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

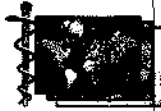
This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) 2. Surname (Last Name) 3. Effective Date (07-August-2008)  
 Waldemar Carlo 13-August-2012

4. Are you the corresponding author?  Yes  No Corresponding Author's Name  
Neil Finer

5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
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\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### Relevant financial activities outside the submitted work





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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	MEDNAX		X
						<b>ADD</b>

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

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**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 13, 2012 5:02:42 PM

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Thanks!!!!

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 1:57 PM  
**To:** Vaucher, Yvonne  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

I talked to Neil earlier today and told him Steph and I would get them all for you!!

THANKS

ROSE

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

---

**From:** Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
**Sent:** Monday, August 13, 2012 4:52 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

Thanks Rose. I was just writing you to ask if how these forms were to be distributed. I will be OOT but have intermittent email access until August 21<sup>st</sup>. The goal is to have the resubmission done by August 24<sup>th</sup>.

Yvonne

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 1:46 PM  
**To:** mperalta@peds.uab.edu; Vaucher, Yvonne; Finer, Neil; Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)); Walsh, Michele ([Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)); mgantz@rti.org; Abbot Laptook; Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)); Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Abhik Das ([adas@rti.org](mailto:adas@rti.org)); Kurt Schibler ([kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)); Rich, Wade; nxs5@case.edu; Betty Vohr ([bvohr@wihri.org](mailto:bvohr@wihri.org)); Kimberly Yolton ([kimberly.yolton@cchmc.org](mailto:kimberly.yolton@cchmc.org)); Roy Heyne ([Roy.Heyne@utsouthwestern.edu](mailto:Roy.Heyne@utsouthwestern.edu)); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; ([apappas@med.wayne.edu](mailto:apappas@med.wayne.edu)); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar ([abodnar@utah.gov](mailto:abodnar@utah.gov)); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu ([JaFuller@salud.unm.edu](mailto:JaFuller@salud.unm.edu)); moshea@wfubmc.edu; Gary Myers

([gary\\_myers@URMC.Rochester.edu](mailto:gary_myers@URMC.Rochester.edu)); [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu)

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Kennedy, Kathleen A; [Jon.E.Tyson@uth.tmc.edu](mailto:Jon.E.Tyson@uth.tmc.edu); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Ed Bell ([edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)); Barbara Stoll ([Barbara.Stoll@oz.ped.emory.edu](mailto:Barbara.Stoll@oz.ped.emory.edu)); Seetha Shankaran ; Krisa Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); [dstevenson@stanford.edu](mailto:dstevenson@stanford.edu); 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); [carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu)

**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*

**Importance:** High

Hi

We have good news from the New England Journal – They say ...changes are requested before it can be accepted.....

Neil, Wally, Myriam, Yvonne, Marie, Abhik and I are working on the revision.

**In the meantime, I need everyone listed in the “TO” line (all of the authors) to completed the ICMJE and the copyright transfer agreement attached to the email and send it back to me by Friday August 17. We will submit all of them centrally to NEJM. This is also under embargo, so is not to be released as the publication could be jeopardized.**

I included the site PI's at the SUPPORT recruiting centers to keep them in the loop – THANKS TO EVERYONE FOR ALL THE HARD WORK- we are almost there.

Rose

**From:** Rich Wade  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
**Date:** Monday, August 13, 2012 5:00:55 PM  
**Attachments:** ICMJE-Disc-100524.pdf  
Rich copyright Vaucher FU NEJM.pdf

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W Rich Forms for Vaucher FU paper NEJM.

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 1:46 PM  
**To:** mperalta@peds.uab.edu; Vaucher, Yvonne; Finer, Neil; Wally Carlo (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); mgantz@rti.org; Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abhik Das (adas@rti.org); Kurt Schibler [kurt.schibler@cchmc.org]; Rich, Wade; nxs5@case.edu; Betty Vohr (bvohr@wihri.org); Kimberly Yolton (kimberly.yolton@cchmc.org); Roy Heyne (Roy.Heyne@utsouthwestern.edu); (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; Acarregui, Michael; Adams-Chapman, Ira; (apappas@med.wayne.edu); srhintz@stanford.edu; (EMcGowan@tufts-nemc.org); richard.ehrenkranz@yale.edu; Anna Bodnar (abodnar@utah.gov); cbauer@peds.med.miami.edu; JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); moshea@wfubmc.edu; Gary Myers (gary\_myers@URMC.Rochester.edu); bpoindex@iupui.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Pablo.Sanchez@UTSouthwestern.edu; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; Ed Bell (edward-bell@uiowa.edu); Barbara Stoll (Barbara.Stoll@oz.ped.emory.edu); Seetha Shankaran ; Krisa Van Meurs (vanmeurs@stanford.edu); dstevenson@stanford.edu; 'Duara, Shahnaz' (SDuara@med.miami.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); dale\_phelps@urmc.rochester.edu; carl\_dangio@urmc.rochester.edu  
**Subject:** \*\*CONFIDENTIAL SUPPORT FU PAPER AND NEJM\*\*  
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Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

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For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) 2. Surname (Last Name) 3. Effective Date (07-August-2008)  
 Wade Rich 13-August-2012

4. Are you the corresponding author?  Yes  No Corresponding Author's Name  
Finer, Neil

5. Manuscript Title  
 Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

6. Manuscript Identifying Number (if you know it)  
 12-08506

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

#### The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD		X ADD
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X

Rich



## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X





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Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
9. Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
11. Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD X

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest  
 Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

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Contribution Number: 12-08506

Short Title or description of Contribution: Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Corresponding Author: Dr. Neil Finer

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If author was a U.S. Government employee at the time the article was written, please check below.

AGREED TO THIS DAY OF 13 / AUG / 2012

PRINTED NAME Wade D Rich

SIGNATURE 

**From:** Ripley, Julie  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, August 13, 2012 4:48:20 PM

---

Hi Rose -

I'll find out from my manager (she's left for the day), and I'll let you know.

Best,  
Julie

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:47 PM  
**To:** Ripley, Julie  
**Subject:** RE: New England Journal of Medicine 12-08506

Do we need to do anything for Dr. Poindexter or simply add her to the revised manuscript?

Thanks  
Rose

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

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

**From:** Ripley, Julie [mailto:jripley@nejm.org]  
**Sent:** Monday, August 13, 2012 4:41 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

Thank you for letting me know.

Best,  
Julie

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 13, 2012 4:26 PM  
**To:** Ripley, Julie; (b)(6)@aol.com  
**Subject:** RE: New England Journal of Medicine 12-08506

Hi

Dr. Anna Dusick died. Dr. Brenda Poindexter's name was inadvertently left off of the author line when the two papers were merged. She was originally listed on Dr. Peralta's submission 12-01618.

Thanks so much for your help

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

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

From: onbehalfof+jripley+nejm.org@manuscriptcentral.com

[mailto:onbehalfof+jripley+nejm.org@manuscriptcentral.com] On Behalf Of jripley@nejm.org

Sent: Monday, August 13, 2012 4:19 PM

To: Higgins, Rosemary (NIH/NICHD) [E]: (b)(6)@aol.com

Subject: New England Journal of Medicine 12-08506

Re: 12-08506 - Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Dear Dr. Higgins:

Thank you for calling earlier today. I was told one of the authors of this manuscript is now deceased. Which author is it?

I will also ask my manager if we need change of author forms to "add" the author that was forgotten when the manuscripts merged. What is the name of that author?

Sincerely,

Julie Ripley

Editorial Assistant

New England Journal of Medicine

10 Shattuck Street

Boston, MA 02115

(617) 734-9800

Fax: (617) 739-9864

<http://www.nejm.org>

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This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance

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upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

**From:** Wally Carlo, M.D.  
**To:** Das, Abhik; Gantz, Marie; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wcarlo@uab.edu; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, August 13, 2012 4:42:56 PM

---

Great idea. Here it is:

"In comparing several secondary outcomes between treatment groups for both arms of this factorial design trial, no adjustments were made for multiple comparisons. Thus, appropriate caution should be used in interpreting the reported results."

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Monday, August 13, 2012 3:41 PM  
**To:** Wally Carlo, M.D.; Gantz, Marie; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wcarlo@uab.edu; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

Good point about the secondary outcomes. Perhaps we should insert the word 'secondary' before 'outcomes' in the first sentence.

Thanks

Abhik

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, August 13, 2012 4:28 PM  
**To:** Gantz, Marie; Vaucher, Yvonne; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wcarlo@uab.edu; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

How about shortening it a bit. I drop the italics part as it may introduce doubt about our primary

outcome. I think this really applies to many secondary outcomes not to components of the primary one.

In comparing several outcomes between treatment groups for both arms of this factorial design trial, no adjustments were made for multiple comparisons. Thus, appropriate caution should be used in interpreting the reported results.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

1700 6th Avenue South

176F Suite 9380R

Birmingham, AL 35233-7335

Phone: 205 934 4680

FAX: 205 934 3100

Cell: 205 (b)(6)

---

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

**Sent:** Monday, August 13, 2012 11:29 AM

**To:** Vaucher, Yvonne; Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarfo@uab.edu](mailto:wacarfo@uab.edu); Myriam Peralta, M.D.

**Cc:** Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: New England Journal of Medicine 12-08506

Yvonne, here is a suggested statement. Per Abhik, we can tweak or delete the italicized part.

In comparing several outcomes between treatment groups for both arms of this factorial design trial, no adjustments were made for multiple comparisons. Thus, appropriate caution should be used in interpreting the reported results.

Marie Gantz, Ph.D.

Senior Research Statistician

RTI International

[mgantz@rti.org](mailto:mgantz@rti.org)

828-351-6255

---

**From:** Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]

**Sent:** Monday, August 13, 2012 11:56 AM

**To:** Gantz, Marie; Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarfo@uab.edu](mailto:wacarfo@uab.edu); Myriam Peralta, M.D.

**Cc:** Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: New England Journal of Medicine 12-08506

OK. How would you like to phrase the "global" statement?



Yvonne

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Monday, August 13, 2012 8:20 AM  
**To:** Das, Abhik; Wally Carlo, M.D.; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarlo@uab.edu](mailto:wacarlo@uab.edu); Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

My preference would be to remove the sentence about the number of statistically significant comparisons that could be due to chance as the editor suggests and replacing it with a global statement. My calculation of the number of differences that could be due to chance was based on the number of FU outcomes we tested, whether or not they were presented in the paper (79 including all the tables we created), but I did not account for the GA strata analyses – if those are included, the number of differences that could be seen by chance would be even higher.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

---

**From:** Das, Abhik  
**Sent:** Monday, August 13, 2012 11:01 AM  
**To:** Wally Carlo, M.D.; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarlo@uab.edu](mailto:wacarlo@uab.edu); Gantz, Marie; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

Agree, that is why I suggest a global statement to allay the statistical reviewer. Or, we can just keep the last sentence in the methods section that the editor took out, which should serve the same purpose.

Thanks

Abhik

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, August 13, 2012 10:58 AM  
**To:** Das, Abhik; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarlo@uab.edu](mailto:wacarlo@uab.edu); Gantz, Marie; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

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Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Monday, August 13, 2012 9:46 AM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu; Gantz, Marie; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

Here is my first take on the comments from the statistical reviewer. Marie needs to chime in as well.

Statistical Reviewer: 1

Comments for the Author:

(b)(4),(b)(6)

Thanks

Abhik

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

From: Vaucher, Yvonne [mailto:[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)]

Sent: Saturday, August 11, 2012 1:03 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'wacarlo@uab.edu'; Gantz, Marie; 'ADHIKARI@ukzn.ac.za'

Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]

Subject: Re: New England Journal of Medicine 12-08506

Miriam, Could you double check the text edits related to the saturation arm?

Marie and Abhik, how do you want to reply to the statistics related questions?

Yvonne

On 8/10/12 2:28 PM, "Higgins, Rosemary (NIH/NICHD) [E]"

<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

>

**From:** [Finer, Neil](#)  
**To:** [Gantz, Marie](#); [Vaucher, Yvonne](#); [Das, Abhik](#); [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [wacarolo@uab.edu](#); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, August 13, 2012 3:13:45 PM

---

This sounds fine  
Neil

---

**From:** [Gantz, Marie \[mailto:mgantz@rti.org\]](mailto:mgantz@rti.org)  
**Sent:** Monday, August 13, 2012 9:29 AM  
**To:** [Vaucher, Yvonne](#); [Das, Abhik](#); [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wacarolo@uab.edu](#); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506

Yvonne, here is a suggested statement. Per Abhik, we can tweak or delete the italicized part.

In comparing several outcomes between treatment groups for both arms of this factorial design trial, no adjustments were made for multiple comparisons. Thus, appropriate caution should be used in interpreting the reported results *because some of significant associations reported may have occurred by chance.*

**Marie Gantz, Ph.D.**  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

---

**From:** [Vaucher, Yvonne \[mailto:yvaucher@ucsd.edu\]](mailto:yvaucher@ucsd.edu)  
**Sent:** Monday, August 13, 2012 11:56 AM  
**To:** [Gantz, Marie](#); [Das, Abhik](#); [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wacarolo@uab.edu](#); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506

OK. How would you like to phrase the "global" statement?

Yvonne

---

**From:** [Gantz, Marie \[mailto:mgantz@rti.org\]](mailto:mgantz@rti.org)  
**Sent:** Monday, August 13, 2012 8:20 AM  
**To:** [Das, Abhik](#); [Wally Carlo, M.D.](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wacarolo@uab.edu](#); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
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Marie

Marie Gantz, Ph.D.  
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828-254-6255

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**Subject:** RE: New England Journal of Medicine 12-08506

Agree, that is why I suggest a global statement to allay the statistical reviewer. Or, we can just keep the last sentence in the methods section that the editor took out, which should serve the same purpose.

Thanks

Abhik

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**To:** Das, Abhik; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wacarlo@uab.edu](mailto:wacarlo@uab.edu); Gantz, Marie; Myriam Peralta, M.D.  
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Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

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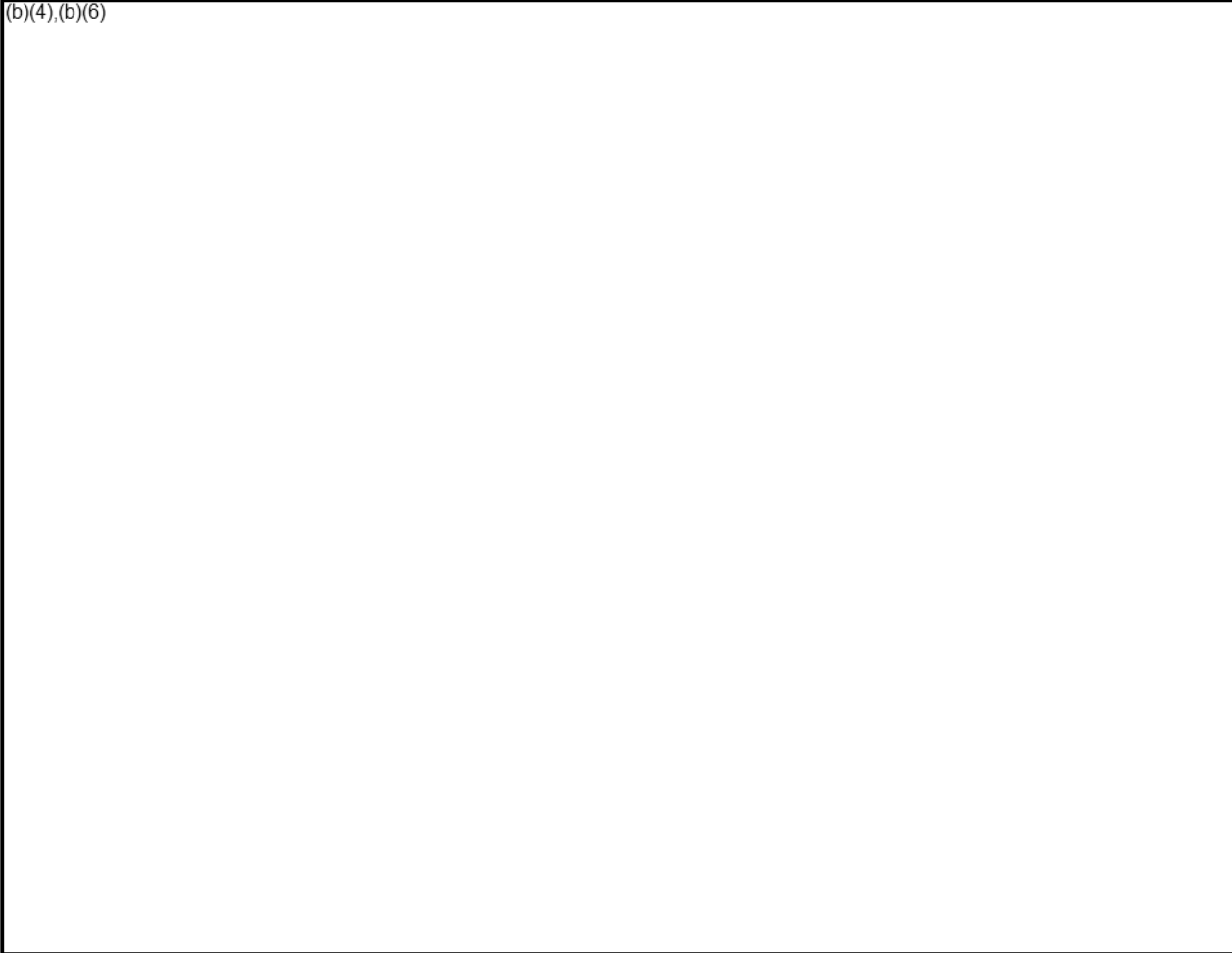
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Here is my first take on the comments from the statistical reviewer. Marie needs to chime in as well.

Statistical Reviewer: 1

Comments for the Author:

(b)(4),(b)(6)



Thanks

Abhik

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]

Sent: Saturday, August 11, 2012 1:03 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'wacarlo@uab.edu'; Gantz, Marie;

'ADHIKARI@ukzn.ac.za'

Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]

Subject: Re: New England Journal of Medicine 12-08506

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Marie and Abhik, how do you want to reply to the statistics related questions?

Yvonne

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<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

>

**From:** [Finer, Neil](#)  
**To:** [Gantz, Marie](#); [Das, Abhik](#); [Wally Carlo, M.D.](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, August 13, 2012 12:03:09 PM

---

I agree  
Thanks Marie  
Neil

---

**From:** [Gantz, Marie \[mailto:mgantz@rti.org\]](mailto:mgantz@rti.org)  
**Sent:** Monday, August 13, 2012 8:20 AM  
**To:** [Das, Abhik](#); [Wally Carlo, M.D.](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); [Myriam Peralta, M.D.](#)  
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Statistical Reviewer: 1  
Comments for the Author:

(b)(4),(b)(6)

(b)(4),(b)(6)

Thanks

Abhik

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Sent: Saturday, August 11, 2012 1:03 PM

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**To:** [Das, Abhik](#); [Gantz, Marie](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, August 13, 2012 11:22:28 AM

---

Me too

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

---

**From:** [Das, Abhik \[mailto:adas@rti.org\]](mailto:adas@rti.org)  
**Sent:** Monday, August 13, 2012 10:21 AM  
**To:** [Gantz, Marie](#); [Wally Carlo, M.D.](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506

Works for me.

Thanks

Abhik

---

**From:** [Gantz, Marie](#)  
**Sent:** Monday, August 13, 2012 11:20 AM  
**To:** [Das, Abhik](#); [Wally Carlo, M.D.](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); [Myriam Peralta, M.D.](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 12-08506

My preference would be to remove the sentence about the number of statistically significant comparisons that could be due to chance as the editor suggests and replacing it with a global statement. My calculation of the number of differences that could be due to chance was based on the number of FU outcomes we tested, whether or not they were presented in the paper (79 including all the tables we created), but I did not account for the GA strata analyses – if those are included, the number of differences that could be seen by chance would be even higher.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-6255

---

**From:** Das, Abhik  
**Sent:** Monday, August 13, 2012 11:01 AM  
**To:** Wally Carlo, M.D.; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wcarlo@uab.edu](mailto:wcarlo@uab.edu); Gantz, Marie; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

Agree, that is why I suggest a global statement to allay the statistical reviewer. Or, we can just keep the last sentence in the methods section that the editor took out, which should serve the same purpose.

Thanks

Abhik

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, August 13, 2012 10:58 AM  
**To:** Das, Abhik; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wcarlo@uab.edu](mailto:wcarlo@uab.edu); Gantz, Marie; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

I do not think we should speculate that the mortality difference could be by chance, particularly in view of the BOOST 2 findings.

Wally Carlo, M.D.  
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University of Alabama at Birmingham  
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176F Suite 9380R  
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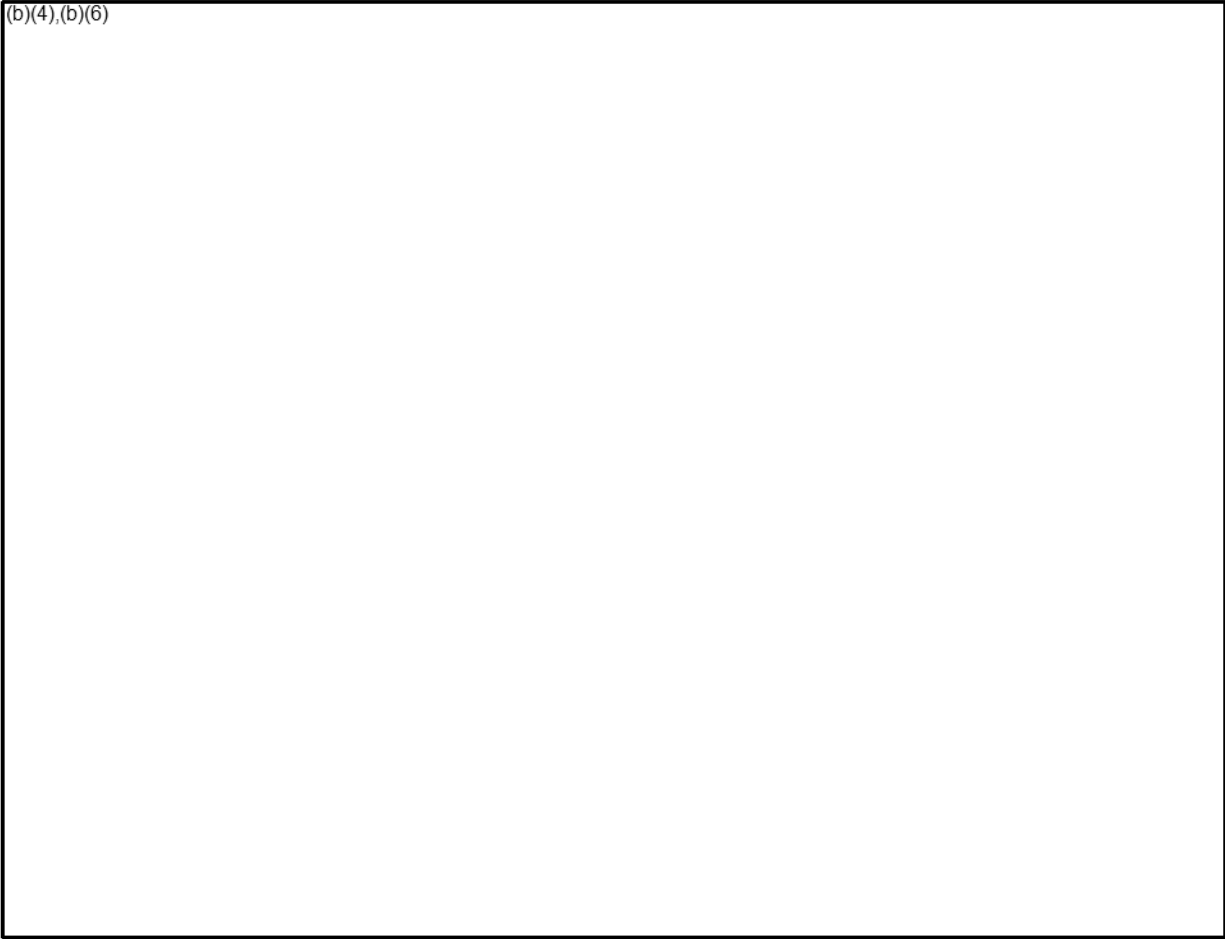
**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Monday, August 13, 2012 9:46 AM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; [wcarlo@uab.edu](mailto:wcarlo@uab.edu); Gantz, Marie; Myriam Peralta, M.D.  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

Here is my first take on the comments from the statistical reviewer. Marie needs to chime in as well.

Statistical Reviewer: 1

Comments for the Author:

(b)(4),(b)(6)



Thanks

Abhik

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]

Sent: Saturday, August 11, 2012 1:03 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'wacarlo@uab.edu'; Gantz, Marie; 'ADHIKARI@ukzn.ac.za'

Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]

Subject: Re: New England Journal of Medicine 12-08506

Miriam, Could you double check the text edits related to the saturation arm?

Marie and Abhik, how do you want to reply to the statistics related questions?

Yvonne

On 8/10/12 2:28 PM, "Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

>

**From:** Myriam Peralta, M.D.  
**To:** Wally Carlo, M.D.; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wacarlo@uab.edu; mgantz@rti.org  
**Cc:** adas@rti.org; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506  
**Date:** Monday, August 13, 2012 10:58:00 AM

---

Yvonne can you send me the comment I did not receive this thanks

---

**From:** Wally Carlo, M.D.  
**Sent:** Monday, August 13, 2012 7:10 AM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'wacarlo@uab.edu'; 'mgantz@rti.org'; Myriam Peralta, M.D.  
**Cc:** 'adas@rti.org'; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 12-08506

This was going to the wrong Myriam.

I am copying her now.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

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

**From:** Vaucher, Yvonne [mailto:vvaucher@ucsd.edu]  
**Sent:** Saturday, August 11, 2012 12:03 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'wacarlo@uab.edu'; 'mgantz@rti.org'; 'ADHIKARI@ukzn.ac.za'  
**Cc:** 'adas@rti.org'; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: New England Journal of Medicine 12-08506

Miriam, Could you double check the text edits related to the saturation arm?

Marie and Abhik, how do you want to reply to the statistics related questions?

Yvonne

On 8/10/12 2:28 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

>

**From:** Roger Faix  
**To:** Kennedy, Kathleen A  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Sunday, August 12, 2012 6:41:22 PM  
**Attachments:** ROP Natural History Study Manuscript (for subcommittee) - RGF.docx

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Hi Kathleen!

I'm finally off service and have had the opportunity to review your manuscript. Let me say that it is one of the best written and best organized of any that I have encountered. I did have a few suggestions and comments noted on the text of the attached version. I propose double strikethrough for deletion and red font for addition. Questions, suggestions, comments are in bold turquoise font. I hope these are useful for you.

Roger

---

**From:** Kennedy, Kathleen A [Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Friday, July 27, 2012 7:53 AM  
**To:** Wrage, Lisa Ann (wrage@rti.org); dale\_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger Faix; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley Yoder  
**Cc:** Archer, Stephanie  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708



## **Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

Kathleen A Kennedy, Lisa A Wrage, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Michelle Walsh, Abbot Laptok, Roger Faix, Brad Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, Wade Rich, Dale L Phelps

### Abbreviations:

GA – gestational age

PMA – postmenstrual age

ROP – retinopathy of prematurity

SUPPORT – Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

### Keywords

retinopathy of prematurity, screening, extremely preterm infants **Add 'validation' as a Keyword?**

### Corresponding author:

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### Acknowledgments:

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

**What This Study Adds**

Our data do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, challenge the accepted notion that the onset of ROP ~~to~~ is better correlated with postmenstrual than chronological age.

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Results:** 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had an ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. (**iw as going to add something about limited generalizability, but on further reading, see that you addressed the issue in the Discussion.**) Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27<sup>6</sup>/<sub>7</sub> weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

## Patients and Methods

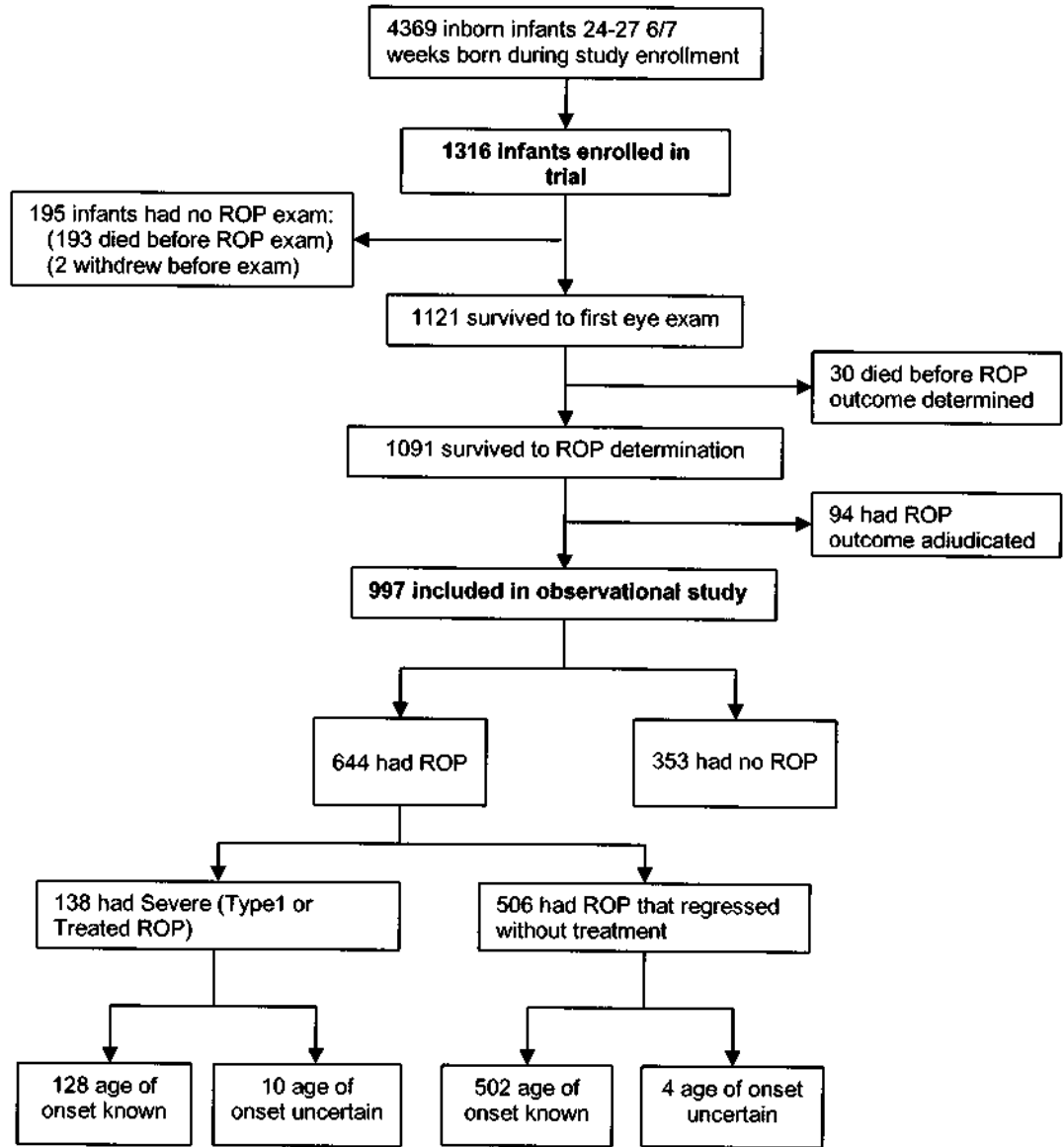
In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0</sup>/<sub>7</sub> – 27<sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: Severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) vs No Severe ROP (full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation. **(Is a passage warranted about the entirely reasonable to focus on ROP, rather than 'death or ROP' as competing outcomes?)**

Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

## Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1) **(Should all Figures and Tables go to the end of the manuscript, with exhortations to See Figure/Table be embed in the text? Perhaps anticipated Journal for submission has different guidelines?)**. 94 of these outcomes were adjudicated. Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. 65% (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

**Figure 1. Flow diagram of patient enrollment**



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

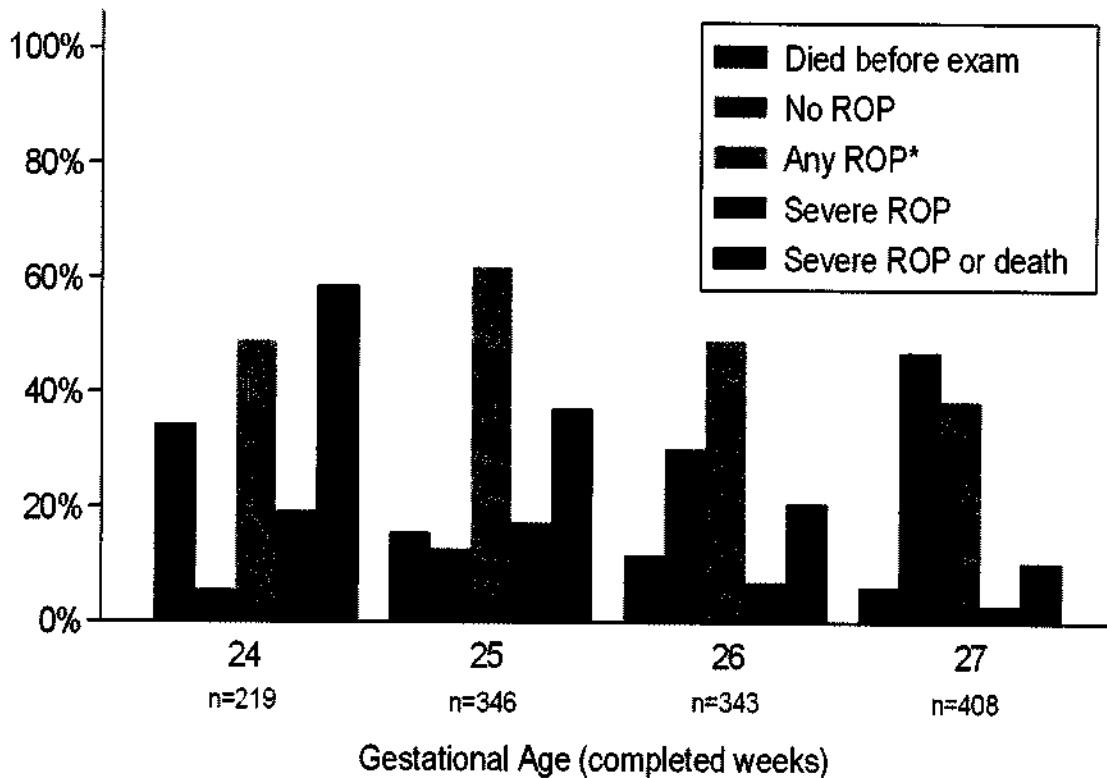
	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
<b>n</b>	<b>1316</b>	<b>997</b>	<b>353</b>	<b>644</b>	<b>138</b>
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup> [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



\*Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/treated) ROP

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a longer duration of supplemental oxygen than infants without ROP.

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [(n (%))]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

<sup>2</sup> missing data

**Are any P values or 95% CIs to be added, or simply a notation that no significant differences were found?**

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

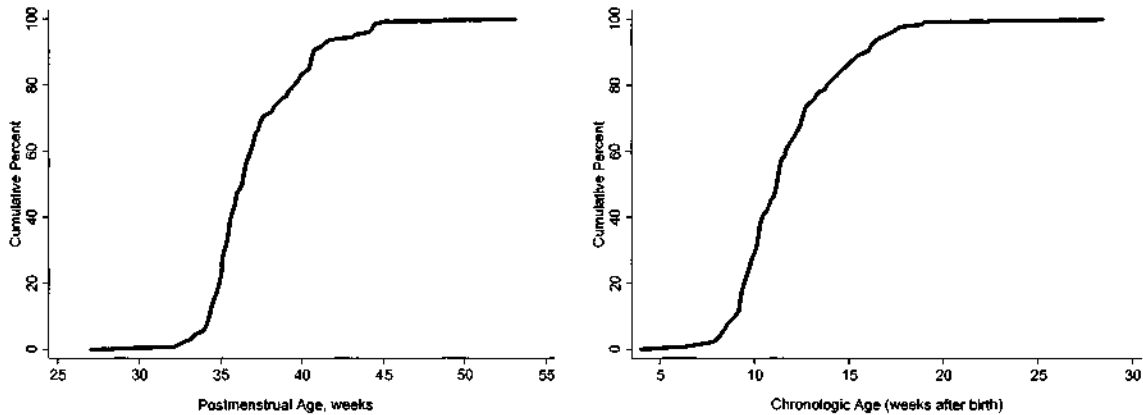
ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

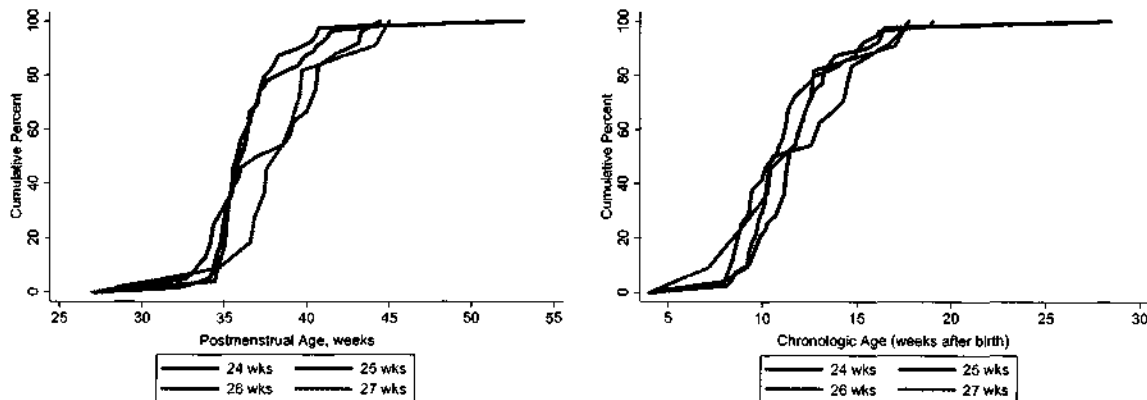


**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**

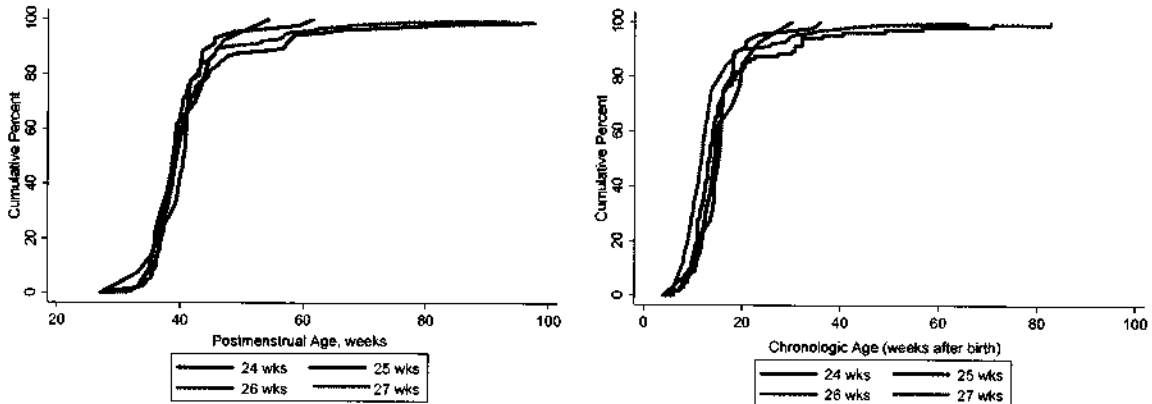


Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

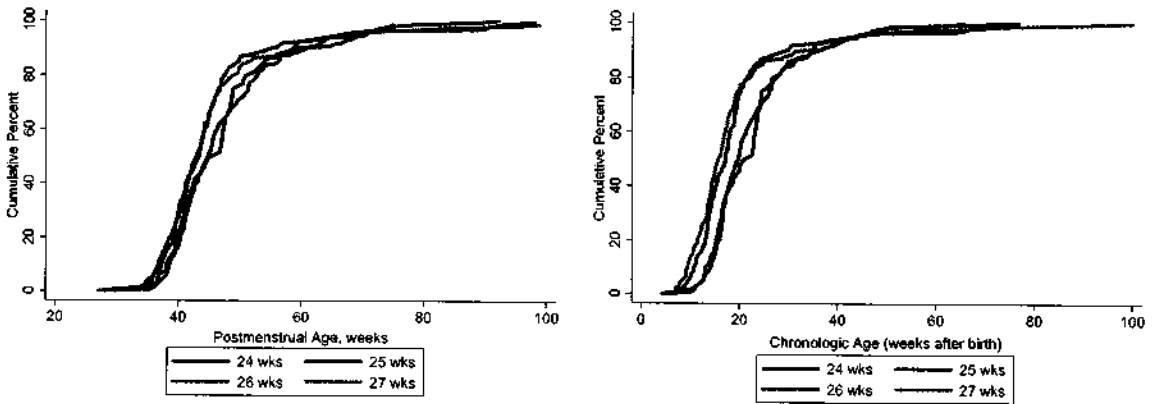
Is Table 3 redundant compared to Figures 3 and 4?

**Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth**

**No ROP**



**Mild/Moderate ROP**



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

<b>Infants with Severe ROP N=138</b>	<b>First exam with severe ROP occurred <u>before</u> discharge to home n=124</b>	<b>First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14</b>
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home**

<b>Worst exam findings prior to discharge either or both eyes:</b>	<b>Severe ROP Group N=14</b>	<b>No Severe ROP Group N=535</b>
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home**

<b>Risk Factor</b>	<b>Severe ROP Group N=14</b>	<b>No Severe ROP Group N=535</b>
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

## Discussion

In prior ROP natural history studies,<sup>3</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>12</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum ( $< 750$ g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological age and severe ROP did not occur before 6 weeks. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT

Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>14</sup>

## Conclusion

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

**One final query: is/was there some unique features about the one outlier patient that might have identified him as someone who could be expected to develop type I ROP lae? (e.g., we noted in our system that there were a small number of kids >30 wks GA and/or 1200 gms BW who developed significant ROP, but all could be anticipated if a few additional criteria were added to these older GA infants, e.g., culture-proven sepsis (not CONS), NEC Bell Stage 2 or above, requirement for iNO)**

## References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006; 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 1988; 81: 697-706.
- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 1998; 338: 1572-1576.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233-250.

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- <sup>9</sup> Good Wv, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
- <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tornqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
- <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.
- <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
- <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
- <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.

**From:** Vaucher, Yvonne  
**To:** [Finer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [wacarlo@uab.edu](#); [Gantz, Marie](#); "Miriam Adhikari"  
**Cc:** [Das, Abhik](#)  
**Subject:** Re: New England Journal of Medicine 12-08506  
**Date:** Friday, August 10, 2012 6:42:38 PM

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Good news. Will do. Thanks to everyone for your help!

On 8/10/12 2:20 PM, "Finer, Neil" <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)> wrote:

>Hi Everyone  
>This just in from NEJM  
>Yvonne and Miriam  
>Would you take the first crack at getting this ready for a reply and copy  
>the rest of us with your suggestions?  
>Many thanks  
>We are close!  
>Thanks you for all your efforts  
>This will get published!!  
>Be well  
>Neil  
>  
>-----Original Message-----  
>From: [onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com)  
>[\[mailto:mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com\]](mailto:mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com) On Behalf Of  
>[editorial@nejm.org](mailto:editorial@nejm.org)  
>Sent: Friday, August 10, 2012 2:07 PM  
>To: Finer, Neil  
>Subject: New England Journal of Medicine 12-08506  
>  
>Dear Dr. Finer:  
>  
>I am writing about your manuscript, "Neurodevelopmental Outcome at 18-22  
>months of the Surfactant Positive Airway Pressure and Pulse Oximetry  
>Randomized Trial (SUPPORT)". Your combined manuscript was evaluated by 2  
>external reviewers, a statistical reviewer, and the editors. While your  
>new manuscript nicely combines key findings of the 2 manuscripts, some  
>further revisions taking into account the reviewer comments (below) and  
>editorial comments (see attached manuscript) are requested before it  
>could be accepted for publication.  
>  
>As you have already substantially revised your initial submission(s), I  
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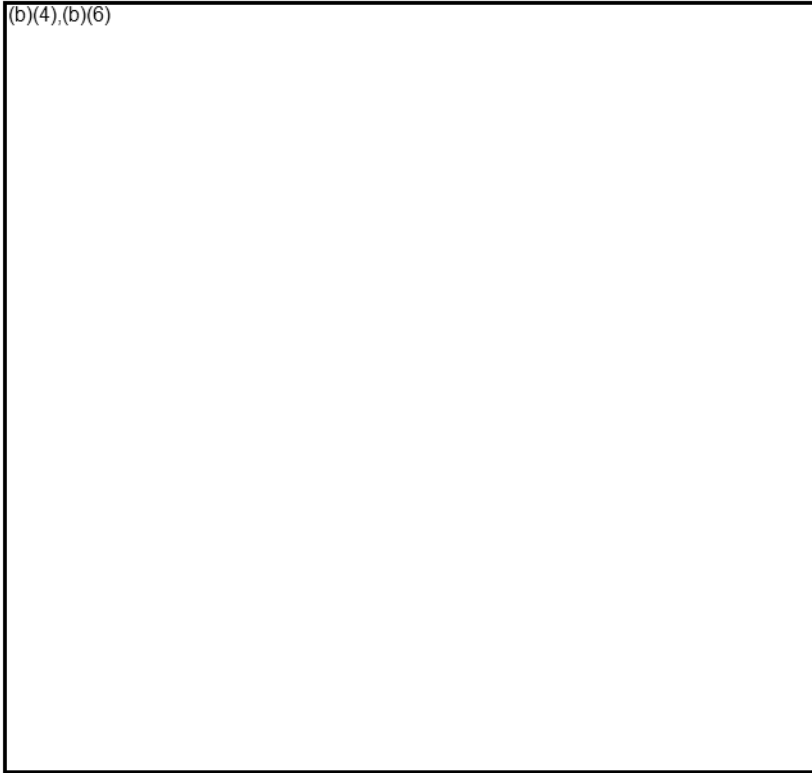
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>Thank you again for your work. Please do not hesitate to contact me if  
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>Sincerely,  
>  
>Caren G. Solomon, MD  
>New England Journal of Medicine  
>10 Shattuck Street  
>Boston, MA 02115  
>(617) 734-9800  
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><http://www.nejm.org>  
>  
>Reviewer: 1  
><b>Comments for the Author</b>  
>This neurodevelopmental outcome study is a follow up of 18-22 month old  
>children who were in the SUPPORT study published in the NEJM in 2010. The  
>study data showed (b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

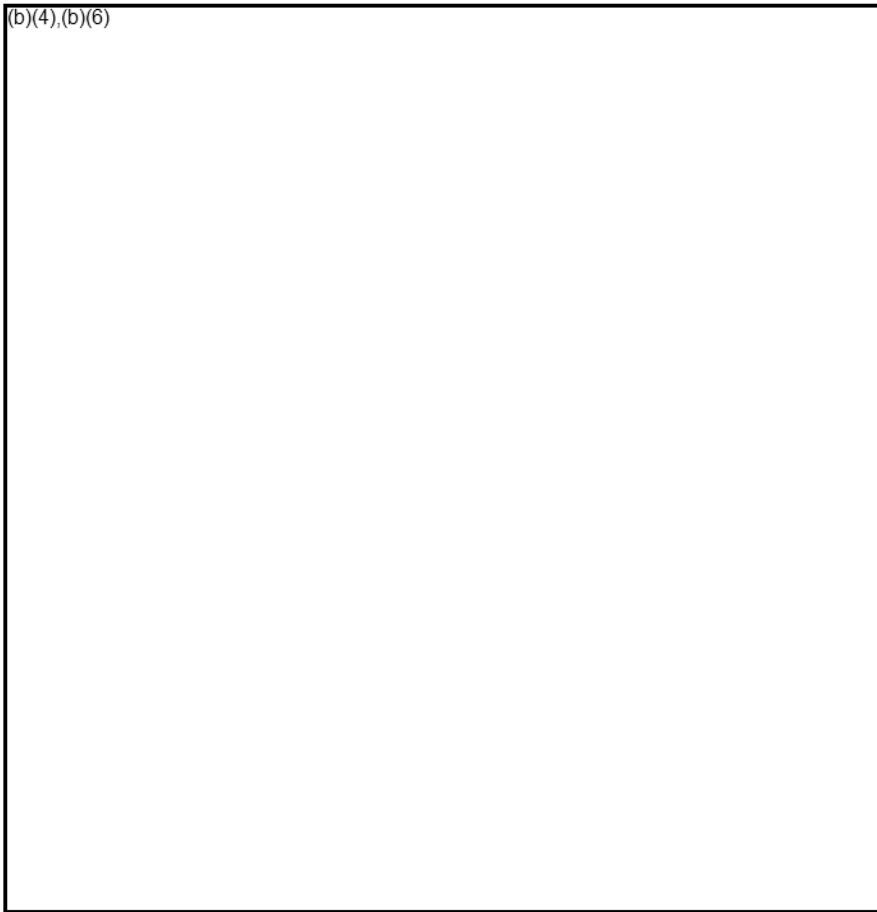


>


>Reviewer: 2

><b>Comments for the Author</b>

(b)(4),(b)(6)



(b)(4),(b)(6)



**From:** [Gantz, Marie](#)  
**To:** [Phelps, Dale](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Das, Abhik](#)  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Friday, August 10, 2012 5:41:19 PM  
**Attachments:** [SUPP10\\_data\\_for\\_infants\\_not\\_meeting\\_ROP\\_surgery\\_criteria\\_10AUG12.rtf](#)

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Dale,

The attached document is the previous output I had sent you on the 23 who did not meet criteria for surgery, but I have added the percent of infants enrolled at center who had ROP surgery without meeting criteria. Let me know if that answers your question.

Marie

**Marie Gantz, Ph.D.**  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-4255

---

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Sunday, July 22, 2012 7:27 PM  
**To:** Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi Marie,

I have carefully reviewed each of these cases and they're an interesting mix\*(see attached).

Although the cases were 'spread over 11 centers', there were two centers that had 5 cases, and the other 9 centers had only 1 or 2 cases. In order to know if there is a problem here, we need to be able to appreciate if the two centers with 5 cases each (your coded centers E and upper case i) were high enrollers overall. Also, while some centers had "only" 1 or 2 cases, some center enrolled less than 10 subjects.

I know we want to keep things coded, but in order to get the full grasp, I need more. Perhaps you could express it as a percentage of enrollees (which would approximate things, but would not reveal a percentages of survivors who got exams) ?

Dale

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Friday, May 25, 2012 11:15 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Rose and Dale,

SUPP10 data for the 23 infants who did not meet criteria for surgery are attached. I've coded the center and infant IDs, but you can see that the 23 infants were spread across 11 centers. Note that there were a couple of cases where "Threshold (New Type 1)" was coded as "Y" on the SUPP10, but the other individual variables (zone, stage and plus disease) did not back that up. I know that when we were doing the original analysis, we queried cases where there were similar disagreements in the data, but I think we must have only queried cases where the ROP final outcome was based on threshold ROP rather than on surgery (these 23 cases were all classified based on surgery). Let me know if you have any questions.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
28-254-0255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, May 25, 2012 9:53 AM  
**To:** Das, Abhik  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Yes – maybe some of them had other issues and we need to know. We also need to know if this is only a few sites or spread across the network.

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](mailto:higginsr@mail.nih.gov)

---

**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Friday, May 25, 2012 9:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Rose:

I was surprised to see that as well. We can pull all the data from the SUPP10 forms for each of these babies for you to review. Is that what you had in mind?

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, May 25, 2012 9:49 AM  
**To:** Das, Abhik  
**Subject:** FW: ROP data from SUPPORT TRIAL FOR DSMC

Abhik

I am a little concerned that we had 23 infants who got ROP surgery, but didn't meet the criteria- we should look at these cases in a little more detail (as well as see if this is site dependent)>

Is it possible to get the SUPP 10 forms on each of these infants – this will help to try to figure out why they had surgery and didn't reach the usual "Threshold" definition??

We need this to be able to explain this to the DSMC.

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](mailto:higginsr@mail.nih.gov)

---

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Thursday, May 24, 2012 5:15 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi Marie,

There are quite a few more cases of treatment before documented criteria for treatment than I had expected.

As we go back to the DSMC with this, I think it would be important to be able to better explain it.

Also, just to confirm with you. Infants who might have had ROP disease worse than Type 1 would also be considered treated appropriately. Did you exclude any infants because they had stage 4a or 4b or stage 5?

If it is going to take a lot of time, please discuss it with Dr. Das first. He and Dr. Higgins and I can discuss whether to go forward.

I do think it will be important to understand and be able to account for at least some of them -- and the fuller clinical ROP picture is likely to do that.

Therefore, I would like to request that you provide the more detailed data.

I also volunteer to individually review the ROP printouts from the subgroups listed below: (there is a nice de-identified format that was used for INS-2 that you could use that gives me basically two pages per infant -- one for each eye)

- 5 who met criteria for surgery, but were not recorded as having had surgery (123-127=5)
- 23 who did receive surgery, but did not meet criteria for surgery

Thanks!

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 1:39 PM  
**To:** Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Dale, do you still need the more detailed data you requested?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-0255

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Thursday, May 24, 2012 4:18 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Thank you Marie,

The answers provide very interesting data for discussion.

We will have some work to do with the Ophthalmologists in the inositol Study.

Particularly: treating in zone II without evidence of plus disease.

One the cases below not meeting criteria is unlikely enough that it is probably a keying error, but I would not want to go back at this point in time to do a query.

Dale

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi all, I included answers to Rose's questions below, based on my preliminary look at the SUPPORT data. I will send more complete answers to Dale's questions when I have them.

Marie

Marie Gantz, Ph.D.  
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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery 127 (based on Wally's paper, this looks like 132) MG: 132 includes infants with severe ROP as defined in the paper who did not have surgery recorded.

Can you tell us how many had each of these categories:

**1. type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);**

MG: 22 met these criteria in at least one eye

**2. zone I, stage 3 ROP without plus disease;**

MG: An additional 6 met these criteria in at least one eye (there were a total of 11 but 5 also met criteria for type I ROP in #1)

**3. zone II, stage 2 or 3 ROP with plus disease.**

MG: An additional 76 met these criteria in at least one eye (there were a total of 80 but 4 also met criteria in #1 or #2)

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

MG: There were 23 who did not meet criteria in #1-3 but who did have surgery:

1 had zone II stage 2 with plus disease missing



2 had zone II stage 2 no plus disease  
18 had zone II stage 3 no plus disease  
1 had zone III stage 3 no plus disease  
1 had missing zone and stage but plus disease

Thanks  
Rose

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**Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

Kathleen A Kennedy, Lisa A Wrage, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Michelle Walsh, Abbot Laptook, Roger Faix, Brad Yoder, Kurt Schibler, Marie G. Gantz, Abhik Das, Nancy Newman, Wade Rich, Dale L Phelps

**Abbreviations:**

GA – gestational age  
PMA – postmenstrual age  
ROP – retinopathy of prematurity  
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

**Keywords**

retinopathy of prematurity, screening, extremely preterm infants

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**Acknowledgments:**

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

**What This Study Adds**

Our data do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, challenge the accepted notion that the onset of ROP ~~to better is more~~ closely correlated with postmenstrual than chronological age.

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Comment [MG1]:** Treatment with scleral buckle and vitrectomy was also included, as noted in the text of the primary paper.

**Results:** 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had an ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>8</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27 <sup>6</sup>/<sub>7</sub> weeks gestational age who were enrolled in the NICHD Surfactant, Positive

Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

### Patients and Methods

In the SUPPORT trial conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0</sup>/<sub>7</sub> – 27<sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: Severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) vs No Severe ROP (full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

### Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). 94 of these outcomes were adjudicated. Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. 65% (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

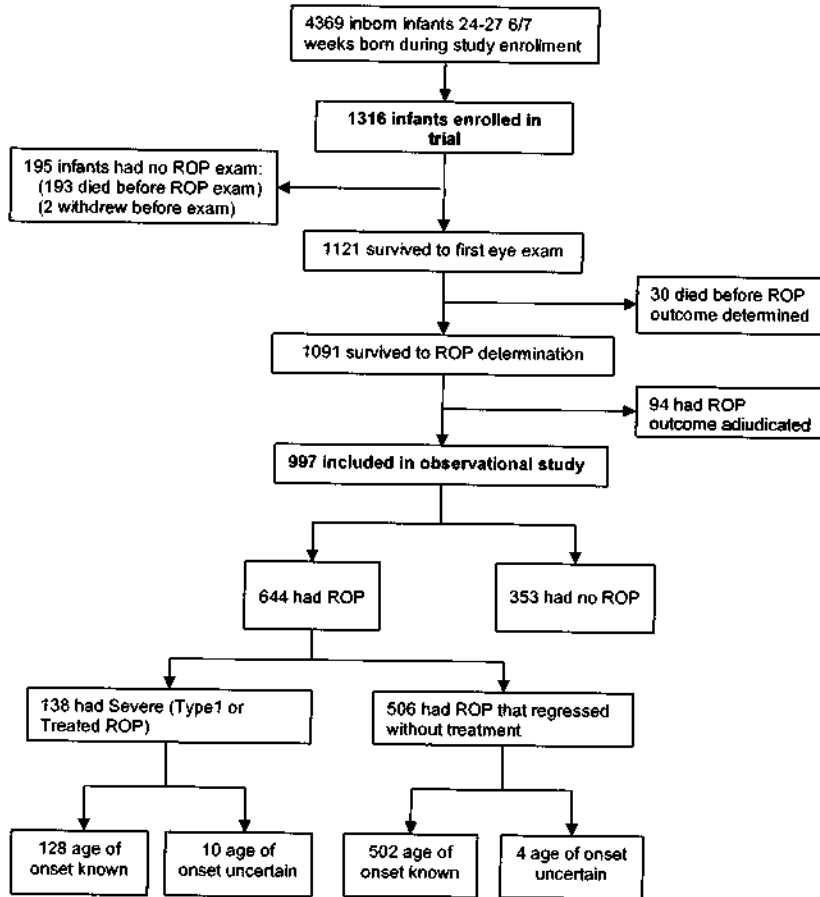
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Comment [MG2]: Treatment with scleral buckle and vitrectomy was also included, as noted in the text of the primary paper.

Comment [MG3]: And if the infant had no known major congenital malformations and full resuscitation was intended.

Comment [MG4]: This might have been implied, but it was not explicitly included in the determination of the primary outcome.

**Figure 1. Flow diagram of patient enrollment**



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

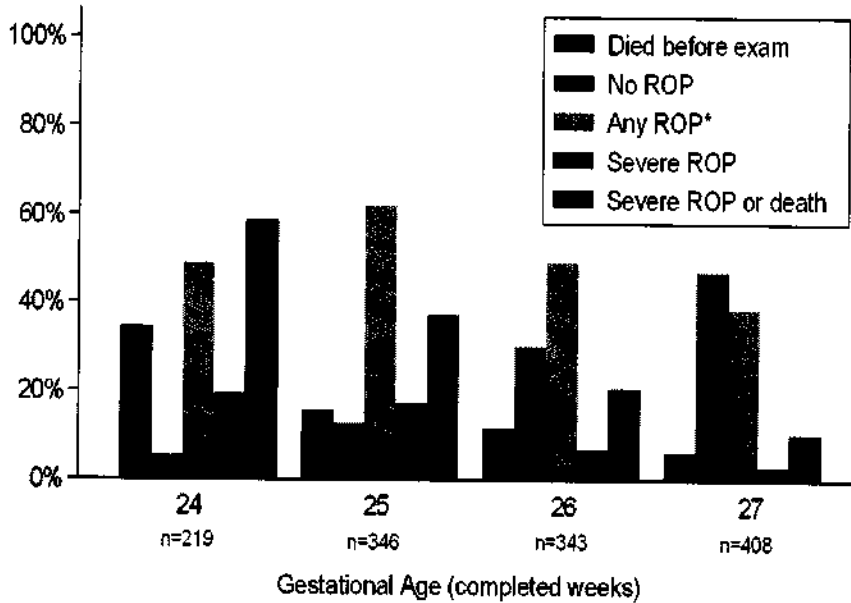
	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup> [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



\*Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/treated) ROP

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a significantly longer duration of supplemental oxygen than infants without ROP.



**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
n	353	644	138
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [(n (%))]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

<sup>2</sup> missing data

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

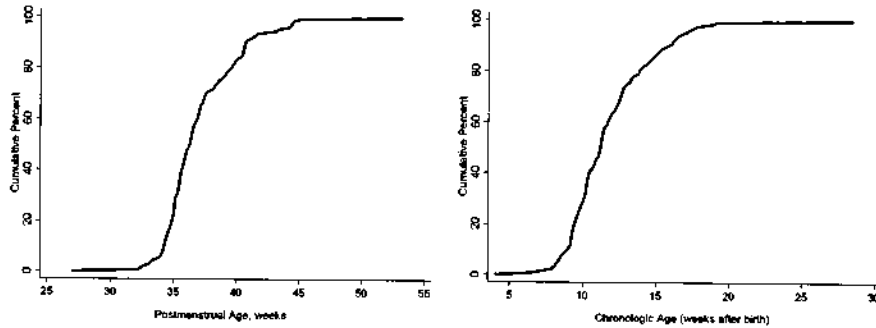
**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

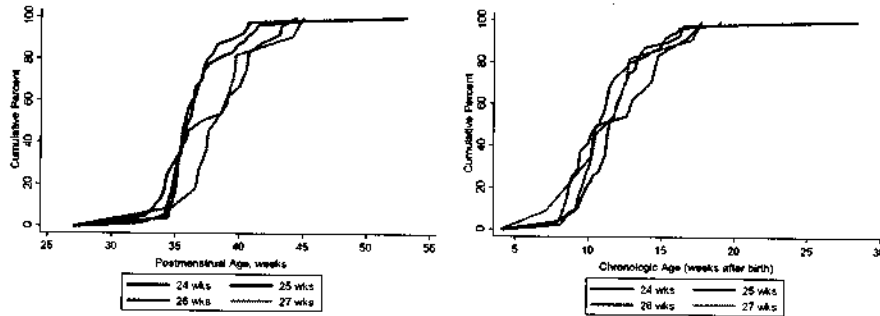
<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**



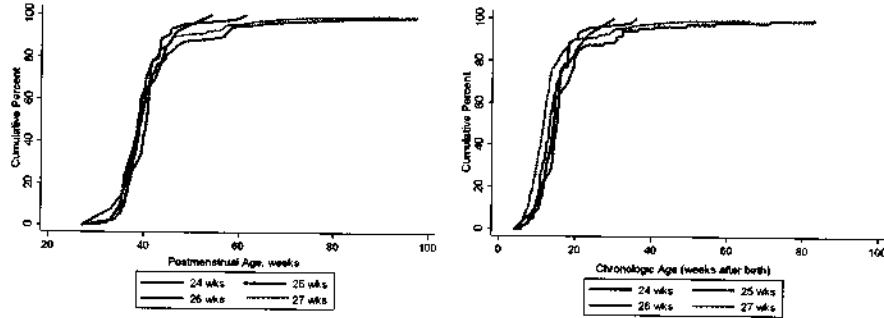
Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

**Comment [MG5]:** Unlike in other studies? Was such a relationship expected? Perhaps describe what was seen instead, and whether any statistical tests were used to compare the distributions, particularly since the discussion seems to argue that the PMA of ROP onset for infants with GA 22-23 weeks could be even early than what we observed in SUPPORT.

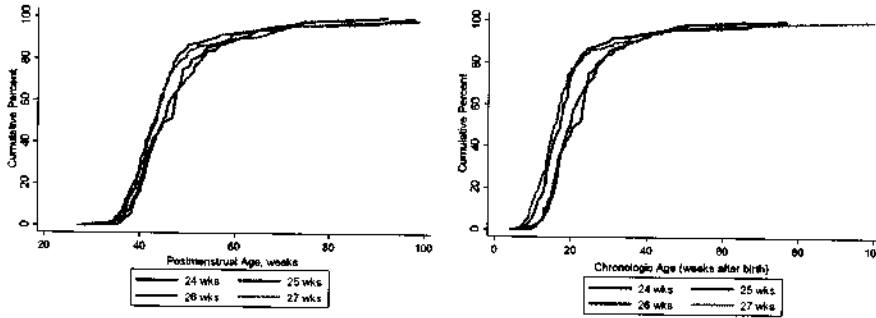
**Comment [MG6]:** Again, not used to determine the primary outcome.

**Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth**

**No ROP**



**Mild/Moderate ROP**



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

**Comment [MG7]:** Did you compare (statistically) whether the distributions were different for A 24-25 vs. 26-27 weeks?

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

<b>Infants with Severe ROP N=138</b>	<b>First exam with severe ROP occurred <u>before</u> discharge to home n=124</b>	<b>First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14</b>
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home**

<b>Worst exam findings prior to discharge either or both eyes:</b>	<b>Severe ROP Group N=14</b>	<b>No Severe ROP Group N=535</b>
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home**

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

### Discussion

In prior ROP natural history studies,<sup>33</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>12</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum (<750g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological age and severe ROP did not occur before 6 weeks. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT

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**Comment [MG8]:** If previous studies stratified on BW rather than on GA, would it be more accurate to say that curves for the *BW strata* overlapped when plotted by PMA, or were curves actually plotted for each week of GA as stated here?

**Comment [MG9]:** If anything, we seem to see the opposite: GA at birth seems to be more related to PMA of onset, but the curves overlap when plotted by chronological age of onset. I'm curious about whether any formal tests were done to compare curves. Are we saying that there is separation between any of the curves for different GAs, or not? It is not clear to me what conclusions are being drawn from the SUPPORT data.

**Comment [MG10]:** Age of onset is *measured* either in terms of PMA or chronological age, so I don't understand this statement. Do you intend to say that GA at birth was related to age of onset measured in either way? If so, I don't necessarily see that from the data presented. GA possibly looks related to PMA, but not really related to chronological age of onset.

**Comment [MG11]:** Chronological age or PMA? Not sure how this sentence leads into/relates to the next one. What "distinction" is meant?

Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>1414</sup>

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### Conclusion

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006; 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 1988; 81: 697-706.
- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. *Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group*. *N Engl J Med* 1998; 338: 1572-1576.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233-250.
- <sup>9</sup> Good Wv, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
- <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tomqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
- <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.

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- <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
- <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
- <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**

10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=A Infant=1 Date of Birth=10/27/08 Gestational Age (weeks)=25 Gestational Age (days)=1 % of infants enrolled at center who had ROP surgery without meeting criteria=1.9

1	12/10/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	12/17/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
3	12/24/08	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
4	12/31/08	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
5	01/02/09	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
6	01/07/09	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None



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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

**Center=A Infant=2 Date of Birth=12/02/08 Gestational Age (weeks)=27 Gestational Age (days)=2 % of infants enrolled at center who had ROP surgery without meeting criteria=1.9**

1	12/31/08	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	01/07/09	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	01/14/09	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
4	01/21/09	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
5	01/27/09	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
6	02/04/09	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
7	02/11/09	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
8	02/18/09	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
9	02/25/09	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
10	03/04/09	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
11	03/11/09	2	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
12	03/24/09	2	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
13	03/30/09	2	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

**Center=B Infant=3 Date of Birth=05/19/07 Gestational Age (weeks)=25 Gestational Age (days)=3 % of infants enrolled at center who had ROP surgery without meeting criteria=1.5**

1	07/05/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	07/17/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	08/02/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
4	08/31/07	2	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
5	09/07/07	2	2=II	3=Stage 3	3=Stage 3	N	Y	0=No surgery this day
6	09/10/07	1	2=II	3=Stage 3	3=Stage 3	N	Y	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	Y	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	Y	1=Laser	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=C Infant=4 Date of Birth=06/28/05 Gestational Age (weeks)=24 Gestational Age (days)=3 % of infants enrolled at center who had ROP surgery without meeting criteria=2.3

1	08/11/05	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	
2	08/19/05	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	
3	08/24/05	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	
4	08/25/05	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	
2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	
2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA

10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=C Infant=5 Date of Birth=07/01/05 Gestational Age (weeks)=25 Gestational Age (days)=5 % of infants enrolled at center who had ROP surgery without meeting criteria=2.3

1	08/18/05	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2	08/25/05	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
3	09/01/05	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	
4	09/08/05	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	
5	09/09/05	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	
2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	
2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=D Infant=6 Date of Birth=06/21/05 Gestational Age (weeks)=26 Gestational Age (days)=1 % of infants enrolled at center who had ROP surgery without meeting criteria=1.6

1	08/02/05	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2	08/16/05	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
3	08/30/05	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
4	09/16/05	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
5	09/28/05	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
6	10/04/05	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
7	10/08/05	1	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	1=Laser	0=None

2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	1=Laser	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY WHO DO NOT MEET @ ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

**Center=D Infant=7 Date of Birth=06/20/06 Gestational Age (weeks)=24 Gestational Age (days)=6 % of infants enrolled at center who had ROP surgery without meeting criteria=1.6**

1	08/10/06	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	08/23/06	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
3	09/04/06	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
4	09/11/06	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
5	09/18/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
6	09/25/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
7	10/11/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
8	10/23/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
9	10/30/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
10	11/15/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
11	12/09/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
12	12/18/06	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
13	10/02/06	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
14	01/04/07	2	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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 SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY WHO ARE NOT MEETING ROP SURGERY CRITERIA  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=E Infant=8 Date of Birth=02/06/07 Gestational Age (weeks)=27 Gestational Age (days)=0 % of infants enrolled at center who had ROP surgery without meeting criteria=8.9

1	03/06/07	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	03/13/07	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	03/20/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
4	03/27/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
5	04/01/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
6	04/06/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
7	04/10/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
8	04/13/07	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
9	04/17/07	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
10	04/19/07	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
11	04/21/07	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
12	04/24/07	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
13	04/28/07	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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 SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=E Infant=9 Date of Birth=09/21/07 Gestational Age (weeks)=24 Gestational Age (days)=0 % of infants enrolled at center who had ROP surgery without meeting criteria=8.9

1	11/06/07	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2	11/13/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
3	11/20/07	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
4	11/26/07	1	2=II	2=Stage 2	2=Stage 2	N	N	1=Laser	0=None
5	12/01/07	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	Y	Y	1=Laser	0=None
6	12/09/07	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
7	12/18/07	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
8	12/26/07	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
9	12/31/07	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
10	01/08/08	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None

1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	1=Laser	0=None
2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	Y	Y	1=Laser	0=None
2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None



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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

**Center=E Infant=10 Date of Birth=03/28/08 Gestational Age (weeks)=25 Gestational Age (days)=0 % of infants enrolled at center who had ROP surgery without meeting criteria=8.9**

1	05/15/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	05/12/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	05/20/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
4	05/27/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
5	06/03/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
6	06/10/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
7	06/12/08	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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 SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY WHO MEET OR ROP SURGERY CRITERIA  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=E Infant=11 Date of Birth=08/10/08 Gestational Age (weeks)=24 Gestational Age (days)=4 % of infants enrolled at center who had ROP surgery without meeting criteria=8.9

1	09/30/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	10/09/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
3	10/16/08	1	2=II	2=Stage 2	2=Stage 2	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	1=Laser	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=E Infant=12 Date of Birth=10/04/08 Gestational Age (weeks)=27 Gestational Age (days)=3 % of infants enrolled at center who had ROP surgery without meeting criteria=8.9

1	11/04/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
2	11/11/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
3	11/18/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
4	11/25/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
5	11/29/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
6	12/02/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
7	12/04/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
8	12/06/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
9	12/07/08	1	2=II	3=Stage 3	3=Stage 3	N	N	3=Both laser/cryo

0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	3=Both laser/cryo	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING FOR SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=F Infant=13 Date of Birth=07/28/08 Gestational Age (weeks)=26 Gestational Age (days)=2 % of infants enrolled at center who had ROP surgery without meeting criteria=0.5

1	09/09/08	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2	09/23/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
3	10/06/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
4	10/20/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
5	10/22/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
6	10/28/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
7	11/05/08	2	2=II	2=Stage 2	2=Stage 2	*	Y	6=Other	0=None
8	11/12/08	2	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
9	12/01/08	2	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None

1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	*	Y	6=Other	0=None
5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

**Center=G Infant=14 Date of Birth=07/12/06 Gestational Age (weeks)=24 Gestational Age (days)=5 % of infants enrolled at center who had ROP surgery without meeting criteria=1.5**

1	08/15/06	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2	08/17/06	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
3	10/11/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
4	10/12/06	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None
5	10/17/06	1	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
6	10/24/06	1	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
7	08/22/06	1	1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
9	11/29/06	1	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
10	12/05/06	1	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
11	12/26/06	2	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
12	03/01/07	2	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None

1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None
5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
1=I	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None
	5=Status post laser/cryo	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	0=No surgery this day	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

**Center=H Infant=15 Date of Birth=10/11/05 Gestational Age (weeks)=25 Gestational Age (days)=4 % of infants enrolled at center who had ROP surgery without meeting criteria=12.5**

1	12/05/05	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
2	12/12/05	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
3	12/19/05	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
4	12/30/05	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
5	01/16/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
6	01/23/06	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
7	01/24/06	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser
8	02/06/06	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
9	02/14/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
10	02/20/06	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day

0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None



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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

Center=1 Infant=16 Date of Birth=08/04/05 Gestational Age (weeks)=25 Gestational Age (days)=1 % of infants enrolled at center who had ROP surgery without meeting criteria=6.8

1	09/26/05	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2	10/03/05	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
3	10/10/05	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
4	10/17/05	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
5	10/20/05	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None
6	10/31/05	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	P=Permanently missing	0=None
7	11/10/05	1	2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	P=Permanently missing	0=None

2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None
2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	P=Permanently missing	0=None
2=II	6=Post laser/cryo (do not use stages)	6=Post laser/cryo (do not use stages)	N	N	P=Permanently missing	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=I Infant=17 Date of Birth=03/09/07 Gestational Age (weeks)=25 Gestational Age (days)=3 % of infants enrolled at center who had ROP surgery without meeting criteria=6.8

1	04/06/07	1	2=II	P=Permanently missing	P=Permanently missing	N	N	0=No surgery this day	0=None
2	04/20/07	1	2=II	P=Permanently missing	P=Permanently missing	N	N	0=No surgery this day	0=None
3	04/27/07	1	2=II	P=Permanently missing	P=Permanently missing	N	N	0=No surgery this day	0=None
4	05/11/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
5	05/17/07	3	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
6	05/29/07	3	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
7	06/19/07	2	P=Permanently missing	P=Permanently missing	P=Permanently missing	Y	Y	0=No surgery this day	0=None
8	06/20/07	2	P=Permanently missing	P=Permanently missing	P=Permanently missing	Y	Y	1=Laser	0=None

2=II	P=Permanently missing	P=Permanently missing	N	N	0=No surgery this day	0=None
2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
P=Permanently missing	P=Permanently missing	P=Permanently missing	Y	Y	0=No surgery this day	0=None
P=Permanently missing	P=Permanently missing	P=Permanently missing	Y	Y	1=Laser	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY WHO MEET ROP SURGERY CRITERIA**  
**10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria**

**Center=I Infant=18 Date of Birth=10/01/07 Gestational Age (weeks)=26 Gestational Age (days)=2 % of infants enrolled at center who had ROP surgery without meeting criteria=6.8**

1	11/02/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	11/16/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	11/30/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
4	12/07/07	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
5	12/14/07	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
6	12/20/07	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
7	12/28/07	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
8	12/30/07	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=I Infant=19 Date of Birth=11/10/07 Gestational Age (weeks)=25 Gestational Age (days)=3 % of infants enrolled at center who had ROP surgery without meeting criteria=6.8

1	12/14/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	12/28/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	01/25/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
4	02/08/08	1	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
5	02/15/08	1	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
6	03/01/08	2	3=III	3=Stage 3	3=Stage 3	N	Y	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	3=III	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	3=III	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	3=III	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=I Infant=20 Date of Birth=04/12/08 Gestational Age (weeks)=24 Gestational Age (days)=0 % of infants enrolled at center who had ROP surgery without meeting criteria=6.8

1	05/23/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	06/06/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	06/20/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
4	06/27/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
5	07/04/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
6	07/11/08	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
7	07/13/08	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing  
**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=J Infant=21 Date of Birth=05/13/07 Gestational Age (weeks)=25 Gestational Age (days)=3 % of infants enrolled at center who had ROP surgery without meeting criteria=3.5

1	06/25/07	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	07/26/07	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
3	07/19/07	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
4	08/01/07	2	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
5	08/07/07	2	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
6	08/13/07	2	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
7	08/14/07	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

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 SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=J Infant=22 Date of Birth=03/23/08 Gestational Age (weeks)=24 Gestational Age (days)=5 % of infants enrolled at center who had ROP surgery without meeting criteria=3.5

1	05/05/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	05/12/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	05/19/08	1	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day
4	05/26/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
5	06/02/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
6	06/09/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
7	06/12/08	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
8	06/13/08	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	1=Stage 1	1=Stage 1	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing  
**SUPP10 DATA FOR SUPPORT INFANTS WITH ROP SURGERY NOT MEETING ROP SURGERY CRITERIA**  
 10AUG12 version adds % of infants enrolled at center who had ROP surgery without meeting criteria

Center=K Infant=23 Date of Birth=04/04/08 Gestational Age (weeks)=24 Gestational Age (days)=3 % of infants enrolled at center who had ROP surgery without meeting criteria=1.9

1	05/21/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
2	05/29/08	1	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day
3	06/11/08	1	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day
4	06/18/08	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
5	06/21/08	1	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser
6	06/25/08	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day
7	07/02/08	1	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day

0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	0=No ROP	0=No ROP	N	N	0=No surgery this day	0=None
0=None	2=II	2=Stage 2	2=Stage 2	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	1=Laser	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None
0=None	2=II	3=Stage 3	3=Stage 3	N	N	0=No surgery this day	0=None



**From:** [Wally Carlo, M.D.](#)  
**To:** [Finer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Vaucher, Yvonne](#); [Gantz, Marie](#); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); "Miriam Adhikari"  
**Cc:** [Das, Abhik](#)  
**Subject:** Re: New England Journal of Medicine 12-08506  
**Date:** Friday, August 10, 2012 5:27:27 PM

---

This is fantastic! Congratulations. They really have accepted it and are trying to expedite it.

Have a great weekend.

Wally

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

**From:** "Finer, Neil" <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>, "[wacarlo@uab.edu](mailto:wacarlo@uab.edu)" <[wacarlo@uab.edu](mailto:wacarlo@uab.edu)>, "Vaucher, Yvonne" <[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)>, "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)>, "[wacarlo@uab.edu](mailto:wacarlo@uab.edu)" <[wacarlo@uab.edu](mailto:wacarlo@uab.edu)>, &apos;Miriam Adhikari&apos; <[ADHIKARI@ukzn.ac.za](mailto:ADHIKARI@ukzn.ac.za)>  
**Cc:** "Das, Abhik" <[adas@rti.org](mailto:adas@rti.org)>  
**Sent:** Fri, Aug 10, 2012 21:21:43 GMT+00:00  
**Subject:** FW: New England Journal of Medicine 12-08506

Hi Everyone  
This just in from NEJM  
Yvonne and Miriam  
Would you take the first crack at getting this ready for a reply and copy the rest of us with your suggestions?  
Many thanks  
We are close!  
Thanks you for all your efforts  
This will get published!!  
Be well  
Neil

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

**From:** [onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com)  
[<mailto:mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com>] On Behalf Of [editorial@nejm.org](mailto:editorial@nejm.org)  
**Sent:** Friday, August 10, 2012 2:07 PM  
**To:** Finer, Neil  
**Subject:** New England Journal of Medicine 12-08506

Dear Dr. Finer:

I am writing about your manuscript, "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)". Your combined manuscript was evaluated by 2 external reviewers, a statistical reviewer, and the editors. While your new manuscript nicely combines key findings of the 2 manuscripts, some further revisions taking into account the reviewer comments (below) and editorial comments (see attached manuscript) are requested before it could be accepted for publication.

As you have already substantially revised your initial submission(s), I wanted to try to consolidate further

the revision process. Thus I am attaching at this time a partially edited version of your manuscript, in which I have inserted (in text and tables) editorial comments/queries and reference to some reviewer comments. These comments are best seen by viewing the print or web version in Word. (I apologize in advance for assorted typos in these comments.) In general, the suggested changes should be incorporated, unless there are places where I have inadvertently changed your meaning.

Remember that the final version of your manuscript should not exceed 2700 words (text) and there should be no more than 5 tables or figures. The abstract should not exceed 250 words. We are also asking that you shorten the title, which should be no more than 75 characters (including spaces).

When you send in your revised manuscript, please provide a point-by-point response to the reviewers' comments in a covering letter. There is no need to provide a point-by-point response to my inserted comments, but I would ask that you let me know (in the associated comment box) anywhere you did not agree with suggested changes (and why).

Please return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. Please include a word count for the text. Any changes in authorship must be made in writing, signed by all authors.

To submit your revision, log into <http://mc.manuscriptcentral.com/nejm> and enter "For Authors." Click on "Manuscripts Awaiting Revision." Proceed to the bottom of the screen, where your article will be listed. Under "Actions," click on "Create a Revision."

If your article contains supplementary material, please review the attached checklist before submitting your revision.

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When you submit your revision, we request that you include a copy of the initial protocol for your trial, all amendments, and a copy of the final protocol. Please also send a copy of your study's statistical analysis plan. In the event that your manuscript is accepted for publication, please be aware that the Journal may

post these documents as supplementary material along with the manuscript.

In addition, please indicate who wrote the first draft of your manuscript. If it was not one of the authors, please name the person or persons and indicate who paid them. If any writing assistance other than copy editing was provided, please name the person or persons and indicate who paid them.

We ask that all manuscripts include full, accurate, and up-to-date reporting of adverse events. In general, this should be in the form of a table containing descriptions of all serious adverse events and all other common or important adverse events. The abstract should contain a statement regarding adverse events.

Please recall that the Journal requires that neither an article

**From:** [Finer, Neil](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]; wacarlo@uab.edu; Vaucher, Yvonne; Gantz, Marie; wacarlo@uab.edu; "Miriam Adhikari"](#)  
**Cc:** [Das, Abhik](#)  
**Subject:** FW: New England Journal of Medicine 12-08506  
**Date:** Friday, August 10, 2012 5:21:11 PM  
**Attachments:** [SUPPORTResubmissionwcoscomments.docx](#)  
[Subgroups.pdf](#)  
[NEJM-CTA-2009.pdf](#)  
[NEJM-inst-for-ICMJE-form-2-10.pdf](#)  
[ICMJE-Disc-100524.pdf](#)  
[NEJM-supplementary-materials-checklist.pdf](#)

---

Hi Everyone

This just in from NEJM

Yvonne and Miriam

Would you take the first crack at getting this ready for a reply and copy the rest of us with your suggestions?

Many thanks

We are close!

Thanks you for all your efforts

This will get published!!

Be well

Neil

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

From: [onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com)

[<mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com>] On Behalf Of [editorial@nejm.org](mailto:editorial@nejm.org)

Sent: Friday, August 10, 2012 2:07 PM

To: [Finer, Neil](#)

Subject: New England Journal of Medicine 12-08506

Dear Dr. Finer:

I am writing about your manuscript, "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)". Your combined manuscript was evaluated by 2 external reviewers, a statistical reviewer, and the editors. While your new manuscript nicely combines key findings of the 2 manuscripts, some further revisions taking into account the reviewer comments (below) and editorial comments (see attached manuscript) are requested before it could be accepted for publication.

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all authors.

To submit your revision, log into <http://mc.manuscriptcentral.com/nejm> and enter "For Authors." Click on "Manuscripts Awaiting Revision." Proceed to the bottom of the screen, where your article will be listed. Under "Actions," click on "Create a Revision."

If your article contains supplementary material, please review the attached checklist before submitting your revision.

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. If not already done, please ask all authors to sign and fax back the enclosed form as soon as possible to (781) 207-6529. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The Universal Disclosure form is also attached. If not already done, each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to [editorial@nejm.org](mailto:editorial@nejm.org) or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them. Please be aware that in the event of publication, each author's submitted disclosure form will be posted on the web (with any dollar amounts redacted).

Please note that if your Journal submission is accepted for publication and subsequently selected as a CME activity, the Accreditation Council for Continuing Medical Education (ACCME) requires that financial disclosure (statement of any author's relevant financial relationships or attestation of no relevant financial relationships) appear with the article. At that time, we will ask you, as the corresponding author, to draft a disclosure statement for your manuscript based on the information in the submitted disclosure forms. Please ask your co-authors to send you copies of their completed disclosure forms for your reference.

If not already done, we also ask that you make clear in your cover letter who designed the study, who gathered the data, who analyzed the data, who vouches for the data and the analysis, who wrote the paper, and who decided to publish the paper. Please state as well if there were any agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. (see the editorial in the September 13, 2001, issue of the Journal). If your manuscript includes subgroup analyses, please report them in accordance with the Journal's guidelines as outlined in the attached Special Report (Wang et al., November 22, 2007).

When you submit your revision, we request that you include a copy of the initial protocol for your trial, all amendments, and a copy of the final protocol. Please also send a copy of your study's statistical analysis plan. In the event that your manuscript is accepted for publication, please be aware that the Journal may post these documents as supplementary material along with the manuscript.

In addition, please indicate who wrote the first draft of your manuscript. If it was not one of the authors, please name the person or persons and indicate who paid them. If any writing assistance other than copy editing was provided, please name the person or persons and indicate who paid them.

We ask that all manuscripts include full, accurate, and up-to-date reporting of adverse events. In general, this should be in the form of a table containing descriptions of all serious adverse events and all other common or important adverse events. The abstract should contain a statement regarding adverse events.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

If you have not done so already, please provide the editors with copies of other manuscripts by you or your coauthors addressing similar or related research questions that are in preparation or under consideration at other journals.

If you have any questions about compliance with these policies, please contact the editorial office for clarification.

We look forward to receiving your revised manuscript, and would ask that you return it no later than August 31,

2012. If this is not possible, please let us know when we can expect it.

Thank you again for your work. Please do not hesitate to contact me if you have any questions.

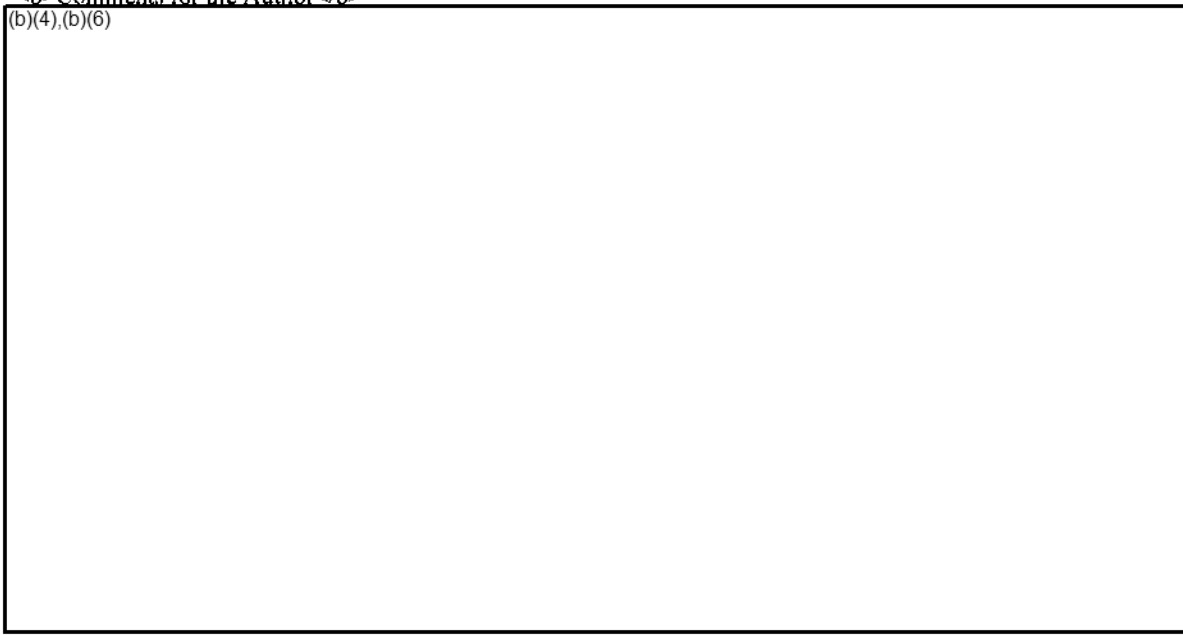
Sincerely,

Caren G. Solomon, MD  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Reviewer: 1

<b>Comments for the Author</b>

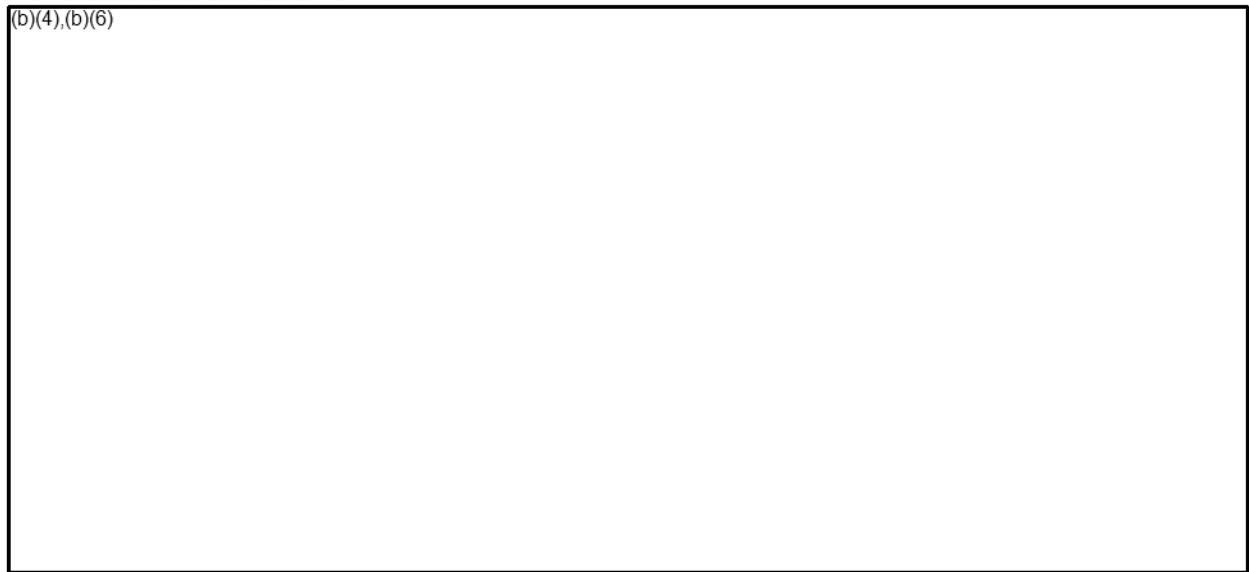
(b)(4),(b)(6)



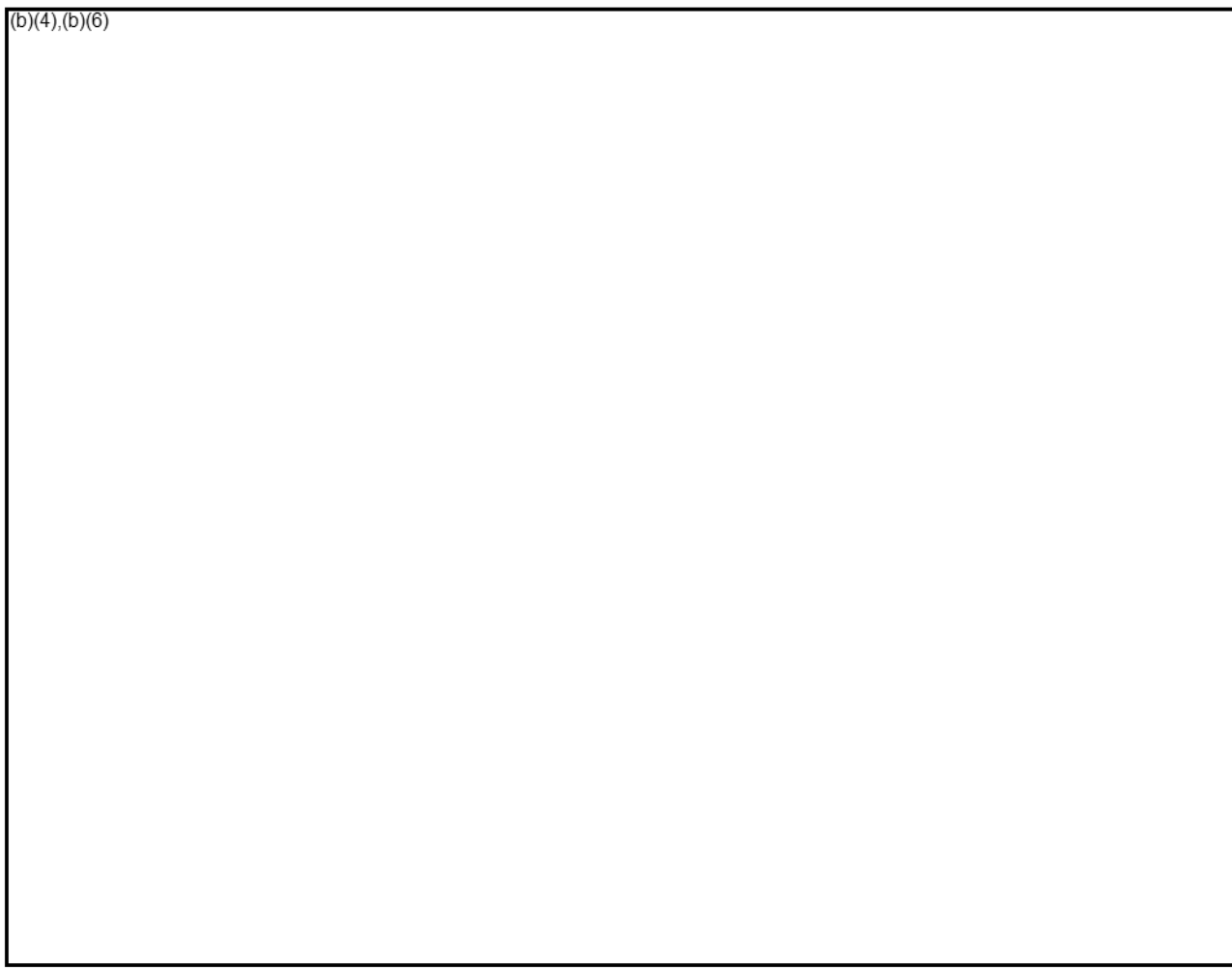
Reviewer: 2

<b>Comments for the Author</b>

(b)(4),(b)(6)



(b)(4),(b)(6)



## Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)<sup>1</sup>

**Comment (GG51):** Please reduce the length of title to 75 characters (including spaces.) (absolute limit)

Yvonne E. Vaucher, MD MPH<sup>1</sup>; \* Myriam Peralta-Carcelen, MD MPH<sup>2</sup>; \* Neil N. Finer, MD<sup>1</sup>; Waldemar A. Carlo, MD<sup>2</sup>; Michele C. Walsh, MD MS<sup>3</sup>; Marie G. Gantz, PhD<sup>4</sup>; Abbot R. Lupton, MD<sup>5</sup>; Bradley A. Yoder, MD<sup>6</sup>; Roger G. Faix, MD<sup>6</sup>; Abhik Das, PhD<sup>7</sup>; Kurt Schibler, MD<sup>8</sup>; Wade Rich, RRT<sup>2</sup>; Nancy S. Newman, RN<sup>4</sup>; Betty R. Vohr, MD<sup>5</sup>; Kimberly Yoltan, PhD<sup>8</sup>; Roy J. Heyne, MD<sup>9</sup>; Deanne E. Wilson-Costello, MD<sup>3</sup>; Patricia W. Evans, MD<sup>10</sup>; Ricki F. Goldstein, MD<sup>11</sup>; Michael J. Acarregui, MD<sup>12</sup>; Ira Adams-Chapman, MD<sup>13</sup>; Athina Pappas, MD<sup>14</sup>; Susan R. Hintz, MD MS Epi<sup>15</sup>; Anna M. Dusick, MD FAAP<sup>16</sup>; Elisabeth C. McGowan, MD<sup>17</sup>; Richard A. Ehrenkranz, MD<sup>18</sup>; Anna Bodnar, MD<sup>6</sup>; Charles R. Bauer, MD<sup>19</sup>; Janell Fuller, MD<sup>20</sup>; T. Michael O'Shea, MD MPH<sup>21</sup>; Gary J. Myers, MD<sup>22</sup>; Rosemary D. Higgins, MD<sup>23</sup> for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

\*Both authors contributed equally to the manuscript

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<sup>15</sup> Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

<sup>16</sup> Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

<sup>17</sup> Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA

<sup>18</sup> Department of Pediatrics, Yale University School of Medicine, New Haven, CT

<sup>19</sup> University of Miami Miller School of Medicine, Miami, FL

<sup>20</sup> University of New Mexico Health Sciences Center, Albuquerque, NM

<sup>21</sup> Wake Forest University School of Medicine, Winston-Salem, NC

<sup>22</sup> Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

<sup>23</sup> *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD



Corresponding author and reprints:

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Email: yvaucher@ucsd.edu

200 West Arbor Drive

San Diego, CA, 92013

Word count: 2668

Text: MeSH terms:

Cerebral palsy  
Infant, Newborn  
Infant, Low Birth Weight  
Infant, Extremely Low Birth Weight  
Infant, Premature  
Infant, Extremely Low Gestational Age  
Infant mortality  
Intellectual disability  
Intensive care, neonatal  
Neurodevelopmental outcome  
Oximetry  
Randomized controlled trial  
Continuous Positive Airway Pressure  
Intubation, intratracheal  
Pulmonary surfactants/therapeutic use  
Oxygen inhalation therapy/methods  
Oxygen administration & dosage  
Retinopathy of prematurity, epidemiology  
Child development  
Developmental disabilities, epidemiology  
Psychomotor disorders, epidemiology  
Follow-up studies

## ABSTRACT

**BACKGROUND:** ~~Early results of the SUPPORT trial showed no significant difference in the outcome of death or BPD between infants receiving early CPAP vs. versus early surfactant, and showed lower rates of severe retinopathy but higher mortality with~~ ~~lower (versus higher) oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality.~~ Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS:** Infants born at 24 0/7 through 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP with a limited ventilation strategy ~~vs. versus~~ early surfactant administration and to lower (85-89%) ~~vs. versus~~ higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months ~~CA corrected age~~.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants; 93.6% (990/1058) of survivors were evaluated at 18-22 months ~~CA corrected age~~. ~~The composite outcome of d~~ Death or NDI was not different ~~in the CPAP (occurred in 27.9% (173/621)) infants in the CPAP group vs. Surfactant (29.9% (183/613)) in the surfactant groups (RR 0.93, 95% CI 0.78 to 1.1, p=0.38); and in -or in the lower (30.2% (185/612)) of the lower oxygen saturation group vs. higher (versus 27.5% (171/622)) of the higher oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality remained was greater in the lower (22.1% (140/633)) compared to the higher (18.2% (118/648)) oxygen saturation group (18.2% versus 22.1%; RR 1.25, 95% CI 1.004 to 1.55, p=0.046).~~

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that not demonstrated significant reductions in mortality and morbidity or improved developmental outcomes with any of these treatments consistently decrease mortality and morbidity or

improve developmental outcome.<sup>13-17</sup> Likewise, the we previously reported results of the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from (-24 through 27 weeks gestation), demonstrated demonstrating that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth, as compared with ~~xxx, did not~~ results in similar reduce rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Comment [C652]: OK?

Comment [C653]: OK as shortened? (else can add back other morbidities, but need to reword slightly for clarity)

Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between infants randomized to the lower (85-89%) versus higher (91-95%) oxygen saturation target group (85-89%) vs. higher oxygen saturation target group (91-95%). However, the risk of ROP-retinopathy of prematurity among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

~~We now report results of our longer term follow-up of the infants in SUPPORT, assessing whether the pre-specified follow-up hypotheses of SUPPORT were 1) that early, non-invasive CPAP with a limited ventilation strategy, compared to early surfactant administration and 2) that lower, compared to higher, oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age(CA).~~

Comment [CG54]: OK?

## METHODS

### Study Design

~~SUPPORT was a randomized controlled trial including 1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, who were enrolled at delivery in the randomized controlled SUPPORT trial.~~ Permutated block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation.<sup>18</sup> Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygen saturation target group) using specially designed blinded oximeters.<sup>24</sup> Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18,24</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data

Comment [CG55]: Note we generally aim to avoid abbreviations that would not be familiar to most readers

Comment [CG56]: Suggest review the details of the limited vent strategy and re the oximeter blinding strategy, in supp web appendix (so readers don't need to go to prior publications to review this.) and then refer to Supp Web appendix for details.

coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were ~~annually~~ annually evaluated for testing reliability. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a non-progressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26,27</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>28</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as ~~stated~~ described above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification, and visual impairment, defined as vision  $< 20/200$ , were based upon examination and parental report.

Certified research staff collected demographic and neonatal outcome data using standard NRN definitions.

Demographic and outcome data collected included gestational age, birthweight, ~~gender~~ sex, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal

marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Socioeconomic data were updated during the 18-22 month visit; these data and were used if data from the neonatal period were not available.

### Outcome

The pre-specified, primary composite outcome for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score < 70, GMFCS  $\geq$  2, moderate or severe CP, or hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality and NDI among survivors. Exploratory secondary outcomes included the individual components of NDI and levels of cognitive delay. The primary composite outcome (~~Death~~ death or NDI), and individual components of NDI were also compared for ~~the~~ higher and lower gestational age strata.

Comment [CG57]: Clarify if prespecified

### Statistical Analysis

The sample size calculations were based on Neonatal Research Network ~~NRN~~ data ~~on~~ for infants born in the year 2000. ~~Details regarding sample size calculations for the SUPPORT trial; details~~ have been previously reported.<sup>18,24</sup> While the sample size for the study was ~~primarily estimated~~ based on ~~the~~ hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in the composite outcome of

Comment [CG58]: OK?

death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Data were entered in on standard forms and were transmitted to RTI International, the Data Coordinating Center for the Neonatal Research Network (NRN), which stored, managed and analyzed the data for this study.

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All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of

infants in each group for whom the primary composite outcome of death or NDI at 18-22 months ~~CA-corrected~~ age could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence

intervals. The denominator ~~that was used to calculate the~~ rate frequency of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Comment [CG59]: OK?

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted, where missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes.<sup>29</sup>

Two-sided p values of < 0.05 were considered ~~statistically significant for all analyses, with~~ no adjustments were made for multiple comparisons. ~~However, given the number of comparisons made, we would expect no~~

Comment [CG10]: OK to delete the sentence that followed given comments of the stat reviewer?

~~more than 4 tests per treatment comparison (CPAP vs. surfactant and low vs. high saturation) to be significant at the 0.05 level on the basis of chance alone.~~

## RESULTS

The ~~pre-specified~~ primary composite outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children lost to follow up, 33 were known to be alive. A neurodevelopmental assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. The presence or absence of NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months corrected age, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

~~Follow-up Cohort Characteristics: Characteristics of the follow-up population are summarized in Table 1.~~

Comment [CGS11]: OK?

~~(Table 1)~~ Almost all mothers received antenatal corticosteroids. At follow up there were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had ~~medical or surgical~~ NEC/necrotizing enterocolitis



and less likely to have been exposed to postnatal corticosteroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

Primary outcome:

The frequency of the composite outcome of death or NDI ~~was not~~ did not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months corrected age (Table 2 a and b). Results from the sensitivity analysis using multiple imputations were virtually identical to the analysis of the non-missing cases, ~~and are not displayed~~ (Results not shown). Neither were ~~there~~ There were also no significant differences in the ~~outcome of death or NDI~~ this outcome between treatment groups in subgroup analyses stratified by gestational age ~~the higher and lower gestational age strata at birth~~ (Appendix A) ~~There was no difference in death~~ The mortality rate was not significantly different between the CPAP and Surfactant arms. ~~Mortality, but was remained~~ significantly higher in the lower ~~compared to the~~ versus higher oxygen saturation target group. There was no ~~evidence of any~~ statistical significant interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all p values > 0.7).

Other outcomes: The incidences of individual components of NDI [cognitive impairment (BSID-III cognitive composite score < 70), gross motor function level  $\geq$  2, moderate/severe cerebral palsy, hearing impairment, and blindness] among survivors were not significantly different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Table 2 a and b) or ~~between the gestational age strata in subgroups stratified by gestational age~~ (Appendix A). However, ~~mortality remained higher in the lower gestational age stratum, mortality was higher in the~~ of Surfactant treatment arm compared to the CPAP arm. Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were ~~increased~~ greater in the higher than lower oxygen saturation target group ~~vs. the~~

Comment [CGS12]: Correct as edited? Else clarify

~~lower oxygen saturation target group~~, the rates of bilateral blindness, blindness of at least one eye, or other vision impairment ~~were did not significantly different between groups at the~~ 18 to 22 months ~~corrected age~~ visit. (Table 3) ~~Neither were~~ There were no significant differences between the CPAP and Surfactant arms or between the lower and higher oxygen saturation target groups in rates of the combined outcome of death or and individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix B). Sixty percent (583/977) of children evaluated at 18-22 months corrected age had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq$  85) evaluations.

**Comment [CGS13]:** As raised by reviewer (and acknowledged in your discussion), available data re visual outcomes are relatively crude. If you have more info re the vis outcomes (as queried by reviewer), recommend include in supp appendix

## DISCUSSION

~~In t~~ This large multicenter trial of tested critical outcome hypotheses related to both ventilatory and oxygenation strategies in a very high risk, extremely premature population infants. We found, we found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. versus early intubation and surfactant administration or between those randomized to the lower vs. versus higher oxygen saturation target groups in the SUPPORT trial. Consistent with our earlier results, the m ~~Mortality rate did not differ significantly between infants randomized to CPAP versus surfactant, and remained significantly higher in the lower compared to the higher oxygen saturation target group. There were no significant differences between the early CPAP versus surfactant group, or between the higher versus lower oxygen saturation groups, in the frequencies among survivors in any of the treatment arms for of NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq$  2), hearing impairment, and bilateral blindness. To our knowledge this is the first large, multicenter, RCT published to~~

**Comment [CGS14]:** OK? (and if yes, insert cross refs)

date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which included pre-specified neurodevelopmental outcome at two years of age, but were not randomized for respiratory interventions, will not be available until 2014.<sup>29</sup>

**Comment [CGS15]:** Correct as edited? Is this one ongoing trial or more than one? ORs suggest reword to note that further data to inform neurodevelopmental outcomes of very premature infants randomized to higher versus lower oxygen saturation targets are expected to be available from another large trial (or trials?) in 2014

Recent trials have raised concerns about using lower oxygen saturation targets because of potentially the possibility of increased mortality in extremely premature infants.<sup>21,31</sup> In SUPPORT, death during initial hospitalization was increased among neonates randomized to the lower oxygen saturation target group. As was published previously reported, the causes of death did not differ significantly between the lower and higher oxygen saturation groups were not different.<sup>24</sup> With longer follow-up, the risk of mortality remained higher in the lower oxygen saturation target group at 18 to 22 months corrected age, as well as in the most immature gestational age stratum of the surfactant administration group. Results of other randomized trials designed to compare neurodevelopmental outcome at two years of age of infants randomized to higher versus lower oxygen saturation targets are expected in 2014.<sup>30</sup>

**Comment [CGS16]:** I think it is important to acknowledge explicitly that the vast majority of deaths had occurred as of the time of the earlier publication (on review of that there were 130 deaths in the lower sat group by hosp discharge vs 107 in higher sat group; at this 18-22 mo f/u, there were 140 and 111, respectively; thus the "continuing" lower mortality is driven by the fact that most deaths occur early.. AS raised by reviewer 2. I think useful to clarify in results the number of death occurring before versus after hospital discharge, and then to include brief comment here re this (spec in view of statistician's comment re acknowledging the marginal p value (the point that this confirmed an earlier finding must also take into account that the numbers did not change much from the earlier time point..))

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>32,33</sup> We previously reported that infants who survived to discharge who were in the lower oxygen saturation target arm had a lower was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) (8.6% vs. 17.9% in the higher saturation group) among survivors to discharge.<sup>24</sup> In our current analyses, we found that eye surgery was more significantly less frequent in the higher-lower oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at the 18 to 22 months visit, we found that there were no, but there were no significant between group differences in other visual outcomes assessed, including the reports of unilateral and bilateral blindness, nystagmus, strabismus or the

**Comment [CGS17]:** This additional subgroup analysis might better to belong in a separate short para addressing the CPAP findings and then noting this one subgroup finding. It is important also to acknowledge the large number of comparisons you performed and the need to interpret subgroup findings with caution

**Comment [CGS18]:** Seems better to belong here. Is this one ongoing trial or more than one? Consider reword to note that "Further data to inform risks of mortality (and neurodevelopmental impairment outcomes and mortality of very premature infants randomized to higher versus lower oxygen saturation targets are expected from another large trial (or trials?) in 2014

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**Comment [CGS19]:** OK?

use of corrective lenses ~~between the lower and higher saturation groups.~~ We did not collect detailed data on visual function at the 18 to 22 months visit.

Comment [CGS20]: OK?

The strengths of this study include the large initial number of extremely premature infants enrolled sample size, providing sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very-high percentage of participants who had comprehensive, standardized neurodevelopmental evaluation at 18-22 months corrected age. As in most trials of interventions starting at birth, generalizability may be limited by requiring antenatal consent, which is associated with enrollment bias.<sup>34,35</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence ~~of NDI~~ previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>36</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no significant differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome.

Comment [CGS21]: Or perhaps "survivors?" (recognizing that f/u rate appears lower than it might since some infants did not survive to f/u.)

In summary, there were no significant differences in the composite outcome of death or NDI or in the individual components of NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher oxygen saturation targets. ~~However, The as mortality remained lower in the higher oxygen saturation group had a lower mortality rate (as was noted on earlier follow-up).~~ but had comparable rates of

Comment [CGS22]: As space allows, suggest reiterate some limitations noted earlier that would still apply to the f/u results—eg issue of crossover from CPAP to intubation (given pre-birth randomization) and (as raise by editorialist for prior paper) that O2 sat's actually ran higher than planned, and less difference between groups than planned.

Comment [CGS23]: Ok to add? Then should cross ref again /and Ok as slightly edited (since one visual outcome was different?..) And might consider noting something of the effect that " although the mortality differences are of marginal stat significance, the 18-22 month outcomes data overall argue against...."

~~at the time of follow up and there were no adverse visual or neurodevelopmental problems, impairment and of major adverse visual outcomes at 18-22 months corrected age; these results argue against~~ lower oxygen saturation targets ~~cannot be recommended~~ in these extremely preterm infants. Early CPAP with a limited ventilation strategy can be considered an alternative to early surfactant even in infants as immature as 24 weeks ~~as mortality was lower in the most immature infants.~~

**Comment [CGS24]:** Would be inclined just to note this conclusion without re-emphasizing this subgroup comparison which you will have discussed above.

**Acknowledgements:**

**Comment [CGS25]:** Please include the list of investigators as part of supp web appendix.

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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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National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

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MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

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University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN;

Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children’s National Medical Center;  
Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University  
School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National  
Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons,  
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PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA  
School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner,  
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Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester;  
Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman,  
MD, Duke University.

Figure: Consort Diagram for SUPPORT

Table 1: Demographic and neonatal characteristics of follow-up cohorts

Table 2: Primary outcome (Death or NDI) and component outcomes: CPAP vs. Surfactant and Lower vs. Higher Oxygen Saturation Target groups

Table 3: Visual outcome: Lower vs. Higher Oxygen Saturation Target groups

Appendix A: Outcomes of SUPPORT treatment arms by gestational age strata

Appendix B: Comparison of cognitive outcomes of SUPPORT treatment arms

## References

1. Wood NS, Marlow N, Costefoe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.

12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.
23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.

24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8-14.
27. Amiel-Tison C GJ. Neurological Development from Birth to Six Years. Baltimore: The Johns Hopkins University Press; 1998.
28. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
29. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
30. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
31. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
32. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
33. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
34. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
35. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
36. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.

**Table 1: Demographics and Clinical Characteristics of the Follow-up (FUP) Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestations-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)

**Comment [CGS26]:** We ask that table fit on one page in print version and this looks questionable. Recommend shorten number of rows in print version to focus on what you consider the more important variables (eg. would remove English as primary language, whether both parents at home (or marriage status...) etc.) Recommend include retain table with all variables in web appendix and in text can refer to this for more details re-baseline data.

Also would note in footnote that data are mean ± SD or n (%) (or just % depending on space in the print version...) (and then can remove the details after each entry).

**Comment [CGS27]:** Recommend not list denominator, but rather list %s and note in footnote where missing data.



Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < highschool degree-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%)	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language -no./total no.(%)	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%)	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months, Mean ± SD)	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

\*p<0.0205, \*\* p<0.01, \*\*\*p<0.001

¶ At 36 weeks postmenstrual age

Comparisons of neonatal outcomes are adjusted for stratification by center and gestational age and for familial clustering

**Comment [CG528]:** Per our format for table 1. Also probably useful to specify that this is for comparison between the two groups

**Table 2: Rates and Relative Risks of Death or NDI- CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups\* in the CPAP versus Surfactant Groups**

**Comment [CGS29]:** Won't work to have a and b portion of table. Either this needs to be 2 separate tables (as I partially edited to include OR, if does not look too unwieldy, could consider combining by having 7 columns -ie rates in each pair of treatments and their ARR (95% CI) and delete column of p values (can include as you wish in an expanded version in supplementary web appendix

**Comment [CGS30]:** As in above table, just note in footnote that you are reporting no/total no (%) so don't need to list for each entry

<u>a. CPAP vs. Surfactant</u>	<u>CPAP</u>	<u>Surfactant</u>	<u>ARR*</u>	<u>p</u>
Death or NDI-no./total no.(%) (primary composite outcome)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

**Table 3: Rates and Relative Risks of Death or NDI in the Lower versus Higher Oxygen Saturation Groups**

	<u>Lower</u>	<u>Higher</u>	<u>ARR*</u>	<u>p</u>
<u>Death or NDI-no./total no.(%)</u> <b>Lower vs. Higher Oxygen Saturation</b>	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
<del>Death or NDI no./total no.(%)</del>				
Death before 18-22 mo CA-no./total no.(%)	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined-no./total no.(%)	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI-no./total no.(%)	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70-no./total no.(%)	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2-no./total no.(%)	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy-no./total no.(%)	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral-no./total no.(%)	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86

**Comment [CG531]:** As in above table, just note in footnote that you are reporting no./total no.(%) so don't need to list for each entry  
NOTE that if these table numbers change, need to change call outs in text accordingly..

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Hearing impairment-no./total no.(%)	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70
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\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Table 34: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower	Higher	ARR*	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23

Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002
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\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness and other abnormal eye findings were not adjusted for study center due to small N)

**Appendix A: Outcomes for treatment groups by gestational age strata**

**CPAP vs. SURFACTANT**

<u>24 0/7-25 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29

**Comment [CGS32]:** Please create separate web appendix for this information (and for other suggested additions.) (See cover letter for relevant info in creating.. note we ask for table of contents with this so easier for readers to navigate.

Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral –no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

<u>26 0/7-27 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

**LOWER VS. HIGHER OXYGEN SATURATION TARGETS**

<u>24 0/7-25 6/7 weeks Gestational Age</u>	Lower	Higher	ARR*	p
Death or NDI-no./total no.(%)	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA-no./total no.(%)	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined-no./total no.(%)	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI-no./total no.(%)	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70-no./total no.(%)	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2-no./total no.(%)	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy-no./total no.(%)	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral -no./total no.(%)	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Hearing impairment-no./total no.(%)	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22



<u>26 0/7-27 6/7 weeks Gestational Age</u>	Lower	Higher	ARR*	P
Death or NDI-no./total no.(%)	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA-no./total no.(%)	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined-no./total no.(%)	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI-no./total no.(%)	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70-no./total no.(%)	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level ≥ 2-no./total no.(%)	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral palsy-no./total no.(%)	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral –no./total no.(%)	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Hearing impairment-no./total no.(%)	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

\*Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms**

**CPAP vs. Surfactant**

	CPAP	SURF	ARR*	p
BSID-III cognitive composite score (adjusted mean $\pm$ standard error)	91.3 $\pm$ 0.7	90.4 $\pm$ 0.8		0.33
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85-no./total no.(%)	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80-no./total no.(%)	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

**Lower vs. Higher Oxygen Saturation Targets**

	<u>LOWER</u>	<u>HIGHER</u>	ARR*	p
BSID-III cognitive composite score (adjusted mean $\pm$ standard error)	91.2 $\pm$ 0.8	90.5 $\pm$ 0.7		0.48
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85-no./total no.(%)	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80-no./total no.(%)	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

\*Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

SPECIAL REPORT

## Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials

Rui Wang, M.S., Stephen W. Lagakos, Ph.D., James H. Ware, Ph.D., David J. Hunter, M.B., B.S., and Jeffrey M. Drazen, M.D.

Medical research relies on clinical trials to assess therapeutic benefits. Because of the effort and cost involved in these studies, investigators frequently use analyses of subgroups of study participants to extract as much information as possible. Such analyses, which assess the heterogeneity of treatment effects in subgroups of patients, may provide useful information for the care of patients and for future research. However, subgroup analyses also introduce analytic challenges and can lead to overstated and misleading results.<sup>1-7</sup> This report outlines the challenges associated with conducting and reporting subgroup analyses, and it sets forth guidelines for their use in the *Journal*. Although this report focuses on the reporting of clinical trials, many of the issues discussed also apply to observational studies.

### SUBGROUP ANALYSES AND RELATED CONCEPTS

#### SUBGROUP ANALYSIS

By “subgroup analysis,” we mean any evaluation of treatment effects for a specific end point in subgroups of patients defined by baseline characteristics. The end point may be a measure of treatment efficacy or safety. For a given end point, the treatment effect — a comparison between the treatment groups — is typically measured by a relative risk, odds ratio, or arithmetic difference. The research question usually posed is this: Do the treatment effects vary among the levels of a baseline factor?

A subgroup analysis is sometimes undertaken to assess treatment effects for a specific patient characteristic; this assessment is often listed as a primary or secondary study objective. For example, Sacks et al.<sup>8</sup> conducted a placebo-controlled trial in which the reduction in the incidence of

coronary events with the use of pravastatin was examined in a diverse population of persons who had survived a myocardial infarction. In subgroup analyses, the investigators further examined whether the efficacy of pravastatin relative to placebo in preventing coronary events varied according to the patients’ baseline low-density lipoprotein (LDL) levels.

Subgroup analyses are also undertaken to investigate the consistency of the trial conclusions among different subpopulations defined by each of multiple baseline characteristics of the patients. For example, Jackson et al.<sup>9</sup> reported the outcomes of a study in which 36,282 postmenopausal women 50 to 79 years of age were randomly assigned to receive 1000 mg of elemental calcium with 400 IU of vitamin D<sub>3</sub> daily or placebo. Fractures, the primary outcome, were ascertained over an average follow-up period of 7.0 years; bone density was a secondary outcome. Overall, no treatment effect was found for the primary outcome; that is, the active treatment was not shown to prevent fractures. The effect of calcium plus vitamin D supplementation relative to placebo on the risk of each of four fracture outcomes was further analyzed for consistency in subgroups defined by 15 characteristics of the participants.

#### HETEROGENEITY AND STATISTICAL INTERACTIONS

The heterogeneity of treatment effects across the levels of a baseline variable refers to the circumstance in which the treatment effects vary across the levels of the baseline characteristic. Heterogeneity is sometimes further classified as being either quantitative or qualitative. In the first case, one treatment is always better than the other, but by various degrees, whereas in the second case, one treatment is better than the other for one subgroup of patients and worse than the other for

another subgroup of patients. Such variation, also called "effect modification," is typically expressed in a statistical model as an interaction term or terms between the treatment group and the baseline variable. The presence or absence of interaction is specific to the measure of the treatment effect.

The appropriate statistical method for assessing the heterogeneity of treatment effects among the levels of a baseline variable begins with a statistical test for interaction.<sup>10-13</sup> For example, Sacks et al.<sup>8</sup> showed the heterogeneity in pravastatin efficacy by reporting a statistically significant ( $P=0.03$ ) result of testing for the interaction between the treatment and baseline LDL level when the measure of the treatment effect was the relative risk. Many trials lack the power to detect heterogeneity in treatment effect; thus, the inability to find significant interactions does not show that the treatment effect seen overall necessarily applies to all subjects. A common mistake is to claim heterogeneity on the basis of separate tests of treatment effects within each of the levels of the baseline variable.<sup>6,7,14</sup> For example, testing the hypothesis that there is no treatment effect in women and then testing it separately in men does not address the question of whether treatment differences vary according to sex. Another common error is to claim heterogeneity on the basis of the observed treatment-effect sizes within each subgroup, ignoring the uncertainty of these estimates.

#### MULTIPLICITY

It is common practice to conduct a subgroup analysis for each of several — and often many — baseline characteristics, for each of several end points, or for both. For example, the analysis by Jackson and colleagues<sup>9</sup> of the effect of calcium plus vitamin D supplementation relative to placebo on the risk of each of four fracture outcomes for 15 participant characteristics resulted in a total of 60 subgroup analyses.

When multiple subgroup analyses are performed, the probability of a false positive finding can be substantial.<sup>7</sup> For example, if the null hypothesis is true for each of 10 independent tests for interaction at the 0.05 significance level, the chance of at least one false positive result exceeds 40%. Thus, one must be cautious in the interpre-

tation of such results. There are several methods for addressing multiplicity that are based on the use of more stringent criteria for statistical significance than the customary  $P<0.05$ .<sup>7,15</sup> A less formal approach for addressing multiplicity is to note the number of nominally significant interaction tests that would be expected to occur by chance alone. For example, after noting that 60 subgroup analyses were planned, Jackson et al.<sup>9</sup> pointed out that "Up to three statistically significant interaction tests ( $P<0.05$ ) would be expected on the basis of chance alone," and then they incorporated this consideration in their interpretation of the results.

#### PRESPECIFIED ANALYSIS VERSUS POST HOC ANALYSIS

A prespecified subgroup analysis is one that is planned and documented before any examination of the data, preferably in the study protocol. This analysis includes specification of the end point, the baseline characteristic, and the statistical method used to test for an interaction. For example, the Heart Outcomes Prevention Evaluation 2 investigators<sup>16</sup> conducted a study involving 5522 patients with vascular disease or diabetes to assess the effect of homocysteine lowering with folic acid and B vitamins on the risk of a major cardiovascular event. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, and stroke. In the Methods section of their article, the authors noted that "Prespecified subgroup analyses involving Cox models were used to evaluate outcomes in patients from regions with folate fortification of food and regions without folate fortification, according to the baseline plasma homocysteine level and the baseline serum creatinine level." Post hoc analyses refer to those in which the hypotheses being tested are not specified before any examination of the data. Such analyses are of particular concern because it is often unclear how many were undertaken and whether some were motivated by inspection of the data. However, both prespecified and post hoc subgroup analyses are subject to inflated false positive rates arising from multiple testing. Investigators should avoid the tendency to prespecify many subgroup analyses in the mistaken belief that these analyses are free of the multiplicity problem.

SPECIAL REPORT

**SUBGROUP ANALYSES IN THE JOURNAL — ASSESSMENT OF REPORTING PRACTICES**

As part of internal quality-control activities at the *Journal*, we assessed the completeness and quality of subgroup analyses reported in the *Journal* during the period from July 1, 2005, through June 30, 2006. A detailed description of the study methods can be found in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org). In this report, we describe the clarity and completeness of subgroup-analysis reporting, evaluate the authors' interpretation and justification of the results of subgroup analyses, and recommend guidelines for reporting subgroup analyses.

Among the original articles published in the *Journal* during the period from July 1, 2005, through June 30, 2006, a total of 95 articles reported primary outcome results from randomized clinical trials. Among these 95 articles, 93 reported results from one clinical trial; the remaining 2 articles reported results from two trials. Thus, results from 97 trials were reported, from which subgroup analyses were reported for 59 trials (61%). Table 1 summarizes the characteristics of the trials. We found that larger trials and multicenter trials were significantly more likely to report subgroup analyses than smaller trials and single-center trials, respectively. With the use of multivariate logistic-regression models, when ranked according to the number of participants enrolled in a trial and compared with trials with the fewest participants, the odds ratio for reporting subgroup analyses for the second quartile was 1.38 (95% confidence interval [CI], 0.45 to 4.20), for the third quartile was 1.98 (95% CI, 0.62 to 6.24), and for the fourth quartile was 8.90 (95% CI, 2.10 to 37.78) ( $P=0.02$ , trend test). The odds ratio for reporting subgroup analyses in multicenter trials as compared with single-center trials was 4.33 (95% CI, 1.56 to 12.16).

Among the 59 trials that reported subgroup analyses, these analyses were mentioned in the Methods section for 21 trials (36%), in the Results section for 57 trials (97%), and in the Discussion section for 37 trials (63%); subgroup analyses were reported in both the text and a figure or table for 39 trials (66%). Other characteristics of the reports

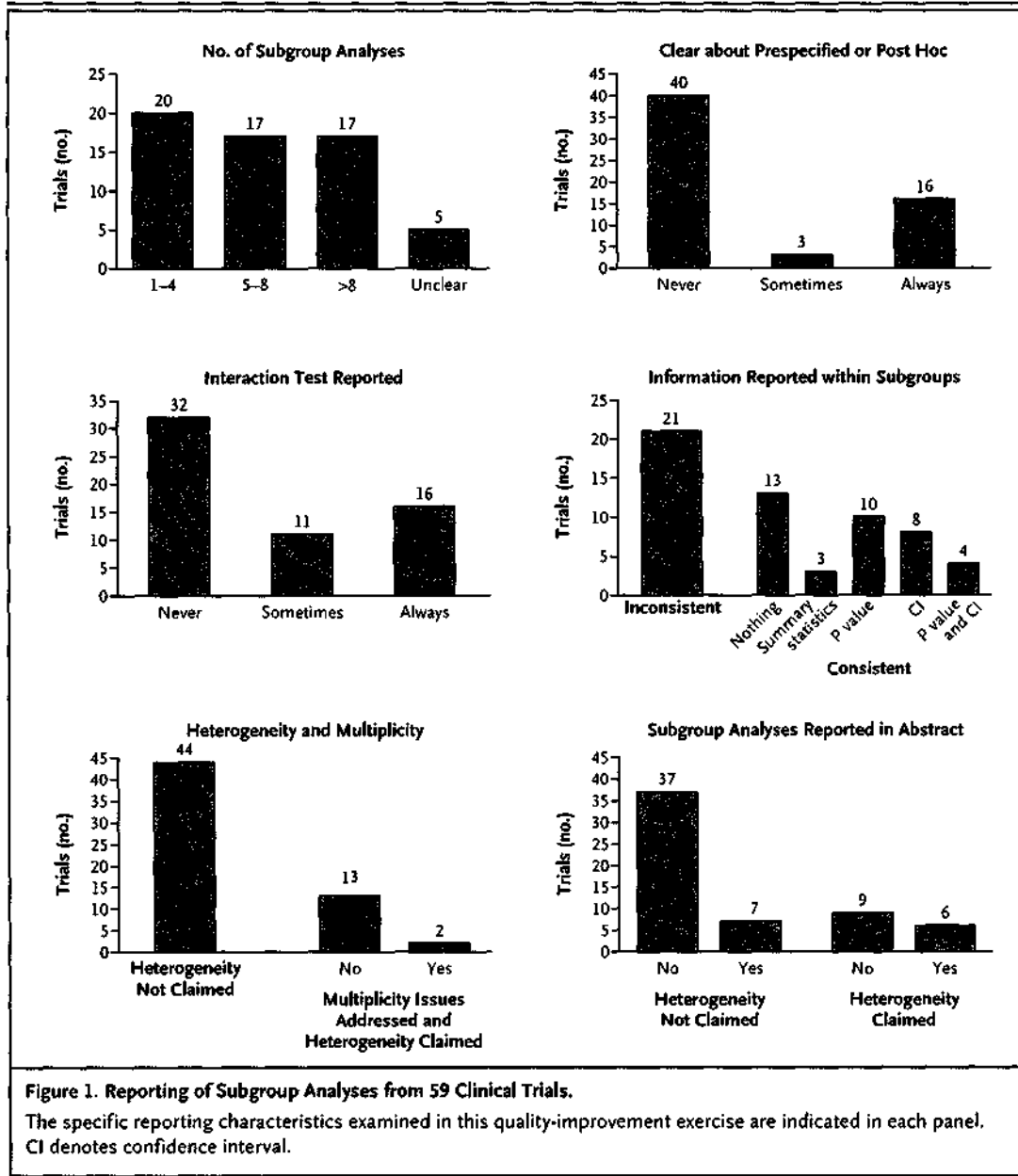
are shown in Figure 1. In general, we are unable to determine the number of subgroup analyses conducted; we attempted to count the number of subgroup analyses reported in the article and found that this number was unclear in nine articles (15%). For example, Lees et al.<sup>17</sup> reported that "We explored analyses of numerous other subgroups to assess the effect of baseline prognostic factors or coexisting conditions on the

**Table 1. Characteristics and Predictors of Reporting Subgroup Analyses in 97 Clinical Trials.\***

Variable	Trials Reporting Subgroup Analyses No. of Trials/ Total No. (%)	P Value†	
		Univariate Odds Ratio	Multivariate Odds Ratio
No. of subjects		0.002†	0.02†
≤218	11/25 (44)		
219–429	13/25 (52)		
430–1012	14/23 (61)		
>1012	21/24 (88)		
Superiority trial		0.25	0.89
Yes	53/84 (63)		
No	6/13 (46)		
Trial sites		0.005	0.05
Single-center	7/21 (33)		
Multicenter	52/76 (68)		
Type of disease studied		0.18	0.37
Cardiovascular	16/20 (80)		
Infectious	2/7 (29)		
Oncologic	9/11 (82)		
Respiratory	7/10 (70)		
Pediatric	5/10 (50)		
Psychiatric or neurologic	6/10 (60)		
Metabolic, endocrine, or gastrointestinal	5/10 (50)		
Gynecologic	3/6 (50)		
Other	6/13 (46)		
Statistically significant primary end point		0.24	0.38
Yes	35/62 (56)		
No	24/35 (69)		

\* A total of 59 trials reported subgroup analyses.

† P values were determined with the use of trend tests.



treatment effect but found no evidence of nominal significance for any biologically likely factor.” For four of these nine articles, we were able to determine that at least eight subgroup analyses were reported. In 40 trials (68%), it was unclear whether any of the subgroup analyses were prespecified or post hoc, and in 3 others (5%) it was unclear whether some were prespecified or post hoc. Interaction tests were reported to have been used to assess the heterogeneity of treatment effects for all subgroup analyses in only 16 trials (27%), and

they were reported to be used for some, but not all, subgroup analyses in 11 trials (19%).

We assessed whether information was provided about treatment effects within the levels of each subgroup variable (Fig. 1). In 25 trials (42%), information about treatment effects was reported consistently for all of the reported subgroup analyses, and in 13 trials (22%), nothing was reported. Investigators in 15 trials (25%), all using superiority designs,<sup>10</sup> claimed heterogeneity of treatment effects between at least one subject sub-

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group and the overall study population (see Table 1 of the Supplementary Appendix). For 4 of these 15 trials, this claim was based on a nominally significant interaction test, and for 4 others it was based on within-subgroup comparisons only. In the remaining seven trials, significant results of interaction tests were reported for some but not all subgroup analyses. When heterogeneity in the treatment effect was reported, for two trials (13%), investigators offered caution about multiplicity, and for four trials (27%), investigators noted the heterogeneity in the Abstract section.

ANALYSIS OF OUR FINDINGS  
AND GUIDELINES FOR REPORTING  
SUBGROUPS

In the 1-year period studied, the reporting of subgroup analyses was neither uniform nor complete. Because the design of future clinical trials can depend on the results of subgroup analyses, uniformity in reporting would strengthen the foundation on which such research is built. Furthermore, uniformity of reporting will be of value in the interval between recognition of a potential subgroup effect and the availability of adequate data on which to base clinical decisions.

Problems in the reporting of subgroup analyses are not new.<sup>1-6,18</sup> Assmann et al.<sup>2</sup> reported shortcomings of subgroup analyses in a review of the results of 50 trials published in 1997 in four leading medical journals. More recently, Hernández et al.<sup>4</sup> reviewed the results of 63 cardiovascular trials published in 2002 and 2004 and noted the same problems. To improve the quality of reports of parallel-group randomized trials, the Consolidated Standards of Reporting Trials statement was proposed in the mid-1990s and revised in 2001.<sup>19</sup> Although there has been considerable discussion of the potential problems associated with subgroup analysis and recommendations on when and how subgroup analyses should be conducted and reported,<sup>19,20</sup> our analysis of recent articles shows that problems and ambiguities persist in articles published in the *Journal*. For example, we found that in about two thirds of the published trials, it was unclear whether any of the reported subgroup analyses were prespecified or post hoc. In more than half of the trials, it was unclear whether interaction tests were used, and in about one third of the trials, within-level results were not presented in a consistent way.

Guidelines for Reporting Subgroup Analysis.

**In the Abstract:**

Present subgroup results in the Abstract only if the subgroup analyses were based on a primary study outcome, if they were prespecified, and if they were interpreted in light of the totality of prespecified subgroup analyses undertaken.

**In the Methods section:**

Indicate the number of prespecified subgroup analyses that were performed and the number of prespecified subgroup analyses that are reported. Distinguish a specific subgroup analysis of special interest, such as that in the article by Sacks et al.,<sup>8</sup> from the multiple subgroup analyses typically done to assess the consistency of a treatment effect among various patient characteristics, such as those in the article by Jackson et al.<sup>9</sup> For each reported analysis, indicate the end point that was assessed and the statistical method that was used to assess the heterogeneity of treatment differences.

Indicate the number of post hoc subgroup analyses that were performed and the number of post hoc subgroup analyses that are reported. For each reported analysis, indicate the end point that was assessed and the statistical method used to assess the heterogeneity of treatment differences. Detailed descriptions may require a supplementary appendix.

Indicate the potential effect on type I errors (false positives) due to multiple subgroup analyses and how this effect is addressed. If formal adjustments for multiplicity were used, describe them; if no formal adjustment was made, indicate the magnitude of the problem informally, as done by Jackson et al.<sup>9</sup>

**In the Results section:**

When possible, base analyses of the heterogeneity of treatment effects on tests for interaction, and present them along with effect estimates (including confidence intervals) within each level of each baseline covariate analyzed. A forest plot<sup>21,22</sup> is an effective method for presenting this information.

**In the Discussion section:**

Avoid overinterpretation of subgroup differences. Be properly cautious in appraising their credibility, acknowledge the limitations, and provide supporting or contradictory data from other studies, if any.

When properly planned, reported, and interpreted, subgroup analyses can provide valuable information. With the availability of Web supplements, the opportunity exists to present more detailed information about the results of a trial. The purpose of the guidelines (see box) is to encourage more clear and complete reporting of subgroup analyses. In some settings, a trial is conducted with a subgroup analysis as one of the primary objectives. These guidelines are directly applicable to the reporting of subgroup analyses in the primary publication of a clinical trial when the subgroup analyses are not among the primary objectives. In other settings, including observational studies, we encourage complete and thorough reporting of the subgroup analyses in the spirit of the guidelines listed.

The editors and statistical consultants of the *Journal* consider these guidelines to be important in the reporting of subgroup analyses. The goal is to provide transparency in the statistical meth-

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ods used in order to increase the clarity and completeness of the information reported. As always, these are guidelines and not rules; additions and exemptions can be made as long as there is a clear case for such action.

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1. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;266:93-8.
2. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;355:1064-9.
3. Pocock SJ, Assmann SF, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med* 2002; 21:2917-30.
4. Hernández A, Boersma E, Murray G, Habbema J, Steyerberg E. Subgroup analyses in therapeutic cardiovascular clinical trials: are most of them misleading? *Am Heart J* 2006;151:257-64.
5. Parker AB, Naylor CD. Subgroups, treatment effects, and baseline risks: some lessons from major cardiovascular trials. *Am Heart J* 2000;139:952-61.
6. Rothwell PM. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 2005; 365:176-86.
7. Lagakos SW. The challenge of subgroup analyses — reporting without distorting. *N Engl J Med* 2006;354:1667-9. [Erratum, *N Engl J Med* 2006;355:533.]
8. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.

9. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; 354:669-83. [Erratum, *N Engl J Med* 2006;354:1102.]
10. Pocock SJ. *Clinical trials: a practical approach*. Chichester, England: John Wiley, 1983.
11. Halperin M, Ware JH, Byar DP, et al. Testing for interaction in an 1xK contingency table. *Biometrika* 1977;64:271-5.
12. Simon R. Patient subsets and variation in therapeutic efficacy. *Br J Clin Pharmacol* 1982;14:473-82.
13. Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics* 1985;41:361-72.
14. Brookes ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters T. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol* 2004;57:229-36.
15. Bailar JC III, Mosteller F, eds. *Medical uses of statistics*. 2nd ed. Waltham, MA: NEJM Books, 1992.
16. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567-77. [Erratum, *N Engl J Med* 2006;355:746.]
17. Lees KR, Zivin JA, Ashwood T, et al. NXY-059 for acute ischemic stroke. *N Engl J Med* 2006;354:588-600.
18. Al-Marzouki S, Roberts J, Marshall T, Evans S. The effect of scientific misconduct on the results of clinical trials: a Delphi survey. *Contemp Clin Trials* 2005;26:331-7.
19. Moher D, Schulz KF, Altman DG, et al. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. (Accessed November 1, 2007, at <http://www.consort-statement.org/>.)
20. International Conference on Harmonisation (ICH). *Guidance for industry: E9 statistical principles for clinical trials*. Rockville, MD: Food and Drug Administration, September 1998. (Accessed November 1, 2007, at [http://www.fda.gov/cder/guidance/ICH\\_E9-fnl.pdf](http://www.fda.gov/cder/guidance/ICH_E9-fnl.pdf).)
21. Cuzick J. Forest plots and the interpretation of subgroups. *Lancet* 2005;365:1308.
22. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354:684-96.

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This form has been adopted by the core member journals of the International Committee of Medical Journal Editors (ICMJE), including the *New England Journal of Medicine*, *Annals of Internal Medicine*, *British Medical Journal*, *Canadian Medical Association Journal*, *Croatian Medical Journal*, *Journal of the American Medical Association*, *Nederlands Tijdschrift voor Geneeskunde (The Dutch Medical Journal)*, *New Zealand Medical Journal*, *The Lancet*, *The Medical Journal of Australia*, *Tidsskrift for Den Norske Lægeforening (The Journal of the Norwegian Medical Association)*, and *Ugeskrift for Læger (Journal of the Danish Medical Association)*. If you are submitting a manuscript to any of these journals, you can expect that they will also use this form.

Best wishes,

The Editorial Staff  
*The New England Journal of Medicine*



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

#### 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

#### 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



## ICMJE Form for Disclosure of Potential Conflicts of Interest

### Section 1. Identifying Information

1. Given Name (First Name) \_\_\_\_\_ 2. Surname (Last Name) \_\_\_\_\_ 3. Effective Date (07-August-2008) \_\_\_\_\_

4. Are you the corresponding author?  Yes  No

5. Manuscript Title \_\_\_\_\_

6. Manuscript Identifying Number (if you know it) \_\_\_\_\_

### Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
2. Consulting fee or honorarium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
3. Support for travel to meetings for the study or other purposes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
5. Payment for writing or reviewing the manuscript	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X ADD
6. Provision of writing assistance, medicines, equipment, or administrative support	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



## ICMJE Form for Disclosure of Potential Conflicts of Interest

The Work Under Consideration for Publication						
Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
7. Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD

\* This means money that your institution received for your efforts on this study.  
 \*\* Use this section to provide any needed explanation.

### Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
2. Consultancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
3. Employment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
4. Expert testimony	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
5. Grants/grants pending	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
6. Payment for lectures including service on speakers bureaus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
7. Payment for manuscript preparation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X



## ICMJE Form for Disclosure of Potential Conflicts of Interest

Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
8. Patents (planned, pending or issued)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			ADD
						X
						ADD
9. Royalties	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
10. Payment for development of educational presentations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
11. Stock/stock options	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
12. Travel/accommodations/meeting expenses unrelated to activities listed**	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD
13. Other (err on the side of full disclosure)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			X
						ADD

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

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Hide All Table Rows Checked 'No'

SAVE



## ICMJE Form for Disclosure of Potential Conflicts of Interest

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### Evaluation and Feedback

Please visit <http://www.icmje.org/cgi-bin/feedback> to provide feedback on your experience with completing this form.



# The NEW ENGLAND JOURNAL of MEDICINE

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## Supplementary Materials Checklist

### **Appendix**

- Please number the pages.
- Provide a table of contents.
- Material should be ordered as follows: the list of investigators (if there is one), text (such as methods), figures, tables, and then references.
- Check the names of the investigators very carefully. Ensure that the name of each investigator is provided in a manner that is to her/his satisfaction.

The *Journal* does not publish errata for supplementary materials, and PubMed is therefore unlikely to correct misspelled or incomplete names.

- The reference citations in the Appendix and corresponding list of references should be self-contained with respect to the Appendix.
- The Appendix must be submitted in two formats: as a single PDF file and as a Word file.

### Figures and Tables

For outcome scales, provide in the legend the range, sign, and minimally important difference (if known). There must be an informative reference citation for the scale.

#### *Figures*

- Figures in the Appendix should be labeled Figure S1, Figure S2, etc.
- Each figure should include a title and a legend, which should appear on the same page as the figure itself.

#### *Tables*

- Tables in the Appendix should be labeled Table S1, Table S2, etc.
- Each table should be accompanied by a title and, if necessary, footnotes.





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## **Please Note:**

- 1) The Appendix will not be edited for style. It will be presented online as additional information provided by the authors.
- 2) Your manuscript will not be accepted for publication until we have received the Appendix in final and appropriate form.

## **Protocol**

- The protocol of a clinical trial should be submitted as a separate PDF file that is independent of the Supplementary Appendix. The editor may require the inclusion of amendments to the protocol (if there are any), and/or the original protocol, in which case, these should be bundled into a single PDF file with the most recent version of the Protocol and a table of contents provided.
- A statistical analysis plan may be included in the protocol, in the same PDF file.

## **Video**

- A video file submitted for posting on the *Journal's* website should be in complete and final format and at as high a resolution as possible. Any editing of the video will be the responsibility of the author.
- Acceptable video formats are:
  - QuickTime
  - AVI
  - MPEG
- A title and a double-spaced legend for the video should be provided in a separate file.

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: PAS SUPPORT SUBMISSIONS  
**Date:** Friday, August 10, 2012 7:29:26 AM

---

What inositol proposal. Is this the toxicity tables?  
This is a descriptive study, so there is no power?  
I am confused. This is not a PAS abstract???

I thought from Maries comments that we should at least look at SGA vs AGA causes of death- again this is descriptive and hypothesis exploring. Will read the comments unfortunate that i could not attend the call.  
I will rebute.  
Will check with Julie: likely will withdraw.  
Michele

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thu 8/9/2012 8:14 AM  
**To:** Walsh, Michele  
**Subject:** RE: PAS SUPPORT SUBMISSIONS

Michele

SUPPORT subcommittee recommended the following:

Walsh – reject due to low power but propose to NEOPROM group as a study when the information on 5000 infants are available

DiFiore – major revision

Ehrenkranz – reject, but combine with a previously approved study from Marie + W

Also – you inositol proposal had a high level of enthusiasm but was rejected due to low power – they suggest a prospective look in the phase 3 trial.

I have attached the reviews, but they are unedited and have NOT yet gone to the PAS abstract review committee – call is next week on Wednesday

Thanks

Rose

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

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Wednesday, August 08, 2012 3:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: PAS SUPPORT SUBMISSIONS

Hi Rose: What were the committee decisions on these?

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Monday, July 09, 2012 12:40 PM  
**To:** 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; [mcw3@cwru.edu](mailto:mcw3@cwru.edu); 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; [dwallace@rti.org](mailto:dwallace@rti.org); [mgantz@rti.org](mailto:mgantz@rti.org); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); nancy newman; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Gabrio, Jenna'; Cunningham, Meg; 'Zaterka-Baxter, Kristin'  
**Subject:** PAS SUPPORT SUBMISSIONS

Hi

Here are 3 SUPPORT PAS abstract submissions. Jenna will set up a call to discuss.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
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301-435-7909  
301-496-5575  
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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer.Stephanie@NIH/NICHD)  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Monday, July 30, 2012 4:15:00 PM

---

ALL SUPPORT KIDS ARE INCLUDED

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Monday, July 30, 2012 4:13 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)

Any reason why this should not be just the same boilerplate as for the SUPPORT FU paper? Should we only include centers for those babies included in this analysis (assuming some died, there may be some centers that didn't get included, but probably not many?)

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Friday, July 27, 2012 9:53 AM  
**To:** Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Higgins, Rosemary (NIH/NICHD) [E]; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Das, Abhik; [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Gantz, Marie; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); [nxs5@cwru.edu](mailto:nxs5@cwru.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu)  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program

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**UT-Houston Medical School**  
**6431 Fannin, Suite 2.106**  
**Houston, TX 77030**  
**713 500-6708**

**From:** Schibler, Kurt  
**To:** Finer, Neil; Kathleen.A.Kennedy@uth.tmc.edu  
**Cc:** Wrage, Lisa Ann (wrage@rti.org); dale\_pheips@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; Rich, Wade; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Monday, July 30, 2012 11:32:00 AM  
**Attachments:** ROP Natural History Study Manuscript (for subcommittee) KRS.doc

---

Hi Kathleen,  
Very nice work. I have attached a version with a few comments mostly related to decreasing the number of figures and tables. Thanks,  
Kurt

On 7/28/12 11:36 AM, "Finer, Neil" <nfiner@ucsd.edu> wrote:

>Hi Kathleen  
>A very extensive review of the ROP Diagnosis especially as it relates to  
>the late onset diagnosis of severe ROP  
>I have been worried about the effects of surgery as a number of our  
>infants who have appeared stable, have been noted to progress within a  
>short interval of surgery for any indication  
>We in fact have been delaying surgery for as long as possible  
>Where you bale to look at the occurrence of surgery for any reason. -  
>hernia repairs, PDA, NEC etc and the timing of progression?  
>The manuscript is very extensive, and I suspect that reviewers will  
>suggest removing much of Figures .3, 4 and 5.  
>Did you do statistics for the data in Table 2? You say the occurrences of  
>these occurred more frequently - does this imply a p value < .05?  
>Can you look and see if the infants with PDA and NEC who had. Surgery had  
>late progression of their ROP  
>Thanks for a very comprehensive and well written manuscript  
>Neil  
>  
>On Jul 27, 2012, at 3:53 PM, "Kennedy, Kathleen A"  
><Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>>  
>wrote:  
>  
>I've attached a draft of the ROP Secondary Study for your review. The  
>manuscript has been formatted for Pediatrics (except that I left the  
>figures in the body of the manuscript to make it easier for you to read).  
> We could add about 200 more words to the manuscript but the abstract is  
>at its limit. I still need to get a boilerplate from Stephanie.  
>  
>If you're receiving this, it's because you have been included as an  
>author based on your membership in the subcommittee for the SUPPORT  
>Trial. Please get your comments/review back to me by Fri Aug 17 so that  
>I can incorporate them and you can meet the journal's authorship  
>requirements.  
>  
>Kathleen A. Kennedy, MD, MPH  
>Richard W. Mithoff Professor of Pediatrics  
>Director, MS in Clinical Research Degree Program

>UT-Houston Medical School  
>6431 Fannin, Suite 2.106  
>Houston, TX 77030  
>713 500-6708  
>  
>  
><ROP Natural History Study Manuscript (for subcommittee).doc>



**Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

Kathleen A Kennedy, Lisa A Wrage, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Michelle Walsh, Abbot Laptok, Roger Faix, Brad Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, Wade Rich, Dale L Phelps

**Abbreviations:**

GA – gestational age  
PMA – postmenstrual age  
ROP – retinopathy of prematurity  
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

**Keywords**

retinopathy of prematurity, screening, extremely preterm infants

**Corresponding author:**

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713 500-0519 (fax)  
Kathleen.A.Kennedy@uth.tmc.edu

**Acknowledgments:**

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

**What This Study Adds**

Our data do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, challenge the accepted notion that the onset of ROP is better correlated with postmenstrual than chronological age.

**Comment [AD1]:** Do you mean "is"?

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Comment [AD2]:** I changed this because death or BPD was the primary outcome for the ventilation arm of the trial.

**Results:** 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had an ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27 6/7 weeks gestational age who were enrolled in the NICHD Surfactant, Positive

Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

#### Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0</sup>/<sub>7</sub> – 27<sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: Severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) vs No Severe ROP (full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

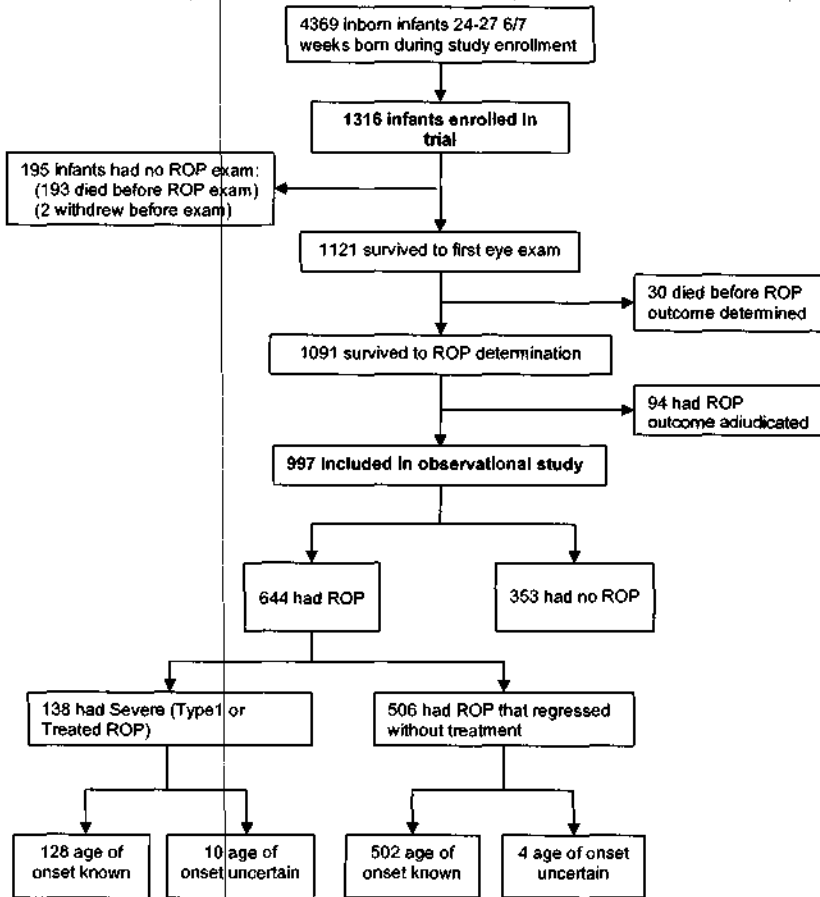
Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in the first either eye.

Comment [AD3]: Do we need to explain this more?

#### Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). 94 of these outcomes were adjudicated. Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. 65% (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

**Figure 1. Flow diagram of patient enrollment**



**Comment [AD4]:** Are the large numbers with unknown age of onset a concern? Should we comment on that in the text?

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

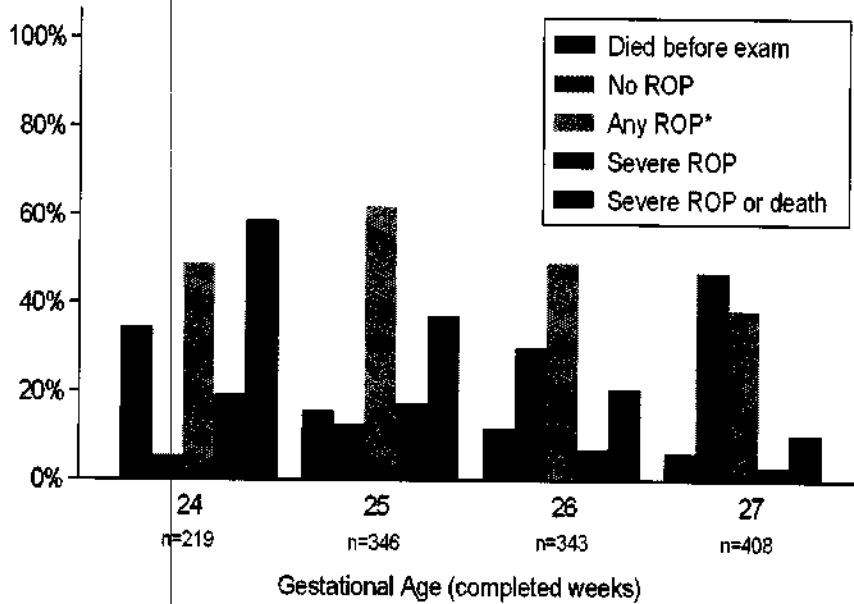
	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
<b>n</b>	<b>1316</b>	<b>997</b>	<b>353</b>	<b>644</b>	<b>138</b>
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup> [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



**Comment [AD5]:** Would one stacked bar (with different color coding for death and different categories of ROP) per GA week be better?

\*Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/untreated) ROP

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a longer duration of supplemental oxygen than infants without ROP.

**Comment [AD6]:** Could this be related to the trial interventions?

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [(n (%))]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

<sup>2</sup> missing data

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

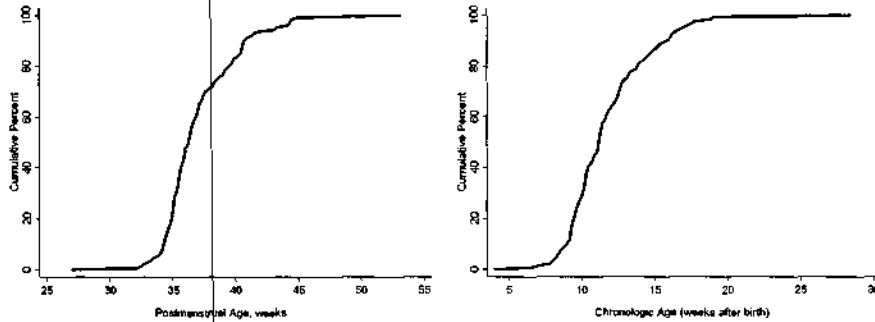
ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)



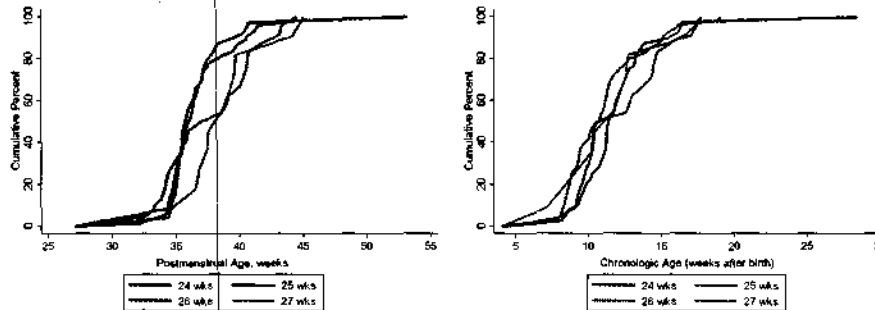
**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



**Comment [AD7]:** Add separate line for any ROP as well?

These distributions were examined separately (not shown) for infants in each of the trial treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**

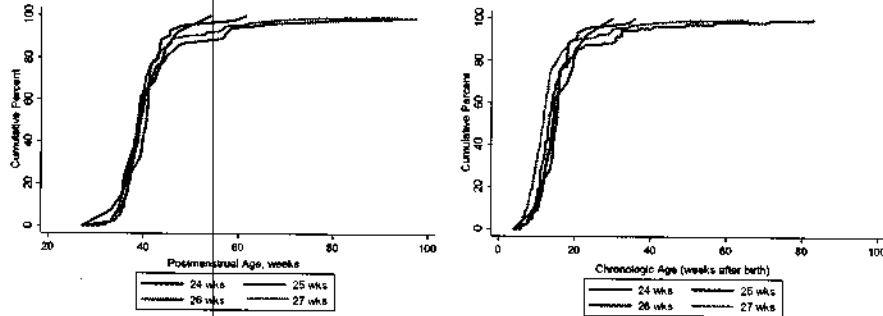


Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

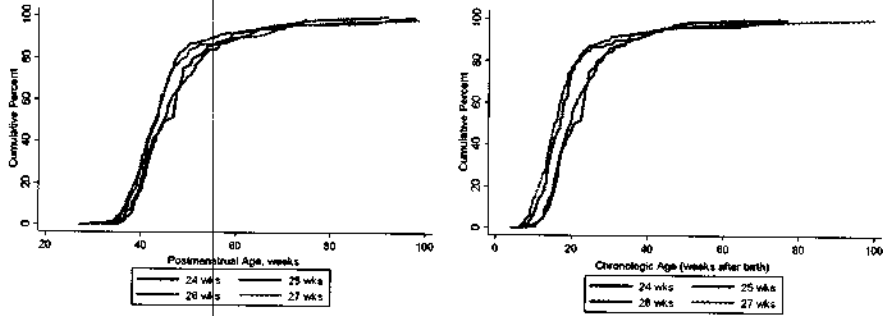
**Comment [AD8]:** Is it necessary to provide some measure of agreement/correlation?

**Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth**

**No ROP**



**Mild/Moderate ROP**



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Comment [AD9]:** Could we also have done some multiple regression modeling to get at this? Factors taken together may achieve better prediction than looked at one to one. However, this may not be the main thrust of the paper.

**Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home**

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

#### Discussion

In prior ROP natural history studies,<sup>33</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>12</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum (<750g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological age and severe ROP did not occur before 6 weeks. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT

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Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future population based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>144</sup>

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### Conclusion

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006; 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 1988; 81: 697-706.
- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 1998; 338: 1572-1576.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233-250.
- <sup>9</sup> Good WV, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
- <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tomqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
- <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.

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- <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
- <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
- <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.

**From:** Gabrio, Jenna  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Laptook, Abbot; mcw3@cwru.edu; Kurt Schibler; ROGER.FAIX@HSC.UTAH.EDU; Vaucher, Yvonne; Myriam Peralta, M.D.; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET  
**Date:** Monday, July 30, 2012 8:59:19 AM

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A friendly reminder for today's call.

**From:** Gabrio, Jenna  
**Sent:** Wednesday, July 25, 2012 10:54 AM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; 'mcw3@cwru.edu'; 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Vaucher, Yvonne'; 'Myriam Peralta, M.D.'; 'Das, Abhik'; 'Wallace, Dennis'; 'Gantz, Marie'; 'wrich@ucsd.edu'; 'nancy newman'; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET

Dear all,

The SUPPORT subcommittee call to discuss the PAS submissions (attached) has been scheduled for:

**Monday, 7/30**  
**4:00pm ET**

Dial:

Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Roger, Michele, Abhik and Marie will be unable to join. Kurt is on service and Myriam is traveling so they may also be unable to join.

Thanks,  
Jenna

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, July 09, 2012 12:40 PM  
**To:** 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; 'mcw3@cwru.edu'; 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Vaucher, Yvonne'; 'Myriam Peralta, M.D.'; 'Das, Abhik'; 'Wallace, Dennis'; 'Gantz, Marie'; 'wrich@ucsd.edu'; 'nancy newman'; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** PAS SUPPORT SUBMISSIONS

Hi

Here are 3 SUPPORT PAS abstract submissions. Jenna will set up a call to discuss.

Thanks

Rose

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Roger Faix"; Gabrio, Jenna; Finer, Neil; Wally Carlo, M.D.; Luptook, Abbot; mcw3@cwru.edu; Kurt Schibler; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; Bradley Yoder  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET  
**Date:** Monday, July 30, 2012 8:22:00 AM

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Thanks

Rose

Rosemary D. Higgins, MD  
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**From:** Roger Faix [<mailto:Roger.Faix@hsc.utah.edu>]  
**Sent:** Sunday, July 29, 2012 7:25 PM  
**To:** Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Luptook, Abbot; mcw3@cwru.edu; Kurt Schibler; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; Bradley Yoder  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET

Hi all!

It appears that my being on service will prevent me from participating in the call after all, BUT I will share my thoughts with Brad Yoder, who will hopefully be able to share them with the group during the teleconference.

Roger

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**From:** Gabrio, Jenna [[jgabrio@rti.org](mailto:jgabrio@rti.org)]  
**Sent:** Wednesday, July 25, 2012 8:54 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Luptook, Abbot; mcw3@cwru.edu; Kurt Schibler; Roger Faix; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; Bradley Yoder  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET

Dear all,

The SUPPORT subcommittee call to discuss the PAS submissions (attached) has been scheduled for:

**Monday, 7/30**

**4:00pm ET**

**Dial:**  
**Within the USA**

(b)(6)

or

**Outside the USA**

(b)(6)

**Then, enter Participant Passcode:**

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Abhik and Marie will be unable to join. Kurt is on service and Myriam is traveling so they may also be unable to join.

Thanks,  
Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, July 09, 2012 12:40 PM  
**To:** 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; [mcw3@cwru.edu](mailto:mcw3@cwru.edu); 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; [wrich@ucsd.edu](mailto:wrich@ucsd.edu); nancy newman; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** PAS SUPPORT SUBMISSIONS

Hi

Here are 3 SUPPORT PAS abstract submissions. Jenna will set up a call to discuss.

Thanks  
Rose

Rosemary D. Higgins, MD  
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**From:** Bradley Yoder  
**To:** Kennedy, Kathleen A; Wrage, Lisa Ann (wrage@rti.org); dale\_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Das, Abhik; Roger Faix; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Friday, July 27, 2012 4:51:28 PM  
**Attachments:** Manuscript.ROP.Natural.History.Study.(for.subcommittee).bay.doc

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Nice information for us all to have.

Thanks Kathleen.

A few questions, comments for you to consider, but nothing major.

Brad Yoder  
Division of Neonatology  
University of Utah SOM

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Friday, July 27, 2012 7:53 AM  
**To:** Wrage, Lisa Ann (wrage@rti.org); dale\_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik; Roger Faix; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley Yoder  
**Cc:** Archer, Stephanie  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
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**Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

Kathleen A Kennedy, Lisa A Wrage, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Michelle Walsh, Abbot Laptook, Roger Faix, Bradley A Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, Wade Rich, Dale L Phelps

**Abbreviations:**

GA – gestational age  
PMA – postmenstrual age  
ROP – retinopathy of prematurity  
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

**Keywords**

retinopathy of prematurity, screening, extremely preterm infants

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**Acknowledgments:**

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

**What This Study Adds**

Our data do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, challenge the accepted notion that the onset of ROP is better correlated with postmenstrual than chronological age.

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Results:** 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had an ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>3</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>8</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27 6/7 weeks gestational age who were enrolled in the NICHD Surfactant, Positive

Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

#### Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0</sup>/<sub>7</sub> – 27<sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: Severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) vs No Severe ROP (full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

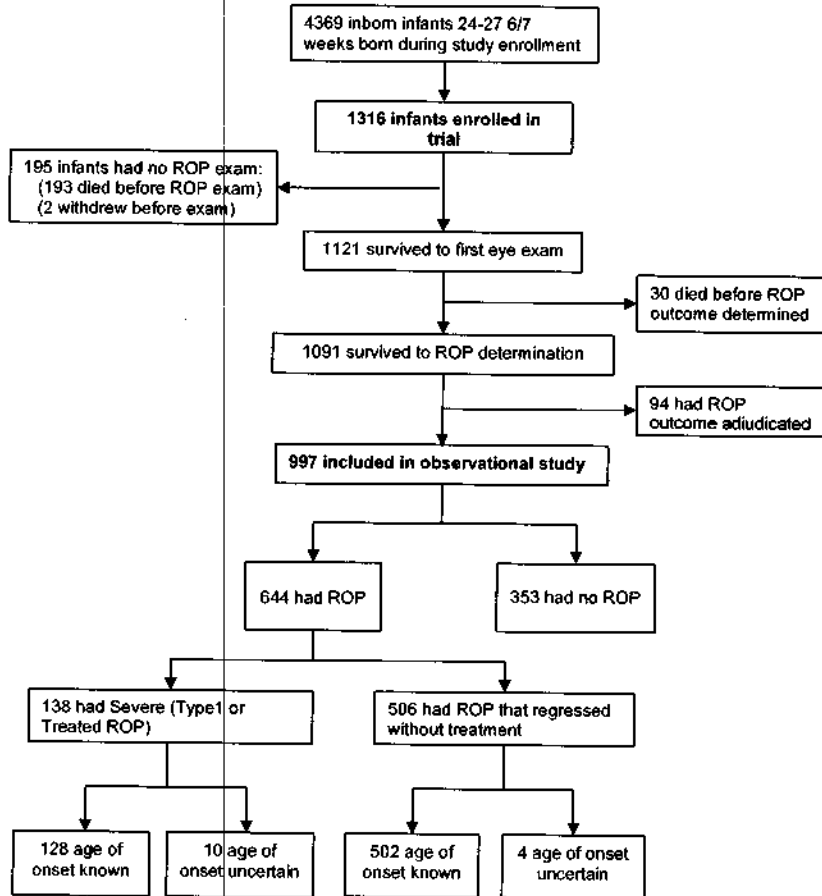
Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

**Comment [BAY1]:** Fairly small numbers overall, though about 7% of the severe ROP group. Would it be unreasonable to assign the age of onset as at the initial exam, or at a mid-point between exams for the purposes of analysis?

#### Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). 94 of these outcomes were adjudicated. Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. 65% (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of patient enrollment



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.



**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

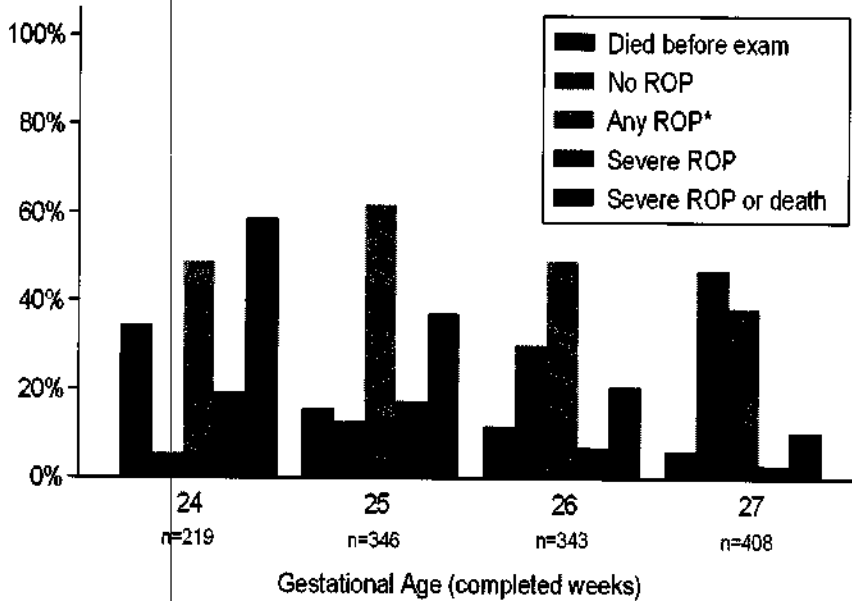
	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup> [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



\*Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/treated) ROP

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a longer duration of supplemental oxygen than infants without ROP.

**Comment [BAY2]:** Sure looks like duration of supplemental O2 is longer; did this analysis include infants with/without ROP who died? IS it also true by non-parametric test?

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [(n (%))]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

<sup>2</sup> missing data

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

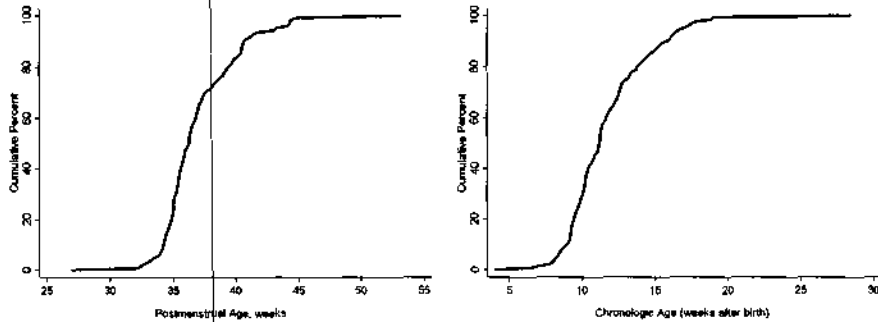
ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type I/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

**Comment [BAY3]:** Is "min" the minimum age or lowest age that any ROP, Type 2 etc was identified? Would probably be helpful to explain this in footnote.

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

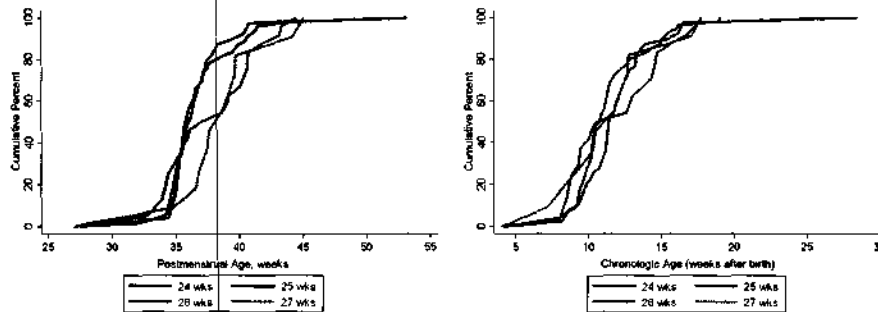
<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**



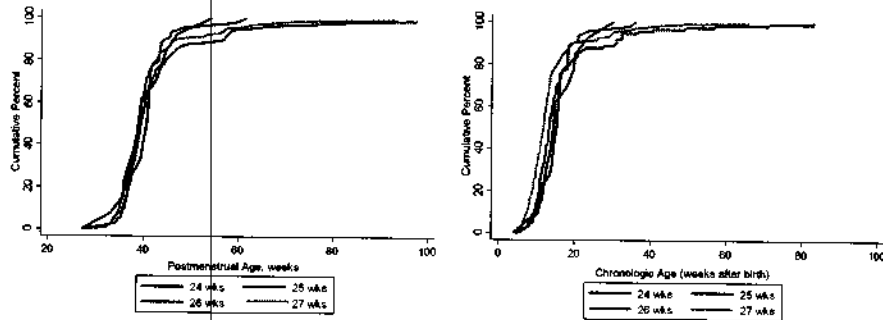
**Comment [BAY4]:** Nice figures, but not sure they add more to the results than the table they are derived from. Couldn't this curve be incorporated into the Figure 4 graphs?

Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

**Comment [BAY5]:** Does this mean vessels within Z3 but no evidence of any ROP changes? Or infants with some stage of ROP in Z3 but not yet meeting "severe" criteria?

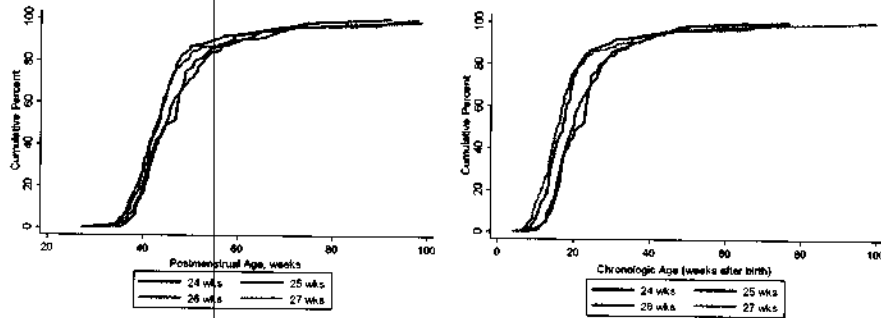
**Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth**

**No ROP**



**Comment [BAY6]:** Nice Figures & data; would it be helpful to include crossing dotted lines that indicate age in weeks when 90% or 95% of the babies have mature vascularity? Example No ROP with dotted line horizontal from 95% and perpendicular from 44 weeks

**Mild/Moderate ROP**



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home**

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

### Discussion

In prior ROP natural history studies,<sup>33</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>12</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum (<750g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological age and severe ROP did not occur before 6 weeks. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

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We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT

Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>144</sup>

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### Conclusion

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006; 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 1988; 81: 697-706.
- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 1998; 338: 1572-1576.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233-250.
- <sup>9</sup> Good WV, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
- <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tornqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
- <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.



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- <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
- <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
- <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.

**From:** [Das, Abhik](#)  
**To:** [Kennedy, Kathleen A](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wrage, Lisa Ann](#)  
**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Friday, July 27, 2012 1:28:20 PM  
**Attachments:** [ROP Natural History Study Manuscript \(for subcommittee\)\\_AD.doc](#)

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Kathleen:

This looks very good. I only have a few minor comments/suggestions in the attached.

Thanks

Abhik

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**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]

**Sent:** Friday, July 27, 2012 9:53 AM

**To:** [Wrage, Lisa Ann](#); [dale\\_phelps@urmc.rochester.edu](#); [Higgins, Rosemary \(NIH/NICHD\)](#); [wcarlo@peds.uab.edu](#); [Das, Abhik](#); [Roger.Faix@hsc.utah.edu](#); [nfiner@ucsd.edu](#); [Gantz, Marie](#); [alaptook@WIHRI.org](#); [nxs5@cwru.edu](#); [wrich@ucsd.edu](#); [kurt.schibler@cchmc.org](#); [Michele.Walsh@UHhospitals.org](#); [Bradley.Yoder@hsc.utah.edu](#)

**Cc:** Archer, Stephanie

**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

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**Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

Kathleen A Kennedy, Lisa A Wrage, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Michelle Walsh, Abbot Laptook, Roger Faix, Brad Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, Wade Rich, Dale L Phelps

**Abbreviations:**

GA – gestational age  
PMA – postmenstrual age  
ROP – retinopathy of prematurity  
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

**Keywords**

retinopathy of prematurity, screening, extremely preterm infants

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**Acknowledgments:**

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

**What This Study Adds**

Our data do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, challenge the accepted notion that the onset of ROP is better correlated with postmenstrual than chronological age.

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Results:** 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had an ROP outcome determined by scheduled examinations. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>3</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>8</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27<sup>6/7</sup> weeks gestational age who were enrolled in the NICHD Surfactant, Positive

Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

#### **Patients and Methods**

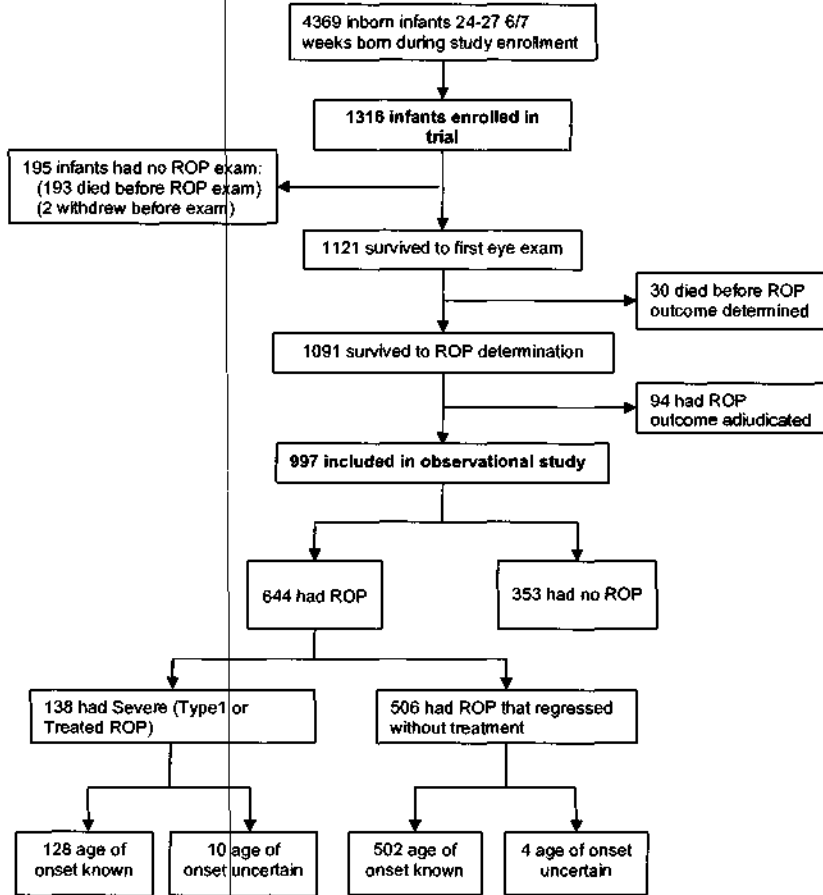
In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0</sup>/<sub>7</sub> – 27<sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: Severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) vs No Severe ROP (full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

#### **Results**

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). 94 of these outcomes were adjudicated. Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. 65% (644/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

**Figure 1. Flow diagram of patient enrollment**



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup> [n (%)]	173 (13.1)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

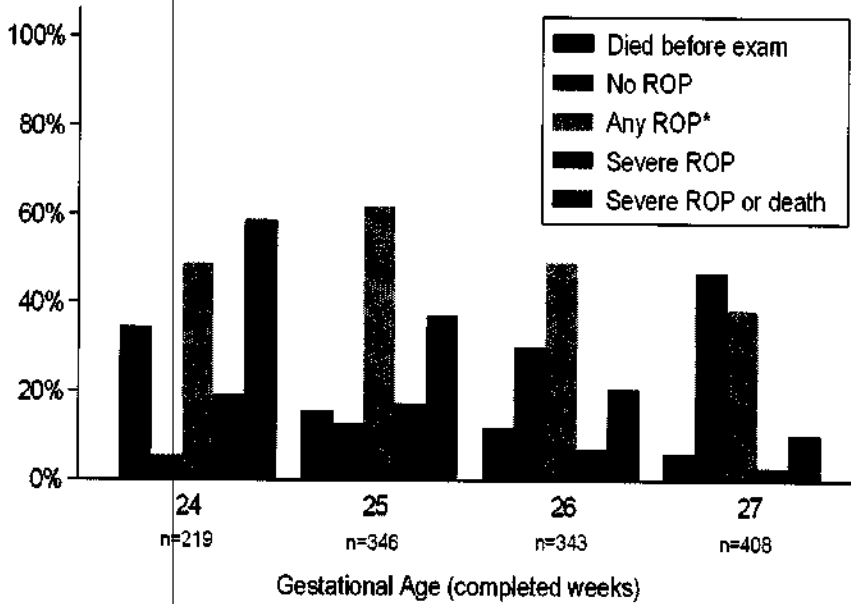
<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.



**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



\*Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/untreated) ROP

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a longer duration of supplemental oxygen than infants without ROP.

**Comment [cc1]:** Any statistically significant?

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [(n (%))]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

<sup>2</sup> missing data

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3. Only one infant had severe ROP on the initial exam; that exam was performed at 33 weeks PMA.

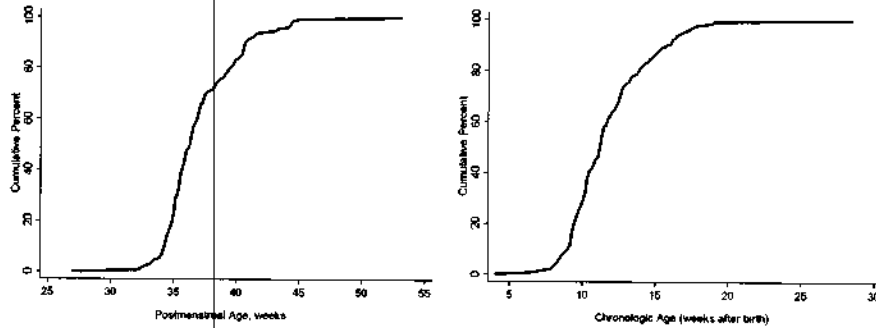
**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

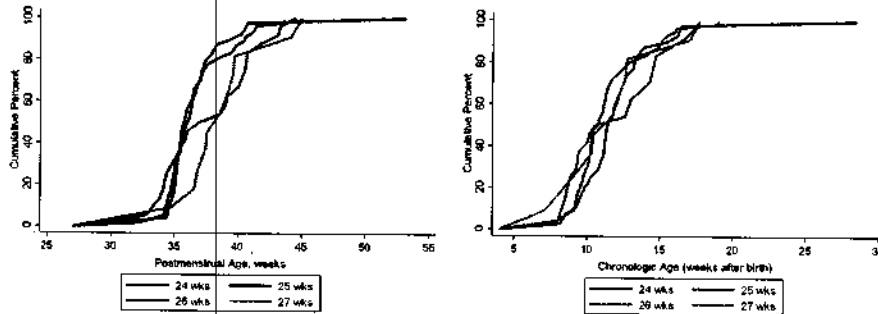
**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



Comment [cc2]: I think this figure could be deleted and described in text.

These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

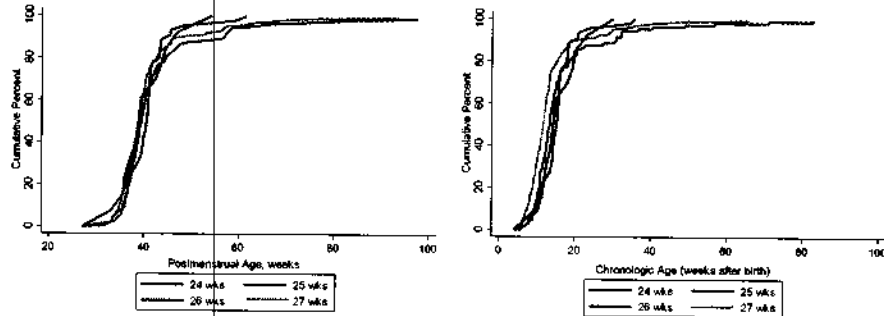
**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**



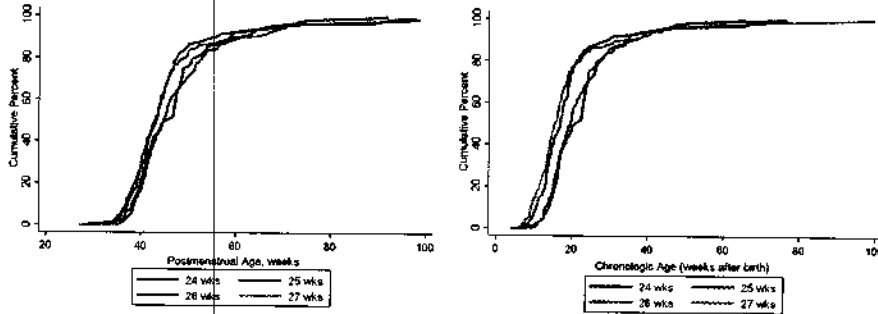
Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP.

**Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth**

**No ROP**



**Mild/Moderate ROP**



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

**Comment [cc3]:** I think this table might be deleted and described in the text.

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam (most recent) prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=I and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=I and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=II and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=II and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home**

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50.0)	148 (27.7)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

**Comment [cc4]:** Statistically significant differences?

### Discussion

In prior ROP natural history studies,<sup>13</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>12</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum (<750g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological age and severe ROP did not occur before 6 weeks. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

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We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT

Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>14+4</sup>

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### Conclusion

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Pediatrics* 1988; 81: 697-706.
- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 1998; 338: 1572-1576.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233-250.
- <sup>9</sup> Good WV, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
- <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tomqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
- <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.

- 
- <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
- <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
- <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.



**From:** [Wally Carlo, M.D.](#)  
**To:** [Kennedy, Kathleen A; wrage@rti.org; dale\\_phelps@urmc.rochester.edu; Higgins, Rosemary \(NIH/NICHD\) \[E\]; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu](#)  
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**Subject:** RE: Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Friday, July 27, 2012 12:59:13 PM  
**Attachments:** [ROP Natural History Study Manuscript \(for subcommittee\)wc.doc](#)

---

Hi Kathleen:

Great job. My comments are on the manuscript. Nothing major.

Wally

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**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Friday, July 27, 2012 8:53 AM  
**To:** Wrage, Lisa Ann (wrage@rti.org); dale\_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD); Wally Carlo, M.D.; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)

I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
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713 500-6708

**From:** Gantz, Marie  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET  
**Date:** Friday, July 27, 2012 12:38:36 PM

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I would vote revise for all, because I think all of them need more work with respect to the analysis plan. I think both the DiFiore and Walsh proposals are important because they could lead to a better understanding of why certain patients died, and I think the way they suggest looking into causes of death is reasonable. I have less background on the WINROP measure to go on, so I can't speak to the scientific importance of that proposal.

Marie

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, July 27, 2012 12:16 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET

Do you think these should be done, revised or rejected?

Thanks  
Rose

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**Sent:** Friday, July 27, 2012 12:13 PM  
**To:** Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Laptook, Abbot; mcw3@cwru.edu; Kurt Schibler; ROGER.FAIX@HSC.UTAH.EDU; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; wrich@ucsd.edu; nancy newman; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET

I will not be able to attend the SUPPORT subcommittee meeting, so I have included my main comments below. Additional (more minor) comments are in the attached.

Marie

DiFiore and Walsh proposals:

For the IH analysis in both of these proposals, I would recommend using Cox survival models with time-varying covariates that would allow the values of the IH predictor variables to differ for each infant and each day of life. This would allow you to use data on all infants. Additional time-varying covariates for the interaction between time and other predictors could be included to test whether causes of death vary over time (addressing the question of whether there are different causes for early and late deaths).

Walsh:

Under methods, I would also suggest doing a bivariate analysis of the reported causes of death by SGA and treatment group (to me this seems like a logical thing to do between steps 3 and 4).

Ehrenkranz:

I think this proposal would benefit from a more sophisticated analysis plan. For example, the stated methods do not include a test of the stated hypothesis that the accuracy of WINROP does not differ between treatment groups. To test that, you would want to compare the sensitivity and specificity of WINROP between the groups (look at rates of true and false negatives/positives, etc.). Also, I think the analysis of time between birth and alarm signal, alarm and pre-threshold, etc., would need to take into account factors such as gestational age, since in Kathleen Kennedy's paper the onset of ROP in SUPPORT infants was related to both chronological age and PMA.

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**From:** Gabrio, Jenna

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**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; mcw3@cwru.edu; 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; 'Bradley.Yoder@hsc.utah.edu'

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin

**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET

Dear all,

The SUPPORT subcommittee call to discuss the PAS submissions (attached) has been scheduled for:

**Monday, 7/30  
4:00pm ET**

**Dial:  
Within the USA**

(b)(6)

or

**Outside the USA**

(b)(6)

**Then enter Participant Passcode:**

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Abhik and Marie will be unable to join. Kurt is on service and Myriam is traveling so they may also be unable to join.

Thanks,  
Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, July 09, 2012 12:40 PM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; mcw3@cwru.edu; 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** PAS SUPPORT SUBMISSIONS

Hi

Here are 3 SUPPORT PAS abstract submissions. Jenna will set up a call to discuss.

Thanks  
Rose

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**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET  
**Date:** Friday, July 27, 2012 12:12:35 PM  
**Attachments:** [Di Fiore, Patterns of intermittent hypoxia associated with mortality, 2012-06-27\\_MG.docx](#)  
[Walsh, Exploration of the Causes of Mortality in the SUPPORT RCT, 2012-06-22\\_MG.docx](#)  
[Ehrenkranz, Interaction of Early Weight Gain & Oxygen Saturation Target on the Development of ROP, 2012-07-02\\_MG.docx](#)

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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin

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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin

**Subject:** PAS SUPPORT SUBMISSIONS

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## **Patterns of intermittent hypoxia associated with mortality in the SUPPORT trial RCT**

J Di Fiore, M Walsh, R Martin, W Carlo, N Finer and the SUPPORT subcommittee

June 27, 2012

### **Background:**

We have previously shown an association between patterns of intermittent hypoxia (IH) and morbidity. In preterm infants of 24-28wks gestation receiving normal clinical care, severe retinopathy of prematurity (ROP) was associated with an increase in the incidence of IH events during the first 8 weeks of life [Di Fiore 2010]. In a comparable cohort of infants enrolled in the SUPPORT trial, we have shown an increase in IH events in the low target group [Di Fiore 2012 in press]. However, there was also a lower incidence of severe ROP in the low target group. Closer examination of the patterns of these IH events revealed differences in timing and patterns. IH events associated with ROP were found to be less severe, longer in duration and occurring with a time interval of 1-20 minutes between events. In contrast, IH patterns in the low compared to high target group revealed no differences in duration or severity and a shorter time interval of <1 minute between IH events.

The time interval between IH events may be crucial for the initiation of an oxidative stress response. Fabian et al have shown, in a rodent model, an increase in superoxide anion concentration, a marker of oxidative stress, during the reoxygenation phase following hypoxic exposure. This increase took a few minutes to occur followed by a return to baseline values after approximately 20 minutes. Therefore, this timing may explain the higher incidence of IH events but lower occurrence of severe ROP in the low target group, in that the IH events in the low target group may occur too close together to allow for an oxidative stress cascade leading to severe ROP.

In addition to a lower incidence of severe ROP, the SUPPORT trial showed a higher mortality in the low target group. Similar quantification of IH patterns in infants who died compared to survivors may give insight into at risk patterns of intermittent hypoxia associated with mortality. Therefore, the purpose of this study is to compare oxygen saturation patterns in infants enrolled in the SUPPORT trial who died compared to survivors.

### **Hypothesis:**

Mortality will be associated with exacerbations in IH patterns including increased incidence, duration, and severity.

### **Methods:**

Oxygen saturation patterns will be reviewed for infants who died and compared to infants who survived in both target groups. Initial variables assessed will include the incidence of IH events <80%, time <80%, <85%, <90%, >95%, severity and mean and baseline oxygen saturation. IH patterns will be calculated using the mean/median, and measures of variability including standard deviation and histogram entropy of the duration of events, and the time interval between events.

The current SUPPORT trial dataset is limited by the long averaging time (16 sec) and low sample rate (10 sec or .1 Hz). The long averaging time will cause an underestimation of the severity of events and the low sample rate will limit our detection of events to those >20 sec in duration. In addition, the SpO2 skewing SUPPORT trial algorithm does not allow for one to one mapping back to the original SpO2 values in certain SpO2 ranges. This will eliminate the ability to use additional mathematical models such as Sample Entropy or Spectral Analysis. However, in our previous infant cohort receiving normal clinical care, spectral analysis has revealed slow wave oscillations in the SpO2 waveform with a cycle length of 4-8 minutes associated with morbidity. Therefore, although we will be unable to apply spectral analysis models to this cohort, our ability to only detect events >20sec with the low sample rate of .1Hz may be adequate to detect incidence and event duration differences associated with mortality.

#### Sample Size:

Sample of convenience based on number of infant deaths with \_\_\_\_\_ age matched controls.?

#### Statistics:

[This is based on our current studies. Will have to be modified for matched controls.] Statistical analysis of all measures will be performed on daily averages computed for each subject. A logarithmic or square root transformation will be applied if the original data are skewed. A t-test will be used for demographic comparisons between infant groups. Longitudinal profiles of deaths and survivors will be estimated and compared using linear mixed models. Models will include terms for gestational age, race, gender, multiple birth, and their interactions with terms involving day. Analyses will be conducted using SAS version 9.2 (SAS Institute, Cary, NC).

#### Issues:

1. Age matched controls or all infants?
2. Early vs late deaths?
3. Low resolution data
4. How to incorporate SGA in analysis?
5. What stats model is used with matched controls?

**Comment [MG1]:** Does this refer to percent time while on oxygen with SpO2 <80%? Not clear to me as written. The variables mentioned in this paragraph are probably based on the previous IH paper, but I think they could use some additional explanation, as indicated by my comments below.

**Comment [MG2]:** How defined?

**Comment [MG3]:** Mean SpO2?

**Comment [MG4]:** How is baseline defined?

**Comment [MG5]:** Mean/median of what?

**Comment [MG6]:** I don't know why this term is used. If age matched controls are selected, they should be selected randomly from the available matches.

**Comment [MG7]:** Of what?

**Comment [MG8]:** I suspect that the plan to use age matched controls is so that you can truncate the survivors' data at the time of death of the matched case. Another way to approach the analysis would be to use a Cox survival model with time-varying covariates. This would allow you to use data from all infants, and the "daily average" would be a time-varying covariate that could have a different value for each infant on each day. That is the approach I would recommend.

**Comment [MG9]:** There should not be a problem with including SGA in the model as a covariate in addition to GA.

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### **Pas 2013 Abstract Proposal**

#### **Interaction of Early Weight Gain and Oxygen Saturation Target on the Development of Retinopathy of Prematurity in Extremely Preterm Infants**

Richard A. Ehrenkranz, MD, Lois E. H. Smith, MD, PhD, Ann Hellström, MD, PhD, Cristina Navarrette, MD, Shahnaz Duara, MD, and Brenda B. Poindexter, MD

#### **Abstract/Synopsis:**

Several years ago, Löfqvist and colleagues (1, 2) described and validated the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm that was developed to identify infants < 32 weeks' gestation who were highly likely to develop severe ROP. This group has also demonstrated that a modification of the WINROP algorithm that used postnatal weight gain changes alone could accurately identify infants at risk (3, 4).

We propose to test the accuracy of the modified WINROP algorithm to identify severe ROP in infants who participated in the NICHD NRN SUPPORT Growth secondary study (5, 6).

**Objective:** To use the modified WINROP algorithm to examine the interaction of early postnatal weight gain and oxygen saturation target on the development of ROP.

**Hypothesis:** We hypothesize that the modified WINROP algorithm will accurately identify infants at risk of severe ROP regardless of the oxygen saturation range targeted.

**Methods:** This will be a secondary analysis of infants whom were enrolled in the NICHD NRN SUPPORT Growth secondary study. The modified WINROP algorithm will be used to identify infants at risk of severe ROP and its accuracy will be determined by comparing the list of infants identified with the final ROP outcomes.

#### **Statement of the problem:**

Availability of experienced ophthalmologists to perform the recommended ROP screening exams and ablative retinal treatment is limited. Therefore, accurate methods, such as WINROP, of identifying patients at greatest risk of severe ROP and of the need for ablative therapy would be beneficial. Furthermore, since lower oxygen saturation target ranges are being used to reduce the risk of severe ROP, it is important to ensure that the accuracy of this predictive method is not influenced by the targeted oxygen saturation range.

#### **Objective:**

To use the modified WINROP algorithm to examine the interaction of early postnatal weight gain and oxygen saturation target on the development of ROP.

#### **Hypotheses:**

1. We hypothesize that the modified WINROP algorithm will accurately identify infants at risk of severe ROP regardless of the oxygen saturation range targeted.

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2. We hypothesize that in those infants identified by the WINROP algorithm as being at high risk for severe ROP, the time between birth and the WINROP Alarm signal, between the Alarm signal and pre-threshold ROP, and between the Alarm signal and ROP treatment is not influenced by the targeted oxygen saturation range.

**Specific Aims:**

1. To determine whether the accuracy of the modified WINROP algorithm to identify infants at risk of severe ROP is influenced by the oxygen saturation target range [LOWER (85-89%) vs HIGHER (91-95%)].
2. To determine whether the time between birth and the WINROP Alarm signal, between the Alarm signal and pre-threshold ROP, and between the Alarm signal and ROP treatment is influenced by the oxygen saturation target range [LOWER (85-89%) vs HIGHER (91-95%)].

**Background/previous studies:**

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that is associated with preterm infants and is a major cause of visual impairment and blindness (7). Routine retinal screening examinations for ROP are recommended for infants with preterm infants with a birth weight (BW) < 1500 g or a gestational age (GA)  $\leq$  32 weeks and selected infants with a BW between 1500-2000 g or a GA > 32 weeks with an unstable course (7). Extremely preterm (EPT) infants, especially those less than 28 weeks' gestation, have the greatest risk of developing severe ROP and the need for ablative treatment according to the recommendations of the Early Treatment for Retinopathy of Prematurity Trial (ETROP) study (8).

Several years ago, Löfqvist and colleagues (1, 2) described and validated the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm that was developed to identify infants < 32 weeks' gestation who were highly likely to develop severe ROP. This group has also demonstrated that a modification of the WINROP algorithm that used postnatal weight gain changes alone could accurately identify infants at risk (3, 4). A clinical prediction model to predict risk of severe ROP has also been described by Binenbaum and co-workers (9) following a secondary analysis of the Premature Infants in Need of Transfusion (PINT) study data; their birth weight-gestational age-weight model was also found to accurately identify infants at high risk of requiring ablative therapy.

The NICHD NRN SUPPORT trial (5) reported that the rates of severe retinopathy or death did not differ significantly between the lower oxygen saturation (85-89%) group and the higher oxygen saturation (91-95%) 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). However, 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), while 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).

The NICHD NRN SUPPORT Growth secondary study (6) was performed to investigate whether infants would have better growth and better growth trajectories at 36 weeks post-menstrual age (PMA) and at 18-22 months corrected age (CA), in the group with the lower oxygen saturation target. The analyses found that oxygen saturation target assignment did not cause a difference in the combined outcome of death or growth failure at 36wks PMA, or at 18-22mos CA.

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Since some clinicians advocate lower oxygen saturation target ranges to prevent ROP, we propose to test the accuracy of the modified WINROP algorithm to identify severe ROP in SUPPORT Growth secondary study participants exposed to lower vs higher oxygen saturation target ranges.

**Methods/Analyses/Outcomes:**

This will be a secondary analysis of infants whom were enrolled in the NICHD NRN SUPPORT Growth secondary study (6). Of 1316 infants 24 0/7 to 27 6/7 weeks' gestation enrolled into the SUPPORT main trial (5), 810 participated in the Growth secondary study; 402 in the LOWER oxygen saturation (85-89%) group and 408 in the HIGHER oxygen saturation (91-95%) group. Of those infants, 333 and 348 respectively, survived to 36 weeks' PMA. The following Table displays the characteristics of the proposed study population [race (% White, % African American, % Hispanic, % Other) and the final SUPPORT ROP outcomes need to added to this table] (7).

Table 1: Characteristics of Study Population

Characteristic	LOWER O <sub>2</sub> Saturation (N= 402)	HIGHER O <sub>2</sub> Saturation (N=408)
Gestational Age (weeks)	26.2 ± 1.1*	26.2 ± 1.1
Birth weight (g)	839 ± 186	840 ± 191
Male (%)	53	58
Race [eg, White (%), African-American (%), Hispanic (%)]		
Survivors to 36 wks PMA [n (%)]	333 (83)	348 (85)
Final SUPPORT ROP Outcomes		
< Stage 3		
Stage 3		
Severe ROP (ie, threshold ROP, laser ablation, bevacizumab)	21/302 (7)	56/314 (18)

\*Mean + sd

For this study, infants will be separated into the oxygen saturation arm into which they were randomized in the SUPPORT trial [LOWER saturation (85-89%) vs HIGHER saturation (91-95%)]. The dataset for the SUPPORT Growth secondary study includes body weight measurements on day of life 1, 7, 14, 21, and 28 and at 32 and 36 weeks' PMA (or discharge, whichever came first). Final ROP outcomes were collected as part of the SUPPORT trial. Although weekly weight measurements are usually required to use WINROP to identify an "Alarm" signal (a post natal growth slowdown), we believe that a sufficient number of measurements were collected in the SUPPORT Growth secondary study to use the online WINROP monitoring system (<https://winrop.com>) to identify infants at risk of severe ROP. In addition, since the infants participating in the SUPPORT trial were all < 29 weeks'

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GA, most "Alarm" signals will likely identify infants at "high risk" of severe ROP. Furthermore, WINROP's accuracy will be determined by comparing each infant's WINROP outcome with his/her final SUPPORT ROP outcomes.

**Outcomes**

Therefore, the primary outcome will be the percentage of infants identified by the modified WINROP algorithm to have severe ROP who experienced a final outcome of severe ROP in the SUPPORT trial. Although severe ROP was defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab in the SUPPORT trial (5), for this secondary study, severe ROP will be defined as Stage 3 ROP or worse.

The influence of oxygen saturation target range on the frequency of WINROP alarm signals will be evaluated with 2 x 2 table and Chi-square analysis:

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	LOWER O <sub>2</sub> Saturation	HIGHER O <sub>2</sub> saturation	Totals
No Alarm signal [n (%)]			
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2Jul12

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### **An Exploration of the Causes of Mortality in the SUPPORT RCT**

M Walsh, J DiFiore, W Carlo, N Finer for the SUPPORT subcommittee

June 22, 2012

#### **Background:**

The EKS NICHD NRN SUPPORT trial randomized neonates to lower (85-89%) and higher (91-95%) saturation targets. 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. (CARLO NEJM 2010). Analyses of the causes of death between the randomized cohorts were not different. (Table 1 Supplementary appendix, NEJM May 2010). When the cohort was seen at follow-up at 18-22months of age, it was noted that there was a disproportionate loss of SGA infants in the followed cohort. This may be an important clue to the potential causes of increased mortality in the lower saturation group. In the original cohort while there was no statistically significant increase in any one cause of mortality, there were some imbalances. In the low saturation group there was a higher number of deaths from NEC (17.7% in lower sat vs 13.1% in higher sat) and a lower number of deaths from RDS (23.8% vs 29%). These findings suggest new avenues for exploration.

Appendix Table 1. Cause of Death in SUPPORT RCT

Category	Lower Saturation	Higher Saturation
RDS	23.8%	29.0%
Infection	19.2%	19.6%
NEC	17.7%	13.1%
BPD	10.8%	9.3%
CNS insult	9.2%	8.4%
Immaturity	5.4%	2.8%
Other	13.8%	17.8%

NEJM 362: 21, 2010.

#### **Hypothesis:**

Mortality among SGA infants randomized to the lower oxygen saturation target group will be higher than that in the high saturation group.

#### **Methods:**

1. We propose to analyze the records of the 247 infants who died in the original trial cohort.
2. We will begin with visual inspection of individual patient data among each randomized cohort of those who died prior to hospital discharge to include:  
Pt ID, birthweight, gestational age, SGA status, gender, race, day of death, cause/causes of death.
3. [We will then proceed to a bivariate analysis of mortality by SGA status and randomized group. All analyses will be conducted by intention to treat.]

Comment [MG1]:

4. Following these analyses, if we see that SGA is an important effect modulator, we will then conduct an analysis of the impact of intermittent hypoxia events in a subset of patients with and without mortality to determine if the patterns of intermittent hypoxia differ. [This protocol will be submitted as a separate secondary proposal by Julie DiFiore.]

**Potential Pitfalls:**

1. Should we adjust for center? If so, power? Or trust to the randomization.
2. Are there different effects by the time of death: causes of early deaths different than late deaths?

**Comment [MG2]:** It seems like a logical step between 3 and 4 would be to do a bivariate analysis of reported cause of death by treatment group and SGA.

**Comment [MG3]:** I assume both analyses would use the same methods? For the DiFiore proposal, I suggested using Cox survival regression with time-varying covariates (so that the IH predictor variables could take on a different value for each infant on each day of life). Using that method would allow you to include all SUPPORT infants.

**Comment [MG4]:** If all infants are included, it should be feasible to include center in the model.

**Comment [MG5]:** This can be tested in a Cox model by including time-varying covariates for the interaction between time and other predictors.

**From:** [Kennedy, Kathleen A](#)  
**To:** [Wrage, Lisa Ann \(lwrage@rti.org\)](#); [dale\\_phelps@urmc.rochester.edu](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [wcarlo@peds.uab.edu](#); [Das, Abhik](#); [Roger.Faix@hsc.utah.edu](#); [nfinen@ucsd.edu](#); [Gantz, Marie](#); [alaptouk@WIHRI.org](#); [nss5@cwru.edu](#); [wrich@ucsd.edu](#); [kurt.schibler@schmc.org](#); [Michele.Walsh@UHhospitals.org](#); [Bradley.Yoder@hsc.utah.edu](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** Onset of ROP Observational Study (SUPPORT Secondary)  
**Date:** Friday, July 27, 2012 9:53:09 AM  
**Attachments:** [ROP Natural History Study Manuscript \(for subcommittee\).doc](#)

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I've attached a draft of the ROP Secondary Study for your review. The manuscript has been formatted for Pediatrics (except that I left the figures in the body of the manuscript to make it easier for you to read). We could add about 200 more words to the manuscript but the abstract is at its limit. I still need to get a boilerplate from Stephanie.

If you're receiving this, it's because you have been included as an author based on your membership in the subcommittee for the SUPPORT Trial. Please get your comments/review back to me by **Fri Aug 17** so that I can incorporate them and you can meet the journal's authorship requirements.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

**From:** Walsh, Michele  
**To:** Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Laptook, Abbot; mcw3@cwru.edu; Kurt Schibler; ROGER.FAIX@HSC.UTAH.EDU; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET  
**Date:** Wednesday, July 25, 2012 12:34:01 PM

---

I will be traveling and not able to join.  
I will send written comments to Rose, Neil and Wally.

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Gabrio, Jenna [mailto:jgabrio@rti.org]  
**Sent:** Wednesday, July 25, 2012 10:54 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Laptook, Abbot; mcw3@cwru.edu; Kurt Schibler; ROGER.FAIX@HSC.UTAH.EDU; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET

Dear all,

The SUPPORT subcommittee call to discuss the PAS submissions (attached) has been scheduled for:

**Monday, 7/30**  
**4:00pm ET**

Dial:  
Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Abhik and Marie will be unable to join. Kurt is on service and Myriam is traveling so they may also be unable to join.

Thanks,



Jenna

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, July 09, 2012 12:40 PM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; mcw3@cwru.edu; 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** PAS SUPPORT SUBMISSIONS

Hi

Here are 3 SUPPORT PAS abstract submissions. Jenna will set up a call to discuss.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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

**From:** Gabrio, Jenna  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Laptook, Abbot; mcw3@cwru.edu; Kurt Schibler; ROGER.FAIX@HSC.UTAH.EDU; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; Bradley.Yoder@hsc.utah.edu  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** RE: PAS SUPPORT SUBMISSIONS Call - 7/30, M, 4:00 PM ET  
**Date:** Wednesday, July 25, 2012 10:56:57 AM  
**Attachments:** Di Fiore, Patterns of intermittent hypoxia associated with mortality, 2012-06-27.docx  
Ehrenkrantz, Interaction of Early Weight Gain & Oxygen Saturation Target on the Development of ROP, 2012-07-02.docx  
Walsh, Exploration of the Causes of Mortality in the SUPPORT RCT, 2012-06-22.docx

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Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

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Jenna

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**Sent:** Monday, July 09, 2012 12:40 PM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; 'Laptook, Abbot'; mcw3@cwru.edu; 'Kurt Schibler'; 'ROGER.FAIX@HSC.UTAH.EDU'; Vaucher, Yvonne; Myriam Peralta, M.D.; Das, Abhik; Wallace, Dennis; Gantz, Marie; wrich@ucsd.edu; nancy newman; 'Bradley.Yoder@hsc.utah.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin  
**Subject:** PAS SUPPORT SUBMISSIONS

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Rose

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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](mailto:higginsr@mail.nih.gov)

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Jean Lowe](#)  
**Subject:** SUPPORT\_OP\_71712  
**Date:** Monday, July 23, 2012 11:55:00 AM  
**Attachments:** [SUPPORT\\_OP\\_71712.docx](#)

---

Stephanie –  
Can you do a title page and boilerplate acknowledgements?  
Thanks  
Rose

**From:** Gantz, Marie  
**To:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Monday, July 23, 2012 10:40:39 AM

---

Dale, I will try to get back to you about this by the end of the week.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
824-514255

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Sunday, July 22, 2012 7:27 PM  
**To:** Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi Marie,

I have carefully reviewed each of these cases and they're an interesting mix\* (see attached).

Although the cases were 'spread over 11 centers', there were two centers that had 5 cases, and the other 9 centers had only 1 or 2 cases. In order to know if there is a problem here, we need to be able to appreciate if the two centers with 5 cases each (your coded centers E and upper case i) were high enrollers overall. Also, while some centers had "only" 1 or 2 cases, some center enrolled less than 10 subjects.

I know we want to keep things coded, but in order to get the full grasp, I need more. Perhaps you could express it as a percentage of enrollees (which would approximate things, but would not reveal a percentages of survivors who got exams) ?

Dale

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Friday, May 25, 2012 11:15 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale  
**Cc:** Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Rose and Dale,

SUPP10 data for the 23 infants who did not meet criteria for surgery are attached. I've coded the center and infant IDs, but you can see that the 23 infants were spread across 11 centers. Note that there were a couple of cases where "Threshold (New Type 1)" was coded as "Y" on the SUPP10, but the other individual variables (zone, stage and plus disease) did not back that up. I know that when we were doing the original analysis, we queried cases where there were similar disagreements in

the data, but I think we must have only queried cases where the ROP final outcome was based on threshold ROP rather than on surgery (these 23 cases were all classified based on surgery). Let me know if you have any questions.

Marie

**Marie Gantz, Ph.D.**  
Senior Research Statistician  
RTPI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-4255

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**Sent:** Friday, May 25, 2012 9:53 AM  
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**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Yes – maybe some of them had other issues and we need to know. We also need to know if this is only a few sites or spread across the network.

Rose

**Rosemary D. Higgins, MD**  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**Sent:** Friday, May 25, 2012 9:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Rose:

I was surprised to see that as well. We can pull all the data from the SUPP10 forms for each of these babies for you to review. Is that what you had in mind?

Thanks

Abhik

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, May 25, 2012 9:49 AM  
**To:** Das, Abhik  
**Subject:** FW: ROP data from SUPPORT TRIAL FOR DSMC

Abhik

I am a little concerned that we had 23 infants who got ROP surgery, but didn't meet the criteria- we should look at these cases in a little more detail (as well as see if this is site dependent)>

Is it possible to get the SUPP 10 forms on each of these infants – this will help to try to figure out why they had surgery and didn't reach the usual "Threshold" definition??

We need this to be able to explain this to the DSMC.

Thanks

Rose

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**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Thursday, May 24, 2012 5:15 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi Marie,

There are quite a few more cases of treatment before documented criteria for treatment than I had expected.

As we go back to the DSMC with this, I think it would be important to be able to better explain it.

Also, just to confirm with you. Infants who might have had ROP disease worse than Type 1 would also be considered treated appropriately. Did you exclude any infants because they had stage 4a or 4b or stage 5?

If it is going to take a lot of time, please discuss it with Dr. Das first. He and Dr. Higgins and I can discuss whether to go forward.

I do think it will be important to understand and be able to account for at least some of them --

and the fuller clinical ROP picture is likely to do that.

Therefore, I would like to request that you provide the more detailed data.

I also volunteer to individually review the ROP printouts from the subgroups listed below: (there is a nice de-identified format that was used for INS-2 that you could use that gives me basically two pages per infant – one for each eye)

- 5 who met criteria for surgery, but were not recorded as having had surgery (123-127=5)
- 23 who did receive surgery, but did not meet criteria for surgery

Thanks!

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 1:39 PM  
**To:** Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Dale, do you still need the more detailed data you requested?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Thursday, May 24, 2012 4:18 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Thank you Marie,

The answers provide very interesting data for discussion.

We will have some work to do with the Ophthalmologists in the inositol Study.

Particularly: treating in zone II without evidence of plus disease.

One the cases below not meeting criteria is unlikely enough that it is probably a keying error, but I would not want to go back at this point in time to do a query.

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC



Hi all, I included answers to Rose's questions below, based on my preliminary look at the SUPPORT data. I will send more complete answers to Dale's questions when I have them.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-0255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery 127 (based on Wally's paper, this looks like 132) MG: 132 includes infants with severe ROP as defined in the paper who did not have surgery recorded.

Can you tell us how many had each of these categories:

**1. type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);**

MG: 22 met these criteria in at least one eye

**2. zone I, stage 3 ROP without plus disease;**

MG: An additional 6 met these criteria in at least one eye (there were a total of 11 but 5 also met criteria for type I ROP in #1)

**3. zone II, stage 2 or 3 ROP with plus disease.**

MG: An additional 76 met these criteria in at least one eye (there were a total of 80 but 4 also met criteria in #1 or #2)

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

MG: There were 23 who did not meet criteria in #1-3 but who did have surgery:

1 had zone II stage 2 with plus disease missing

2 had zone II stage 2 no plus disease

18 had zone II stage 3 no plus disease

1 had zone III stage 3 no plus disease

1 had missing zone and stage but plus disease

Thanks  
Rose

Rosemary D. Higgins, MD  
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**Cc:** adas@rti.org  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Sunday, July 22, 2012 7:28:09 PM  
**Attachments:** Summary of 23 cases of ROP in SUPPORT that received surgery for ROP.docx

---

Hi Marie,

I have carefully reviewed each of these cases and they're an interesting mix\*(see attached).

Although the cases were 'spread over 11 centers', there were two centers that had 5 cases, and the other 9 centers had only 1 or 2 cases. In order to know if there is a problem here, we need to be able to appreciate if the two centers with 5 cases each (your coded centers E and upper case i) were high enrollers overall. Also, while some centers had "only" 1 or 2 cases, some center enrolled less than 10 subjects.

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**Cc:** Das, Abhik  
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**To:** Gantz, Marie  
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**Sent:** Thursday, May 24, 2012 4:18 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Thank you Marie,

The answers provide very interesting data for discussion.

We will have some work to do with the Ophthalmologists in the inositol Study.

Particularly: treating in zone II without evidence of plus disease.

One the cases below not meeting criteria is unlikely enough that it is probably a keying error, but I would not want to go back at this point in time to do a query.

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi all, I included answers to Rose's questions below, based on my preliminary look at the SUPPORT data. I will send more complete answers to Dale's questions when I have them.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-0255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie

**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery 127 (based on Wally's paper, this looks like 132) MG: 132 includes infants with severe ROP as defined in the paper who did not have surgery recorded.

Can you tell us how many had each of these categories:

**1. type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);**

MG: 22 met these criteria in at least one eye

**2. zone I, stage 3 ROP without plus disease;**

MG: An additional 6 met these criteria in at least one eye (there were a total of 11 but 5 also met criteria for type I ROP in #1)

**3. zone II, stage 2 or 3 ROP with plus disease.**

MG: An additional 76 met these criteria in at least one eye (there were a total of 80 but 4 also met criteria in #1 or #2)

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

MG: There were 23 who did not meet criteria in #1-3 but who did have surgery:

1 had zone II stage 2 with plus disease missing

2 had zone II stage 2 no plus disease

18 had zone II stage 3 no plus disease

1 had zone III stage 3 no plus disease

1 had missing zone and stage but plus disease

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)

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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)



Summary of 23 cases of ROP in SUPPORT that received surgery for ROP, but did not technically meet Type 1 (or worse) ROP criteria: Table 2: Summary of 23 cases of ROP in SUPPORT that received surgery for ROP, but did not technically meet Type 1 (or worse) ROP criteria:

Center	Case #	PMA @ Rx	Treated Without criteria	Claimed type 1, not doc.	Justifiably scary	Comments
A	1 2	35+3 44	X X		Ss	Very fast early Z II - Stage 3 Long time Z-I to Z II- stage 3, Rx after discharge
B	3	41		X		41, treated after discharge
C	4 5	32+3 35+3	X X		Ss	Z II, S-3, VERY early Rx Z II, S-3
D	6 7	40 52	X X			Z II, S-3 forever, gave in Z II, S-3 longer, Rx after discharg Had been regressing
E	8 9 10 11 12	39 33 35+3 34 37	X (X) X X X	Plus p Rx (X)		Examined almost every wk Laser twice, met criteria at 2nd (but Z & S missing there, not technically recorded) Z II, S-3 Z II, S-2 called it 'type 1', but ... Z II, S-3 did both laser & cryo VERY freq exams
F	13	32+3	X			Z II, S-3 awfully early
G	14	38	X			Z II, S3, 8 week gap in exams ? 30 PMA then next 38, ?unstable
H	15	40	X			Z II, S3 -- S2, was regressing, documented
I	16 17 18 19 20	36+3 40+3 39 36+3 37	X X X X X	X		Z II, S-3 Poorly documented, claimed T-1 Z II, S-3 ZONE III, S-3 Rx zone III ! Z II, S-3
J	21 22	39 36	X X			Z II, S-3 Z II, S-3
K	23	35+3	X		+/-	Z II, S-3

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
To: "Chris T. Cordle" <chris.cordle@abbott.com>  
Cc: "Phelps, Dale" <Dale\_Phelps@URMC.Rochester.edu>, "Kevin B. Mahan" <Kevin.B.Mahan@abbott.com>, Larry W Williams <Larry.Williams@abbott.com>, "Das, Abhik" <adas@rti.org>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Nolen, Tracy" <tnolen@rti.org>  
Date: 07/10/2012 02:54 PM  
Subject: RE: INS-3 Protocol needed for internal review asap

---

Chris

Here is the latest version of the protocol for your review.

On another note – I noticed on the agenda for next week's call that there were plans for meetings over the weekend of Sept 15-16. I have a prior commitment for that weekend. My understanding was that we would have a pre-meeting prior to the FDA meeting. When we originally were selecting dates for the letter, we looked at being available for half the prior day in case the meeting was scheduled in the morning. Since the FDA meeting is in the afternoon, this can be efficiently accomplished on 9/17 in the AM. I am having our office staff arrange a room here at our offices at NICHD for the morning and will have the RTI staff and Dale Phelps join us.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Chris T. Cordle [<mailto:chris.cordle@abbott.com>]  
**Sent:** Monday, July 09, 2012 2:10 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Phelps, Dale'; Kevin B. Mahan; Larry W Williams  
**Subject:** RE: INS-3 Protocol needed for internal review asap

Great.

Thanks!

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
To: "Phelps, Dale" <Dale\_Phelps@URMC.Rochester.edu>, "Chris T. Cordle" <chris.cordle@abbott.com>  
Cc: Larry W Williams <Larry.Williams@abbott.com>, "Kevin B. Mahan" <Kevin.B.Mahan@abbott.com>  
Date: 07/09/2012 02:02 PM  
Subject: RE: INS-3 Protocol needed for internal review asap

---

I am trying to review this today as I just received it this morning, but have several meetings this afternoon. Will get it to you once RTI and I have reviewed. It will be a "draft" form. We will have a final form for signature.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
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301-496-5575  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Monday, July 09, 2012 2:01 PM  
**To:** 'Chris T. Cordle'; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Larry W Williams; Kevin B. Mahan  
**Subject:** RE: INS-3 Protocol needed for internal review asap

Hi Chris,  
All edits are entered and circulated to NRN collaborators this am. There are only a couple of small knots to untie, and then I think Rose will be able to send it to you.

Dale

**From:** Chris T. Cordle [<mailto:chris.cordle@abbott.com>]  
**Sent:** Monday, July 09, 2012 10:22 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Larry W Williams; Kevin B. Mahan; Phelps, Dale  
**Subject:** INS-3 Protocol needed for internal review asap

Hi Rose,

As you may recall from the June teleconference, we have scheduled the internal AN review of the INS-3 protocol for July 19. We had indicated that AN would need the protocol to circulate to our reviewers by "the beginning of July". We now need to receive the new version of the draft protocol as soon as

possible so that we can take advantage of the July 19 meeting. This is the last internal review meeting scheduled before we need to send the protocol to FDA in the Briefing Documents package so it is vital that we get the revised protocol quickly. When can we expect the document? Please note that an electronic copy will meet our needs.

Thanks for your help!

Chris [attachment "Protocol INS-3 2012-07-10.docx" deleted by Chris T. Cordle/COLUMBUS/ROSS PRODUCTS DIVISION/US]

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Vaucher, Yvonne"; Wally Carlo, M.D.](#)  
**Cc:** [Finer, Neil; Myriam Peralta, M.D.; "Das, Abhik"; mgantz@rti.org](#)  
**Subject:** RE: FINAL SUPPORT FU PAPER and Review Response  
**Date:** Friday, July 13, 2012 2:27:00 PM

---

Agree!  
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  
CDBPM, NIH  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

**From:** Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
**Sent:** Friday, July 13, 2012 2:27 PM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
**Subject:** RE: FINAL SUPPORT FU PAPER and Review Response

Submitted today.  
Let's cross our fingers.  
Thank you everyone for all your help lo these many months.

Yvonne

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

**From:** Vaucher, Yvonne  
**Sent:** Friday, July 13, 2012 7:30 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
**Subject:** RE: FINAL SUPPORT FU PAPER and Review Response

Hooray!

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Friday, July 13, 2012 7:03 AM  
**To:** Vaucher, Yvonne; Wally Carlo, M.D.  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
**Subject:** RE: FINAL SUPPORT FU PAPER and Review Response

I am good with this -  
Anyone have any objections??

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 CDBPM, NIH  
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-----Original Message-----

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Thursday, July 12, 2012 5:39 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.  
Cc: Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: FINAL SUPPORT FU PAPER and Review Response

All,

LAST CHANCE. This is it.....the FINAL FINAL! Will resubmit tomorrow.

Yvonne

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, July 10, 2012 8:43 AM  
To: Vaucher, Yvonne; Wally Carlo, M.D.  
Cc: Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

Can we get the final draft for submission??

Thanks

Rose

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

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Wednesday, June 27, 2012 11:03 PM  
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER



All,

This conclusion is fine with me.

Yvonne

---

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
Sent: Monday, June 25, 2012 5:55 AM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

Dear Yvonne, Rose, Neil, Myriam, Abhik, and Marie:

I believe we have not addressed well two comments made by two different reviewers. These comments are related and address our interpretation of the results.

I think this is an important issue. I have reviewed our two NEJM papers and the BOOST II trials NEJM paper. These are below.

I provide at the end of the comments two sentences to add to the paper at the end of the Discussion.

Reviewer: "A remarkable finding with broad implications for families and physicians is not fully addressed by the authors. Even though infants exposed to higher oxygen have much higher rates of eye surgery for retinopathy of prematurity (13.2 vs. 6.5 p <0.0001), they do not have higher rates of blindness as defined by the complete loss of mono or diocular vision. In light of the mortality advantage in the higher saturation group, this is a critical finding which is not sufficiently emphasized."

Reviewer: "The conclusion summarizes the study findings - it would be important for the authors to provide some thoughts on how these results may affect the future management of these patients, in the context of current evidence."

We said before in the O2 sat NEJM paper: "At the present time, caution should be exercised regarding a strategy of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality".

Ben Stenson et al (BOOST II) said in their NEJM meta-analysis: "Until longer-term data on survival and morbidity are available, we consider it prudent not to target an SpO<sub>2</sub> of 85 to 89% in infants born earlier than 28 weeks of gestation.

Final recommendations await information on the primary outcomes of disability-free survival, anticipated in 2014 (Current Controlled Trials number, ISRCTN00842661 [U.K. trial]; and Australian New Zealand Clinical Trials Registry numbers, ACTRN12605000055606 [Australian trial] and ACTRN12605000253606 [New Zealand trial])."

I think we need to move the field forward and add at the end of the Conclusion something like this:

"As mortality remained lower in the higher oxygen saturation group at the time of follow up and there were no adverse visual or neurodevelopmental problems, lower oxygen saturation targets cannot be recommended in these extremely preterm infants. Early CPAP with a limited ventilation strategy can be considered an alternative to early surfactant even in infants as immature as 24 weeks as mortality was lower in the most immature infants."

I think it would be great to have something like this. It is not a strong recommendation, yet it provides interpretation of the results and putting them into clinical perspective.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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Director, Newborn Nurseries  
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Cell: 205 (b)(6)

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Sunday, June 24, 2012 9:00 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally Carlo, M.D.; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

The reply to reviewers is attached as are the highlighted combined paper and tables and the review letters from the NEJM for each paper. Please comment, diet. Marie and Abhik...be sure our replied re the sensitivity analyses and multiple imputations are stated correctly.

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Friday, June 22, 2012 5:59 AM  
To: Vaucher, Yvonne  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; mgantz@rti.org  
Subject: SUPPORT FU PAPER

Yvonne  
Are we close on submitting the SUPPORT FU paper?  
Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: New England Journal of Medicine - 12-08506  
**Date:** Friday, July 13, 2012 2:24:00 PM

---

SUPPORT FU paper submitted to nejm

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
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-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
Sent: Friday, July 13, 2012 2:05 PM  
To: yvaucher@ucsd.edu; mperalta@peds.uab.edu; nfiner@ucsd.edu; wcarlo@peds.uab.edu;  
michele.walsh@cwru.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu;  
roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; wrich@ucsd.edu; nxs5@cwru.edu;  
BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com;  
Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org;  
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emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com;  
cbauer@peds.med.miami.edu; jfuller@salud.unm.edu; moshea@wfubmc.edu; gary\_myers@urmc.rochester.edu;  
Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@aol.com  
Subject: New England Journal of Medicine - 12-08506

Dear Dr. Finer and co-authors,

Thank you for re-submitting your manuscript, "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)" to the New England Journal of Medicine.

Your manuscript has been forwarded to members of our editorial staff, who will make an initial evaluation and decide whether it merits further consideration. You will be notified of the decision as soon as possible.

Your new manuscript ID is 12-08506.

If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at <http://mc05.manuscriptcentral.com/nejm> and edit your user information as appropriate. You may also view the status of your manuscript at any time by checking For Authors section of the site.

We are undertaking evaluation of your manuscript with the understanding that neither the substance of the article nor the figures or tables have been published or will be submitted for publication elsewhere during the period of review.

Please provide the editors with copies of other manuscripts by you or your coauthors addressing similar or related research questions that are in preparation or under consideration at other journals. This does not apply to abstracts published in connection with scientific meetings or to news reports based on presentations at such meetings.

The Journal's policy is explained more fully at <http://www.nejm.org/page/author-center/editorial-policies>.

Please call us at 617-734-9800 if you have any questions.

Sincerely,

Jeffrey M. Drazen, M.D.  
Editor-in-Chief  
New England Journal of Medicine  
Distinguished Parker B. Francis Professor of Medicine  
Harvard Medical School

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

**From:** [Gantz, Marie](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Vaucher, Yvonne](#); [Wally Carlo, M.D.](#)  
**Cc:** [Finer, Neil](#); [Myriam Peralta, M.D.](#); [Das, Abhik](#)  
**Subject:** RE: FINAL SUPPORT FU PAPER and Review Response  
**Date:** Friday, July 13, 2012 10:20:36 AM

---

All looks fine to me.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

From: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#) [<mailto:higginsr@mail.nih.gov>]  
Sent: Friday, July 13, 2012 10:03 AM  
To: 'Vaucher, Yvonne'; Wally Carlo, M.D.  
Cc: [Finer, Neil](#); [Myriam Peralta, M.D.](#); [Das, Abhik](#); [Gantz, Marie](#)  
Subject: RE: FINAL SUPPORT FU PAPER and Review Response

I am good with this -  
Anyone have any objections??  
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  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

From: [Vaucher, Yvonne](#) [<mailto:yvaucher@ucsd.edu>]  
Sent: Thursday, July 12, 2012 5:39 PM  
To: [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); Wally Carlo, M.D.  
Cc: [Finer, Neil](#); [Myriam Peralta, M.D.](#); 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
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All,

LAST CHANCE. This is it.....the FINAL FINAL! Will resubmit tomorrow.

Yvonne

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, July 10, 2012 8:43 AM  
To: Vaucher, Yvonne; Wally Carlo, M.D.  
Cc: Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

Can we get the final draft for submission??

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overnight delivery use Rockville, MD 20852  
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higginsr@mail.nih.gov

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Sent: Wednesday, June 27, 2012 11:03 PM  
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

All,

This conclusion is fine with me.

Yvonne

---

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
Sent: Monday, June 25, 2012 5:55 AM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
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Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Sunday, June 24, 2012 9:00 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally Carlo, M.D.; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

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Subject: SUPPORT FU PAPER

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**Subject:** RE: FINAL SUPPORT FU PAPER and Review Response  
**Date:** Thursday, July 12, 2012 5:39:36 PM  
**Attachments:** NEJMCCombinedSUPPORTResubmissionRepy071212FINAL.doc  
Consort Figure CombinedFinal071212.doc  
NEJMCCombined paperand tables Highlighted Double spaced 071212FINAL.docx

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Subject: SUPPORT FU PAPER

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Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852  
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SANTA BARBARA • SANTA CRUZ

YVONNE VAUCHER, M.D., MPH  
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PROFESSOR OF PEDIATRICS  
92103-8774  
DEPARTMENT OF PEDIATRICS  
DIVISION OF NEONATOLOGY

200 WEST ARBOR DRIVE, MC

SAN DIEGO, CA

TEL: (619) 543-3793

FAX: (619) 543-3812

~~August 11, 2014~~ July 12, 2012

Dear Editor:

Thank you for your review of our companion manuscripts "Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Two Different Oxygen Saturation Targets" and "Early CPAP versus Surfactant in Extremely preterm Infants Neurodevelopmental Outcomes in Early Childhood." As recommended, we are resubmitting a single manuscript "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)" which concisely combines our companion manuscripts. We have responded to the editors and reviewers' comments, which have strengthened our combined manuscript. As indicated below, we have addressed the issues concerning (b)(4)

(b)(4) The condensed manuscript does not exceed 2700 words, has a total of 3 tables, 1 figure and a supplemental web appendix.

**Response to Reviewers 1 and 2 and Statistical Reviewer for "Early CPAP versus Surfactant in Extremely preterm Infants Neurodevelopmental Outcomes in Early Childhood." (12-01547)**

Response to Reviewer 1

- 1) (b)(4)
- 2)
- 3)

(b)(4)

4)

5)

6)

Response to Reviewer 2

(b)(4)

1)

2)

3)

4)

5)

6)

7)

Response to Statistical Reviewer 1 (Reviewer comments were combined for both papers)

Response to General Comments for both manuscripts [12-01547 (Early CPAP vs. Surfactant) and 12-01618 (Levels of oxygen saturation)]

1) The papers have been condensed and combined.

2) (b)(4)

(b)(4)

3)

**Comments for 12-01547 (Early CPAP vs. Surfactant)**

1) **The error in the Abstract has been corrected in the rewritten, combined abstract.**

2) (b)(4)

3)

4)

**Comments for 12-01618 (Levels of oxygen saturation)**

1) (b)(4)

2)

**Anonymous Review**

The manuscripts have been combined as suggested.

Recommendations for the clinician with regards to the use of early CPAP vs. intubation and lower vs. higher oxygen saturation ranges are contained in the summary of each primary paper ("Early CPAP versus Surfactant in Extremely Preterm Infants." NEJM 2010;362:1970-9; "Target

**Ranges of Oxygen Saturation in Extremely Preterm Infants." NEJM 2010;362:1959-69.) Since**

**the**

(b)(4)

(b)(4)

Conclusions are restated in the conclusion

**Response to Reviewers 1 and 2 and Statistical Reviewer for "Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Two Different Oxygen Saturation Targets"**

Response to Reviewer 1

(b)(4)

Response to Reviewer 2

(b)(4)

(b)(4)

**Response to Statistical Reviewer Reviewer 1:**

**Comments pertaining to both manuscripts:**

1) The papers have been combined.

2) (b)(4)

3)

**Comments for 12-01547 (Early CPAP vs. Surfactant)**

1) The error in the Abstract has been corrected in the rewritten, combined abstract.



2)

(b)(4)

3)

(b)(4)

4)

(b)(4)

Comments for 12-01618 (Levels of oxygen saturation)

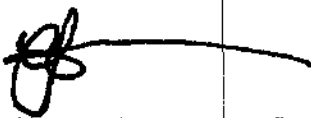
1)

(b)(4)

2)

Thank you for the opportunity to resubmit our manuscript. We believe that we have responded satisfactorily to the reviewers' questions, comments and suggestions.

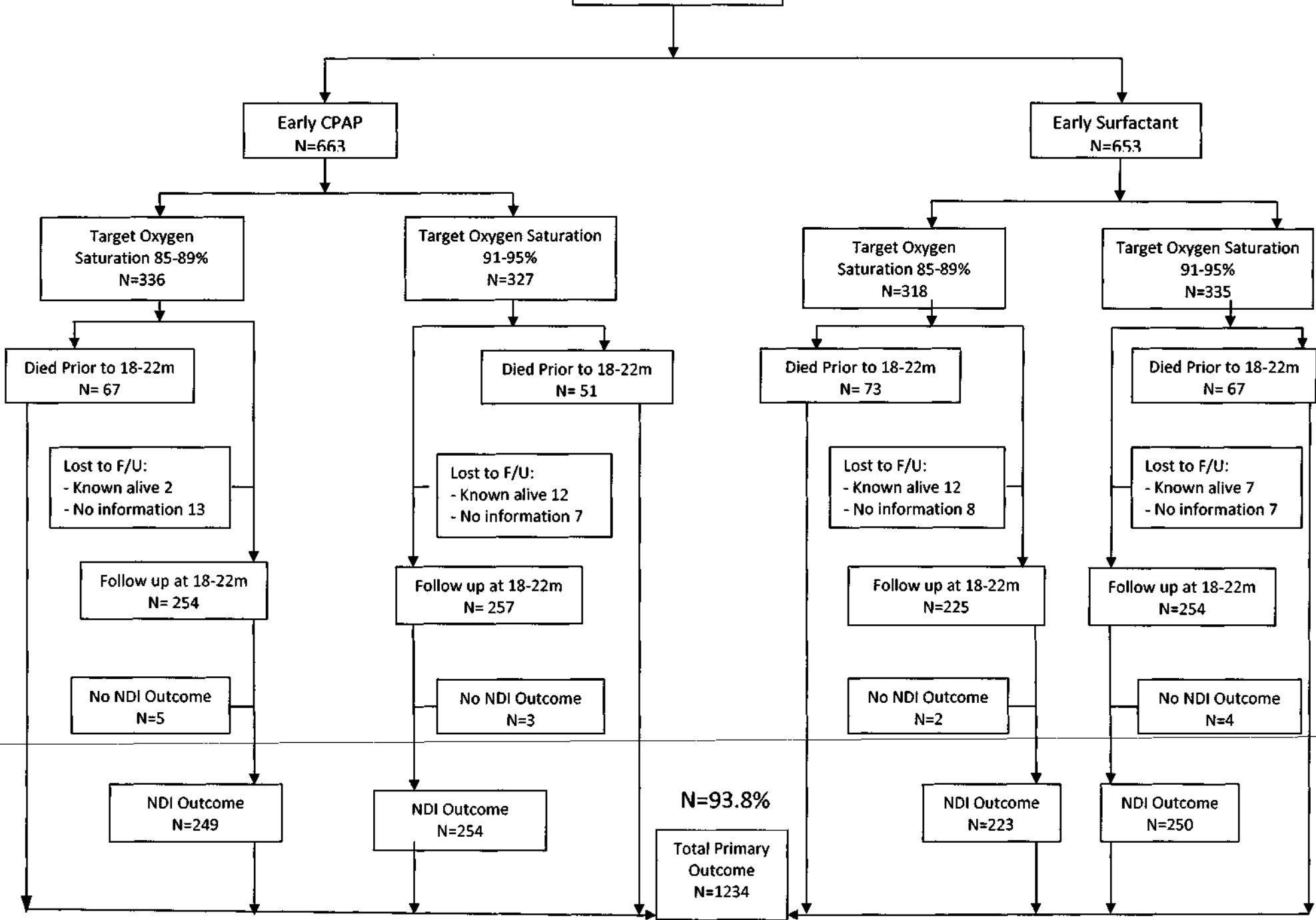
Sincerely,



Yvonne Vaucher, M.D., MPH  
Professor of Pediatrics,  
Division of Neonatology

**SUPPORT TRIAL**

**N=1316**



Primary Outcome

Primary Outcome

## Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Yvonne E. Vaucher, MD MPH<sup>1</sup>; \* Myriam Peralta-Carcelen, MD MPH<sup>2</sup>; \* Neil N. Finer, MD<sup>1</sup>; Waldemar A. Carlo, MD<sup>2</sup>; Michele C. Walsh, MD MS<sup>3</sup>; Marie G. Gantz, PhD<sup>4</sup>; Abbot R. Lupton, MD<sup>5</sup>; Bradley A. Yoder, MD<sup>6</sup>; Roger G. Faix, MD<sup>6</sup>; Abhik Das, PhD<sup>7</sup>; Kurt Schibler, MD<sup>8</sup>; Wade Rich, RRT<sup>2</sup>; Nancy S. Newman, RN<sup>4</sup>; Betty R. Vohr, MD<sup>5</sup>; Kimberly Yolton, PhD<sup>8</sup>; Roy J. Heyne, MD<sup>9</sup>; Deanne E. Wilson-Costello, MD<sup>3</sup>; Patricia W. Evans, MD<sup>10</sup>; Ricki F. Goldstein, MD<sup>11</sup>; Michael J. Acarregui, MD<sup>12</sup>; Ira Adams-Chapman, MD<sup>13</sup>; Athina Pappas, MD<sup>14</sup>; Susan R. Hintz, MD MS Epi<sup>15</sup>; Anna M. Dusick, MD FAAP<sup>16</sup>; Elisabeth C. McGowan, MD<sup>17</sup>; Richard A. Ehrenkranz, MD<sup>18</sup>; Anna Bodnar, MD<sup>6</sup>; Charles R. Bauer, MD<sup>19</sup>; Janell Fuller, MD<sup>20</sup>; T. Michael O'Shea, MD MPH<sup>21</sup>; Gary J. Myers, MD<sup>22</sup>; Rosemary D. Higgins, MD<sup>23</sup> for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

\*Both authors contributed equally to the manuscript

Corresponding author and reprints:

---

<sup>1</sup> Department of Pediatrics, University of California at San Diego, San Diego, CA

<sup>2</sup> Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

<sup>3</sup> Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

<sup>4</sup> Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC

<sup>5</sup> Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

<sup>6</sup> Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT

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<sup>9</sup> Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

<sup>10</sup> Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX

<sup>11</sup> Department of Pediatrics, Duke University, Durham, NC

<sup>12</sup> Department of Pediatrics, University of Iowa, Iowa City, IA (current affiliation Children's Hospital at Providence, Anchorage, AK)

<sup>13</sup> Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

<sup>14</sup> Department of Pediatrics, Wayne State University, Detroit, MI

<sup>15</sup> Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

<sup>16</sup> Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

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<sup>22</sup> Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

<sup>23</sup> *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

**Yvonne E. Vaucher, M.D., M.P.H.**

**Telephone: 619-543-3759**

**University of California, San Diego**

**Fax: 619-543-3812**

**Division of Neonatology**

**Email: yvaucher@ucsd.edu**

**200 West Arbor Drive**

**San Diego, CA, 92013**

**Text: MeSH terms:**

**Cerebral palsy**

**Infant, Newborn**

**Infant, Low Birth Weight**

**Infant, Extremely Low Birth Weight**

**Infant, Premature**

**Infant, Extremely Low Gestational Age**

**Infant mortality**

**Intellectual disability**

**Intensive care, neonatal**

**Neurodevelopmental outcome**

**Oximetry**

**Randomized controlled trial**

**Continuous Positive Airway Pressure**

**Intubation, intratracheal**

**Pulmonary surfactants/therapeutic use**

**Oxygen inhalation therapy/methods**

**Oxygen administration & dosage**

**Retinopathy of prematurity, epidemiology**

**Child development**

**Developmental disabilities, epidemiology**

**Psychomotor disorders, epidemiology**

**Follow-up studies**

## **ABSTRACT**

**BACKGROUND:** The SUPPORT trial showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS:** Infants born at 24 0/7 through 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP with a limited ventilation strategy vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months CA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants; 93.6% (990/1058) of survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [29.9% (183/613)] groups (RR 0.93, 95% CI 0.78 to 1.1, p=0.38) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)] oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality remained greater in the lower [22.1% (140/633)] compared to the higher [18.2% (118/648)] oxygen saturation group (RR 1.25, 95% CI 1.004 to 1.55, p=0.046).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

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## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between the lower oxygen saturation target group (85-89%) vs. higher oxygen saturation target group (91-95%). However, the risk of ROP among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

The pre-specified follow-up hypotheses of SUPPORT were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age (CA).

## **METHODS**

### **Study Design**

1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation.<sup>18</sup> Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygen saturation target group) using specially designed blinded oximeters.<sup>24</sup> Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18,24</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

### **Assessments**

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment

assignments and were annually evaluated for testing reliability. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26,27</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>28</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification, and visual impairment, defined as vision  $< 20/200$ ), were based upon examination and parental report.

Certified research staff collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

### Outcome

The pre-specified, primary composite outcome for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could



not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score < 70, GMFCS  $\geq$  2, moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality and NDI among survivors. Exploratory secondary outcomes included the individual components of NDI and levels of cognitive delay. The primary composite outcome (Death or NDI), and individual components of NDI were also compared for the higher and lower gestational age strata.

### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18,24</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in the composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for

whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted, where missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes.<sup>29</sup> Two-sided p values of  $< 0.05$  were considered statistically significant for all analyses, with no adjustments made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 4 tests per treatment comparison (CPAP vs. surfactant and low vs. high saturation) to be significant at the 0.05 level on the basis of chance alone.

## RESULTS

The pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children lost to follow up, 33 were known to be alive. A neurodevelopmental assessment was performed at

18-22 months corrected age for 990/1058 (93.6%) children. NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months corrected age, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers received antenatal steroids. At follow up there were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

Primary outcome: The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months corrected age (Table 2 a/b). Results from the sensitivity analysis using multiple imputations were virtually identical to the analysis of the non-missing cases, and are not displayed. Neither were there significant differences in the outcome of death or NDI between treatment groups in the higher and lower gestational age strata. (Appendix A) There was no difference in death between the CPAP and Surfactant arms. Mortality remained significantly higher in the lower compared to the higher saturation target group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all  $p$  values  $> 0.7$ ).

**Other outcomes:** The incidences of individual components of NDI [cognitive impairment (BSID-III cognitive composite score < 70), gross motor function level  $\geq 2$ , moderate/severe cerebral palsy, hearing impairment, and blindness] among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Table 2 a and b) or between the gestational age strata (Appendix A). However, mortality remained higher in the lower gestational age stratum of Surfactant treatment compared to the CPAP arm. Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen saturation target group vs. the lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month visit. (Table 3) Neither were there differences between the CPAP and Surfactant arms or between the lower and higher saturation target groups in the combined outcome of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix B). Sixty percent (583/977) of children evaluated at 18-22 months corrected age had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations.

## **DISCUSSION**

This trial tested critical outcome hypotheses related to both ventilatory and oxygenation strategies in a very high risk, extremely premature population. We found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant administration or between those randomized to the lower vs. higher oxygen saturation target groups in the SUPPORT trial. Mortality remained significantly higher in the lower compared to the higher oxygen saturation target group. There were no significant

differences among survivors in any of the treatment arms for NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq$ 2), hearing impairment, and bilateral blindness. To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which included pre-specified neurodevelopmental outcome at two years of age, but were not randomized for respiratory interventions, will not be available until 2014.<sup>30</sup>

Recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>21,31</sup> In SUPPORT, death during initial hospitalization was increased among neonates randomized to the lower-oxygen-saturation target group. As was published previously, causes of death between the lower and higher oxygen saturation groups were not different.<sup>24</sup> Mortality remained higher in the lower oxygen saturation target group at 18 to 22 months corrected age as well as in the most immature gestational age stratum of the surfactant administration group.

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>32,33</sup> We previously reported that the lower oxygen saturation target was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) among survivors to discharge.<sup>24</sup> Eye surgery was more frequent in the higher oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at the 18 to 22 months visit, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher saturation groups.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had comprehensive, standardized neurodevelopmental evaluation at 18-22 months corrected age. As in most trials of interventions starting at birth, generalizability may be limited by requiring antenatal consent which is associated with enrollment bias.

<sup>34,35</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>36</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome.

In summary, there were no significant differences in the composite outcome of death or NDI or in the individual components of NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation targets. However, as mortality remained lower in the higher oxygen saturation group at the time of follow up and there were no adverse visual or neurodevelopmental problems, lower oxygen saturation targets cannot be recommended in these extremely preterm infants. Early CPAP with a limited ventilation strategy can be considered an alternative to early surfactant even in infants as immature as 24 weeks as mortality was lower in the most immature infants.

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**Figure: Consort Diagram for SUPPORT**

**Table 1: Demographic and neonatal characteristics of follow-up cohorts**

**Table 2: Primary outcome (Death or NDI) and component outcomes: CPAP vs. Surfactant and Lower vs. Higher Oxygen Saturation Target groups**

**Table 3: Visual outcome: Lower vs. Higher Oxygen Saturation Target groups**

**Appendix A: Outcomes of SUPPORT treatment arms by gestational age strata**

**Appendix B: Comparison of cognitive outcomes of SUPPORT treatment arms**

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.

12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.
23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.



24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8-14.
27. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
28. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
29. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
30. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
31. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
32. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
33. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
34. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
35. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
36. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.

**Table 1: Demographics and Characteristics of Follow-up (FUP) Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)

Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < highschool degree-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%)	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language -no./total no.(%)	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%)	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months, Mean ± SD)	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

¶ At 36 weeks postmenstrual age

Comparisons of neonatal outcomes are adjusted for stratification by center and gestational age and for familial clustering

**Table 2: Death or NDI: CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups\***

<b><u>a. CPAP vs. Surfactant</u></b>	<b><u>CPAP</u></b>	<b><u>Surfactant</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

<b><u>b. Lower vs. Higher Oxygen Saturation</u></b>	<b><u>Lower</u></b>	<b><u>Higher</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA-no./total no.(%)	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined-no./total no.(%)	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI-no./total no.(%)	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70-no./total no.(%)	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2-no./total no.(%)	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy-no./total no.(%)	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral-no./total no.(%)	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment-no./total no.(%)	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial

clustering (except blindness was not adjusted for study center due to small N)

**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower	Higher	ARR*	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness and other abnormal eye findings were not adjusted for study center due to small N)

## Appendix A: Outcomes for treatment groups by gestational age strata

### CPAP vs. SURFACTANT

<u>24 0/7-25 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral –no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

<u>26 0/7-27 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50



**LOWER VS. HIGHER OXYGEN SATURATION TARGETS**

<b><u>24 0/7-25 6/7 weeks Gestational Age</u></b>	<b>Lower</b>	<b>Higher</b>	<b>ARR*</b>	<b>p</b>
Death or NDI-no./total no.(%)	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA-no./total no.(%)	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined-no./total no.(%)	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI-no./total no.(%)	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70-no./total no.(%)	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2-no./total no.(%)	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy-no./total no.(%)	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral –no./total no.(%)	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Hearing impairment-no./total no.(%)	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22

<u>26 0/7-27 6/7 weeks Gestational Age</u>	Lower	Higher	ARR*	P
Death or NDI-no./total no.(%)	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA-no./total no.(%)	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined-no./total no.(%)	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI-no./total no.(%)	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70-no./total no.(%)	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level ≥ 2-no./total no.(%)	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral palsy-no./total no.(%)	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral –no./total no.(%)	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Hearing impairment-no./total no.(%)	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

\*Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms**

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score (adjusted mean ± standard error)	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85-no./total no.(%)	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80-no./total no.(%)	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05
<u>Lower vs. Higher Oxygen Saturation Targets</u>	<u>LOWER</u>	<u>HIGHER</u>	ARR*	p
BSID-III cognitive composite score (adjusted mean ± standard error)	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85-no./total no.(%)	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80-no./total no.(%)	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

\*Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT FU PAPER  
**Date:** Wednesday, July 11, 2012 10:23:37 AM

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FYI

**From:** Gantz, Marie  
**Sent:** Wednesday, July 11, 2012 10:19 AM  
**To:** 'Vaucher, Yvonne'  
**Cc:** Das, Abhik  
**Subject:** RE: SUPPORT FU PAPER

It's a little tricky, because the protocol only lists blindness and CP under secondary outcomes (like you noted) but in the table shells at the end of the protocol, each component of NDI is included. It's further complicated, however, by the fact that the NDI definition in use when the protocol was written was based on the Bayley II rather than III, so the components in the table include MDI and PDI, not the cognitive composite score. I think the intention was to include all the components, but strictly speaking, that's not what was done. Thus, I suppose it's safest to call the individual components exploratory outcomes. Death (with no specific time period) is listed as a secondary outcome on page 21, and NDI is listed on page 11, so I think we can include those as pre-specified. I suggest the following:

Other pre-specified outcomes at 18 to 22 months CA were mortality and NDI among survivors. Exploratory secondary outcomes included the individual components of NDI and levels of cognitive delay.

This is also shorter than what you have now. If you want help shortening the manuscript to within the page limit, let me know and I'd be happy to make some suggestions.

Marie

Marie Gantz, Ph.D.  
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828-254-6255

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

**From:** Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
**Sent:** Tuesday, July 10, 2012 3:16 PM  
**To:** Gantz, Marie  
**Subject:** RE: SUPPORT FU PAPER

Marie,

I see the confusion. Here is the dilemma. The prespecified outcomes were the composite death or NDI, any CP (severity not specified) and blindness in at least one eye (pg 10-11 of the protocol). Of the individual components of NDI, only blindness is actually a prespecified component of NDI since we used moderate-severe CP rather than any CP. I deleted the part about mortality being prespecified since I realized that it really wasn't prespecified as a separate variable. My rephrasing still isn't quite right because it would include blindness as an exploratory analysis. I appreciate your help in rephrasing this accurately. We do need less words to meet the guidelines (2700)

Yvonne

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

From: Gantz, Marie [<mailto:mgantz@rti.org>]  
Sent: Tuesday, July 10, 2012 9:16 AM  
To: Vaucher, Yvonne; Das, Abhik  
Subject: RE: SUPPORT FU PAPER

Yvonne, comments are in the attached. You addressed most issues -- the only one that remains for me is confusion on page 7 about what outcomes were pre-specified vs. exploratory. I think the wording makes it easy to miss that the exploratory outcomes involving NDI components were the composite outcomes with death.

Marie

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
Sent: Friday, July 06, 2012 3:54 PM  
To: Gantz, Marie; Das, Abhik  
Cc: Vaucher, Yvonne  
Subject: RE: SUPPORT FU PAPER

Marie,  
Marie and Abhik,

Here is the final revised manuscript. Please review comments to see if they addressed your issues. Last para is changed per Wally and a comment in the discussion about other studies added by Neil. We are now 45 words over the 2700 word limit.

Thanks.

Yvonne

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

From: Gantz, Marie [<mailto:mgantz@rti.org>]  
Sent: Thursday, July 05, 2012 11:14 AM  
To: Vaucher, Yvonne  
Subject: RE: SUPPORT FU PAPER

Made a few minor edits.

Marie

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
Sent: Wednesday, June 27, 2012 10:52 PM  
To: Gantz, Marie  
Subject: RE: SUPPORT FU PAPER

Marie,  
Here are the Appendices.

Yvonne

---

From: Gantz, Marie [[mgantz@rti.org](mailto:mgantz@rti.org)]  
Sent: Tuesday, June 26, 2012 2:04 PM  
To: Das, Abhik; Vaucher, Yvonne  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT FU PAPER

My comments and edits are attached (added to Abhik's). Tables 2 and 3 are OK.  
Can you please send me the appendices so I can check those numbers?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

From: Gantz, Marie  
Sent: Monday, June 25, 2012 5:44 PM

To: Gantz, Marie; Das, Abhik; 'Vaucher, Yvonne'  
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'  
Subject: RE: SUPPORT FU PAPER

I did not make it through everything today, but I will finish up tomorrow morning.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
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[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

From: Gantz, Marie  
Sent: Monday, June 25, 2012 10:25 AM  
To: Das, Abhik; 'Vaucher, Yvonne'  
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'  
Subject: RE: SUPPORT FU PAPER

I have yet to look at this, but I will try to get comments/edits to you by the end of the day.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

From: Das, Abhik  
Sent: Monday, June 25, 2012 10:19 AM  
To: Vaucher, Yvonne  
Cc: Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'  
Subject: RE: SUPPORT FU PAPER

Yvonne:

This is looking great. A few minimal comments and suggested tweaks are in the attached.

Thanks

Abhik

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
Sent: Sunday, June 24, 2012 10:14 PM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; Das, Abhik; Gantz, Marie  
Subject: RE: SUPPORT FU PAPER

All,

Sorry, first email sent off too soon by mistaken click before I reread and attached Table 3 and consort diagram. There is considerable overlap in the reviewers comments and the statistical reviewer was the same for both papers. However, this reply answers specifically all questions in the order they were given by each reviewer for each paper. I can consolidate the answers if you think that would be better. Feel free to edit. Your guidance is appreciated.

PS..In the first email that was "edit" not "diet"! Must have remorseful about that piece of rhubarb pie I just ate. Very good though.

Yvonne

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From: Vaucher, Yvonne  
Sent: Sunday, June 24, 2012 7:02 PM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
Subject: RE: SUPPORT FU PAPER

Consort figure

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From: Vaucher, Yvonne  
Sent: Sunday, June 24, 2012 7:01 PM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
Subject: RE: SUPPORT FU PAPER

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From: Vaucher, Yvonne  
Sent: Sunday, June 24, 2012 7:00 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
Subject: RE: SUPPORT FU PAPER

The reply to reviewers is attached as are the highlighted combined paper and tables and the review letters from the NEJM for each paper.  
Please comment, diet. Marie and Abhik...be sure our replied re the sensitivity



analyses and multiple imputations are stated correctly.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Friday, June 22, 2012 5:59 AM  
To: Vaucher, Yvonne  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; mgantz@rti.org  
Subject: SUPPORT FU PAPER

Yvonne  
Are we close on submitting the SUPPORT FU paper?  
Thanks  
Rose

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

**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NTH/NICHD) [E]  
**Subject:** SUPPPORT Manuscript  
**Date:** Tuesday, July 10, 2012 7:56:26 PM

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Rose,

After Wally and Neil's additions we are over the 2700 word limit. In the methods we describe the collection of outcomes including reshospitalizations, interim medical history, medications. (last para of assessments). Since we didn't report any of these I would like to delete that line which would give us 2700 words.

Yvonne

**Yvonne E. Vaucher, M.D., M.P.H.**  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
**Subject:** RE: SUPPORT FU PAPER  
**Date:** Tuesday, July 10, 2012 3:23:19 PM

---

All,

Marie still has a question with phrasing. I see her point. As soon as we sort it out I will send the final.

Yvonne

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, July 10, 2012 8:43 AM  
**To:** Vaucher, Yvonne; Wally Carlo, M.D.  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
**Subject:** RE: SUPPORT FU PAPER

Can we get the final draft for submission??

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
and Perinatology Branch CDBPM, NIH  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

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

**From:** Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
**Sent:** Wednesday, June 27, 2012 11:03 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
**Subject:** RE: SUPPORT FU PAPER

All,

This conclusion is fine with me.

Yvonne

---

**From:** Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
**Sent:** Monday, June 25, 2012 5:55 AM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
**Subject:** RE: SUPPORT FU PAPER

Dear Yvonne, Rose, Neil, Myriam, Abhik, and Marie:

I believe we have not addressed well two comments made by two different reviewers. These comments are related and address our interpretation of the results.

I think this is an important issue. I have reviewed our two NEJM papers and the BOOST II trials NEJM paper. These are below.

I provide at the end of the comments two sentences to add to the paper at the end of the Discussion.

Reviewer: "A remarkable finding with broad implications for families and physicians is not fully addressed by the authors. Even though infants exposed to higher oxygen have much higher rates of eye surgery for retinopathy of prematurity (13.2 vs. 6.5 p <0.0001), they do not have higher rates of blindness as defined by the complete loss of mono or diocular vision. In light of the mortality advantage in the higher saturation group, this is a critical finding which is not sufficiently emphasized."

Reviewer: "The conclusion summarizes the study findings - it would be important for the authors to provide some thoughts on how these results may affect the future management of these patients, in the context of current evidence."

We said before in the O2 sat NEJM paper: "At the present time, caution should be exercised regarding a strategy of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality".

Ben Stenson et al (BOOST II) said in their NEJM meta-analysis: "Until longer-term data on survival and morbidity are available, we consider it prudent not to target an SpO2 of 85 to 89% in infants born earlier than 28 weeks of gestation. Final recommendations await information on the primary outcomes of disability-free survival, anticipated in 2014 (Current Controlled Trials number, ISRCTN00842661 [U.K. trial]; and Australian New Zealand Clinical Trials Registry numbers, ACTRN12605000055606 [Australian trial] and ACTRN12605000253606 [New Zealand trial])."

I think we need to move the field forward and add at the end of the Conclusion something like this:

"As mortality remained lower in the higher oxygen saturation group at the time of follow up and there were no adverse visual or neurodevelopmental problems, lower oxygen saturation targets cannot be recommended in these extremely preterm infants. Early CPAP with a limited ventilation strategy can be considered an alternative to early surfactant even in infants as immature as 24 weeks as mortality was lower in the most immature infants."

I think it would be great to have something like this. It is not a strong recommendation, yet it provides interpretation of the results and putting them into clinical perspective.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham

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Director, Newborn Nurseries  
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-----Original Message-----

From: Vaucher, Yvonne [mailto:yyvaucher@ucsd.edu]  
Sent: Sunday, June 24, 2012 9:00 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally Carlo, M.D.; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

The reply to reviewers is attached as are the highlighted combined paper and tables and the review letters from the NEJM for each paper. Please comment, diet. Marie and Abhik...be sure our replied re the sensitivity analyses and multiple imputations are stated correctly.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Friday, June 22, 2012 5:59 AM  
To: Vaucher, Yvonne  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; mgantz@rti.org  
Subject: SUPPORT FU PAPER

Yvonne  
Are we close on submitting the SUPPORT FU paper?  
Thanks  
Rose

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

**From:** Wally Carlo, M.D.  
**To:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Namasivayam Ambalavanan  
**Subject:** RE: SUPPORT ROP secondary study  
**Date:** Thursday, July 05, 2012 10:12:56 AM

---

Hi Dale:

I understand. I will offer this to someone else. I think it will be a good paper.

Rose:

Ambal and I had suggested an analysis on stage/zone of ROP by treatment group in SUPPORT O2 target trial (see email trail). One of my neonatologists is interested. We will write a brief protocol. I know you are interested in ROP, so we would love to work with you on this. I think the time for resolution of ROP is also an important new message that could be reported as part of this study.

Wally

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FAX: 205 934 3100  
Cell: 205 (b)(6)

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Wednesday, July 04, 2012 7:42 PM  
**To:** Wally Carlo, M.D.  
**Subject:** RE: SUPPORT ROP secondary study

Hi Wally,

I am still not able to think about this. It may be a good paper, but you really need to work with an ophthalmologist.

I'm not permitted to start anything new until the Inositol primary papers are completed.

Dale

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, April 21, 2011 10:26 AM  
**To:** Phelps, Dale; higginsr@mail.nih.gov  
**Cc:** Namasivayam Ambalavanan  
**Subject:** SUPPORT ROP secondary study

Hi Dale and Rose:

Ambal and I were wondering if it would be good to have a secondary paper on the SUPPORT trial to report by treatment groups the specific stages of ROP in each group, specific zones of involvement, and retinal detachment. This paper could also include a prediction of visual findings at 18-22 months based on eye exams and/or other risk factors.

You are the experts in ophthalmology so if you think we should do it, you should take the lead.

Wally

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Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
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Cell: 205 (b)(6)

**From:** Ehrenkranz, Richard  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Smith, Lois; Navarrete, Cristina; Shahnaz Duara; Poindexter, Brenda B  
**Subject:** WINROP abstract proposal  
**Date:** Monday, July 02, 2012 5:12:18 PM  
**Attachments:** Abstract proposal 2Jul12.docx

---

Rose:

Here is our final abstract proposal using the WINROP algorithm to examine SUPPORT Trial Growth secondary study data.

Richard

Lois: Please forward the final version to Ann.

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
PO Box 208064  
New Haven, CT 06520-8064  
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The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.



## **Pas 2013 Abstract Proposal**

### **Interaction of Early Weight Gain and Oxygen Saturation Target on the Development of Retinopathy of Prematurity in Extremely Preterm Infants**

Richard A. Ehrenkranz, MD, Lois E. H. Smith, MD, PhD, Ann Hellström, MD, PhD, Cristina Navarrette, MD, Shahnaz Duara, MD, and Brenda B. Poindexter, MD

#### **Abstract/Synopsis:**

Several years ago, Löfqvist and colleagues (1, 2) described and validated the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm that was developed to identify infants < 32 weeks' gestation who were highly likely to develop severe ROP. This group has also demonstrated that a modification of the WINROP algorithm that used postnatal weight gain changes alone could accurately identify infants at risk (3, 4).

We propose to test the accuracy of the modified WINROP algorithm to identify severe ROP in infants who participated in the NICHD NRN SUPPORT Growth secondary study (5, 6).

Objective: To use the modified WINROP algorithm to examine the interaction of early postnatal weight gain and oxygen saturation target on the development of ROP.

Hypothesis: We hypothesize that the modified WINROP algorithm will accurately identify infants at risk of severe ROP regardless of the oxygen saturation range targeted.

Methods: This will be a secondary analysis of infants whom were enrolled in the NICHD NRN SUPPORT Growth secondary study. The modified WINROP algorithm will be used to identify infants at risk of severe ROP and its accuracy will be determined by comparing the list of infants identified with the final ROP outcomes.

#### **Statement of the problem:**

Availability of experienced ophthalmologists to perform the recommended ROP screening exams and ablative retinal treatment is limited. Therefore, accurate methods, such as WINROP, of identifying patients at greatest risk of severe ROP and of the need for ablative therapy would be beneficial. Furthermore, since lower oxygen saturation target ranges are being used to reduce the risk of severe ROP, it is important to ensure that the accuracy of this predictive method is not influenced by the targeted oxygen saturation range.

#### **Objective:**

To use the modified WINROP algorithm to examine the interaction of early postnatal weight gain and oxygen saturation target on the development of ROP.

#### **Hypotheses:**

1. We hypothesize that the modified WINROP algorithm will accurately identify infants at risk of severe ROP regardless of the oxygen saturation range targeted.

2. We hypothesize that in those infants identified by the WINROP algorithm as being at high risk for severe ROP, the time between birth and the WINROP Alarm signal, between the Alarm signal and pre-threshold ROP, and between the Alarm signal and ROP treatment is not influenced by the targeted oxygen saturation range.

### **Specific Aims:**

1. To determine whether the accuracy of the modified WINROP algorithm to identify infants at risk of severe ROP is influenced by the oxygen saturation target range [LOWER (85-89%) vs HIGHER (91-95%)].
2. To determine whether the time between birth and the WINROP Alarm signal, between the Alarm signal and pre-threshold ROP, and between the Alarm signal and ROP treatment is influenced by the oxygen saturation target range [LOWER (85-89%) vs HIGHER (91-95%)].

### **Background/previous studies:**

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that is associated with preterm infants and is a major cause of visual impairment and blindness (7). Routine retinal screening examinations for ROP are recommended for infants with preterm infants with a birth weight (BW) < 1500 g or a gestational age (GA)  $\leq$  32 weeks and selected infants with a BW between 1500-2000 g or a GA > 32 weeks with an unstable course (7). Extremely preterm (EPT) infants, especially those less than 28 weeks' gestation, have the greatest risk of developing severe ROP and the need for ablative treatment according to the recommendations of the Early Treatment for Retinopathy of Prematurity Trial (ETROP) study (8).

Several years ago, Löfqvist and colleagues (1, 2) described and validated the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm that was developed to identify infants < 32 weeks' gestation who were highly likely to develop severe ROP. This group has also demonstrated that a modification of the WINROP algorithm that used postnatal weight gain changes alone could accurately identify infants at risk (3, 4). A clinical prediction model to predict risk of severe ROP has also been described by Binenbaum and co-workers (9) following a secondary analysis of the Premature Infants in Need of Transfusion (PINT) study data; their birth weight-gestational age-weight model was also found to accurately identify infants at high risk of requiring ablative therapy.

The NICHD NRN SUPPORT trial (5) reported that the rates of severe retinopathy or death did not differ significantly between the lower oxygen saturation (85-89%) group and the higher oxygen saturation (91-95%) 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). However, 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), while 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).

The NICHD NRN SUPPORT Growth secondary study (6) was performed to investigate whether infants would have better growth and better growth trajectories at 36 weeks post-menstrual age (PMA) and at 18-22 months corrected age (CA), in the group with the lower oxygen saturation target. The analyses found that oxygen saturation target assignment did not cause a difference in the combined outcome of death or growth failure at 36wks PMA, or at 18-22mos CA.

Since some clinicians advocate lower oxygen saturation target ranges to prevent ROP, we propose to test the accuracy of the modified WINROP algorithm to identify severe ROP in SUPPORT Growth secondary study participants exposed to lower vs higher oxygen saturation target ranges.

**Methods/Analyses/Outcomes:**

This will be a secondary analysis of infants whom were enrolled in the NICHD NRN SUPPORT Growth secondary study (6). Of 1316 infants 24 0/7 to 27 6/7 weeks' gestation enrolled into the SUPPORT main trial (5), 810 participated in the Growth secondary study; 402 in the LOWER oxygen saturation (85-89%) group and 408 in the HIGHER oxygen saturation (91-95%) group. Of those infants, 333 and 348 respectively, survived to 36 weeks' PMA. The following Table displays the characteristics of the proposed study population [race (% White, % African American, % Hispanic, % Other) and the final SUPPORT ROP outcomes need to added to this table] (7).

Table 1: Characteristics of Study Population

Characteristic	LOWER O <sub>2</sub> Saturation (N= 402)	HIGHER O <sub>2</sub> Saturation (N=408)
Gestational Age (weeks)	26.2 ± 1.1*	26.2 ± 1.1
Birth weight (g)	839 ± 186	840 ± 191
Male (%)	53	58
Race [eg, White (%), African-American (%), Hispanic (%)]		
Survivors to 36 wks PMA [n (%)]	333 (83)	348 (85)
Final SUPPORT ROP Outcomes		
< Stage 3		
Stage 3		
Severe ROP (ie, threshold ROP, laser ablation, bevacizumab)	21/302 (7)	56/314 (18)

\*Mean + sd

For this study, infants will be separated into the oxygen saturation arm into which they were randomized in the SUPPORT trial [LOWER saturation (85-89%) vs HIGHER saturation (91-95%)]. The dataset for the SUPPORT Growth secondary study includes body weight measurements on day of life 1, 7, 14, 21, and 28 and at 32 and 36 weeks' PMA (or discharge, whichever came first). Final ROP outcomes were collected as part of the SUPPORT trial. Although weekly weight measurements are usually required to use WINROP to identify an "Alarm" signal (a post natal growth slowdown), we believe that a sufficient number of measurements were collected in the SUPPORT Growth secondary study to use the online WINROP monitoring system (<https://winrop.com>) to identify infants at risk of severe ROP. In addition, since the infants participating in the SUPPORT trial were all < 29 weeks'

GA, most "Alarm" signals will likely identify infants at "high risk" of severe ROP. Furthermore, WINROP's accuracy will be determined by comparing each infant's WINROP outcome with his/her final SUPPORT ROP outcomes.

**Outcomes**

Therefore, the primary outcome will be the percentage of infants identified by the modified WINROP algorithm to have severe ROP who experienced a final outcome of severe ROP in the SUPPORT trial. Although severe ROP was defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab in the SUPPORT trial (5), for this secondary study, severe ROP will be defined as Stage 3 ROP or worse.

The influence of oxygen saturation target range on the frequency of WINROP alarm signals will be evaluated with 2 x 2 table and Chi-square analysis:

**Table 2: Alarm Signal Status and Oxygen Saturation Target Range**

	LOWER O <sub>2</sub> Saturation	HIGHER O <sub>2</sub> saturation	Totals
No Alarm signal [n (%)]			
Alarm signal [n (%)]			
Totals			

In addition, the influence of oxygen saturation target range on the median time [wks (range)] from birth to alert, from alarm to pre-threshold disease, and from alarm to ROP treatment (ie laser ablative therapy) will be compared:

**Table 3: Time from Birth and Alarm Signal to ROP Outcomes by Oxygen Saturation Target Range**

	LOWER O <sub>2</sub> Saturation	HIGHER O <sub>2</sub> saturation	p-value
Birth to Alarm signal (wks)*			
Alarm to Pre-threshold ROP (wks)			
Alarm to ROP treatment (wks)			

\* Median (range)

**References:**

1. Löfqvist C, Andersson E, Sigurdsson, Engström E, Härd A, Niklasson A, Smith LEH, Hellström A. Longitudinal postnatal weight and insulin-like growth factor I measurements in the prediction of retinopathy of prematurity. Arch Ophthalmol 2006; 124:1711-1718.
2. Löfqvist C, Hansen-Pupp I, Andersson E, Holm K, Smith LEH, Ley D, Hellström A. Validation of a new retinopathy of prematurity screening method monitoring longitudinal postnatal weight and insulin-like growth factor 1. Arch Ophthalmol 2009; 127:622-627.
3. Hellström A, Härd A, Engström E, Niklasson A, Smith L, Löfqvist C. Early weight gain predicts retinopathy in preterm infants: New, simple, efficient approach to screening. Pediatr 2009; 123:e638-e645.

2Jul12

4. Wu C, Löfqvist C, Smith LEH, VanderVeen DK, Hellström A, for the WINROP Consortium. Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants: A multicenter study analyzing weight velocity deviations for the prediction of retinopathy of prematurity. *Arch Ophthalmol* E-Pub April 9, 2012; doi: 10.1001/archophthalmol.2012.243
5. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Targets Ranges of Oxygen Saturation in Extremely Preterm Infants. *N Engl J Med* 2010; 362:1959-1969. Epub 2010 May 16.
6. Navarrete CT, Wrage LA, Duara Shahnaz, on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network. Growth outcomes of preterm infants exposed to different oxygen saturation target ranges from birth. *E-PAS2012:2755.5*.
7. AAP Policy Statement. Screening Examination of Premature Infants for Retinopathy of Prematurity. *Pediatrics*. 2006; 117:572-576.
8. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003; 121:1684-94.
9. Binenbaum G, Ying G, Quinn GE, Dreiseitl S, Karp K, Roberts RS, Karpalani H and the Premature Infants in Need of Transfusion Study Group. A clinical prediction model to stratify retinopathy of prematurity risk using postnatal weight gain. *Pediatr* 2011; 127:e607-e614.

**From:** [Wally Carlo, M.D.](mailto:Wally_Carlo_M.D.)  
**To:** [Walsh, Michele; Higgins, Rosemary \(NIH/NICHD\) \[E\]; nfiner@ucsd.edu](mailto:Walsh_Michele; Higgins_Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu)  
**Cc:** [adas@rti.org](mailto:adas@rti.org); [jmd3@case.edu](mailto:jmd3@case.edu)  
**Subject:** RE: Secondary to Support -Mortality  
**Date:** Thursday, June 28, 2012 10:18:33 AM

---

Hi Michele:

Got it.

wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

---

**From:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Thursday, June 28, 2012 8:15 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Cc:** [adas@rti.org](mailto:adas@rti.org); [jmd3@case.edu](mailto:jmd3@case.edu)  
**Subject:** RE: Secondary to Support -Mortality

Hi Wally:

I think your analyses with Marie looked at sustained hypoxia (baseline sat is one measure of this between the randomized groups (lower vs higher sat). This analysis is a bit different, we propose to look at intermittent hypoxia events and see if these differed between those who died and those who lived as it is possible that there is individual variation in this response.

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Thursday, June 28, 2012 8:24 AM  
**To:** '[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)'; '[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)'; Walsh, Michele  
**Cc:** '[adas@rti.org](mailto:adas@rti.org)'; '[jmd3@case.edu](mailto:jmd3@case.edu)'  
**Subject:** Re: Secondary to Support -Mortality

I will get a call set up

Thanks

Rose

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, June 28, 2012 07:42 AM  
**To:** Finer, Neil <nfiner@ucsd.edu>; Walsh, Michele <Michele.Walsh@UHhospitals.org>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Adas@rti.org <Adas@rti.org>; jmd3@case.edu <jmd3@case.edu>  
**Subject:** Re: Secondary to Support -Mortality

The one concern us that we looked at this already, maybe in a slightly different way. Marie worked hard on the model, and we as a group decided the signal. (possible effect) was probably too small. We did this as part of the ROP and mortality analyses.

Wally

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

**From:** "Finer, Neil" <nfiner@ucsd.edu>  
**To:** "Walsh, Michele" <Michele.Walsh@UHhospitals.org>  
**Cc:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Adas@rti.org" <Adas@rti.org>, "jmd3@case.edu" <jmd3@case.edu>  
**Sent:** Thu, Jun 28, 2012 10:58:52 GMT+00:00  
**Subject:** Re: Secondary to Support -Mortality

We need to do this  
I support moving this ahead  
Neil

On Jun 27, 2012, at 8:13 PM, "Walsh, Michele"  
<Michele.Walsh@UHhospitals.org<mailto:Michele.Walsh@UHhospitals.org>> wrote:

Hi:

Here is a secondary proposal for an abstract to further explore mortality.  
A second proposal to analyze intermittent hypoxia by randomized  
Sat group in those who died and in survivors will follow shortly  
From Julie DiFiore.

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<mailto:michele.walsh@cwru.edu>  
Phone: (216) 844-3387  
Fax: (216) 844-3380

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**From:** [Wally Carlo, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Secondary to Support -Mortality  
**Date:** Thursday, June 28, 2012 8:27:07 AM

---

THX

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Thursday, June 28, 2012 7:26 AM  
**To:** Wally Carlo, M.D.  
**Cc:** Das, Abhik  
**Subject:** RE: Secondary to Support -Mortality

I just asked Jenna to set up a call with the entire subcommittee. We will make sure Marie is available.

Thanks  
Rose

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

---

**From:** Wally Carlo, M.D. [mailto:[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)]  
**Sent:** Thursday, June 28, 2012 8:25 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** RE: Secondary to Support -Mortality

We should get Marie on the call.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, June 28, 2012 7:24 AM  
**To:** Wally Carlo, M.D.; 'nfiner@ucsd.edu'; 'Michele.Walsh@UHhospitals.org'  
**Cc:** 'adas@rti.org'; 'jmd3@case.edu'  
**Subject:** Re: Secondary to Support -Mortality

I will get a call set up  
Thanks  
Rose

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, June 28, 2012 07:42 AM  
**To:** Finer, Neil <nfiner@ucsd.edu>; Walsh, Michele <Michele.Walsh@UHhospitals.org>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Adas@rti.org <Adas@rti.org>; jmd3@case.edu <jmd3@case.edu>  
**Subject:** Re: Secondary to Support -Mortality

The one concern us that we looked at this already, maybe in a slightly different way. Marie worked hard on the model, and we as a group decided the signal. (possible effect) was probably too small. We did this as part of the ROP and mortality analyses.

Wally

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

**From:** "Finer, Neil" <nfiner@ucsd.edu>  
**To:** "Walsh, Michele" <Michele.Walsh@UHhospitals.org>  
**Cc:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Adas@rti.org" <Adas@rti.org>, "jmd3@case.edu" <jmd3@case.edu>  
**Sent:** Thu, Jun 28, 2012 10:58:52 GMT+00:00  
**Subject:** Re: Secondary to Support -Mortality

We need to do this  
I support moving this ahead  
Neil

On Jun 27, 2012, at 8:13 PM, "Walsh, Michele"

<Michele.Walsh@UHhospitals.org<mailto:Michele.Walsh@UHhospitals.org>> wrote:

Hi:

Here is a secondary proposal for an abstract to further explore mortality.  
A second proposal to analyze intermittent hypoxia by randomized  
Sat group in those who died and in survivors will follow shortly  
From Julie DiFiore.

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<mailto:michele.walsh@cwru.edu>  
Phone: (216) 844-3387  
Fax: (216) 844-3380

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<SUPPORT Mortality Abstract 2012 v1.doc>

**From:** [Ehrenkranz, Richard](#)  
**To:** [Lois Smith](#); [Navarrete, Cristina](#); [Shahnaz, Duara](#); [Poindexter, Brenda B](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#)  
**Subject:** WINROP analysis of SUPPORT trial data  
**Date:** Wednesday, June 27, 2012 3:51:57 PM  
**Attachments:** [Abstract proposal 27Jun12.docx](#)

---

Hi:

Here is a revised abstract proposal. Although it is due by July 2<sup>nd</sup>, I would like to submit it on Friday June 29<sup>th</sup>, so please let me know what you think?

Richard

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
PO Box 208064  
New Haven, CT 06520-8064  
tele: 203-688-2320  
fax: 203-688-5426

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of the Freedom of Information and Privacy Act

Page 1000 of 2000

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of the Freedom of Information and Privacy Act

Page 1001 of 2000

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of the Freedom of Information and Privacy Act

Page 1002 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act



Page 1003 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

**From:** [Ehrenkranz, Richard](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: preemie iNO  
**Date:** Wednesday, June 27, 2012 3:39:16 PM

---

Yes. But my availability should not determine the date/time of the call.  
Richard

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
PO Box 208064  
New Haven, CT 06520-8064  
tele: 203-688-2320  
fax: 203-688-5426

The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, June 27, 2012 2:49 PM  
**To:** Ehrenkranz, Richard  
**Cc:** Krisa P Van Meurs  
**Subject:** preemie iNO

Richard

There is likely to be a PAS abstract submission for a study to look at early indomethacin and IVH from the preemie iNO study being proposed by Marty Keszler from Brown. Would you like us to include you in the review?

Let me know

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
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:** [Walsh, Michele](#)  
**To:** [Wally Carlo M.D.](#); [Einer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; [Adas@rti.org](#)  
**Cc:** [jmd3@case.edu](#)  
**Subject:** Secondary to Support -Mortality  
**Date:** Wednesday, June 27, 2012 2:16:37 PM  
**Attachments:** [SUPPORT Mortality Abstract 2012 v1.doc](#)

---

Hi:

Here is a secondary proposal for an abstract to further explore mortality.  
A second proposal to analyze intermittent hypoxia by randomized  
Sat group in those who died and in survivors will follow shortly  
From Julie DiFiore.

*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](mailto:michele.walsh@cwru.edu)  
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(b)(4)

of the Freedom of Information and Privacy Act

Page 1007 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

**From:** Gantz, Marie  
**To:** Das, Abhik; Vaucher, Yvonne  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT FU PAPER  
**Date:** Tuesday, June 26, 2012 5:04:21 PM  
**Attachments:** [Table 1Combined\\_Final062012Highlighted062412\\_MG.docx](#)  
[NEJMCombinedSUPPORTResubmissionReply062412\\_AD\\_MG.doc](#)  
[CombinedSUPPORT\\_NDOutcome\\_YVFinal062012Double.spacedHighlighted062412\\_AD\\_MG.docx](#)

---

My comments and edits are attached (added to Abhik's). Tables 2 and 3 are OK. Can you please send me the appendices so I can check those numbers?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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

**From:** Gantz, Marie  
**Sent:** Monday, June 25, 2012 5:44 PM  
**To:** Gantz, Marie; Das, Abhik; 'Vaucher, Yvonne'  
**Cc:** 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** RE: SUPPORT FU PAPER

I did not make it through everything today, but I will finish up tomorrow morning.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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

**From:** Gantz, Marie  
**Sent:** Monday, June 25, 2012 10:25 AM  
**To:** Das, Abhik; 'Vaucher, Yvonne'  
**Cc:** 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** RE: SUPPORT FU PAPER

I have yet to look at this, but I will try to get comments/edits to you by the end of the day.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org

828-254-6255

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

From: Das, Abhik  
Sent: Monday, June 25, 2012 10:19 AM  
To: Vaucher, Yvonne  
Cc: Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'  
Subject: RE: SUPPORT FU PAPER

Yvonne:

This is looking great. A few minimal comments and suggested tweaks are in the attached.

Thanks

Abhik

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
Sent: Sunday, June 24, 2012 10:14 PM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; Das, Abhik; Gantz, Marie  
Subject: RE: SUPPORT FU PAPER

All,

Sorry, first email sent off too soon by mistaken click before I reread and attached Table 3 and consort diagram. There is considerable overlap in the reviewers comments and the statistical reviewer was the same for both papers. However, this reply answers specifically all questions in the order they were given by each reviewer for each paper. I can consolidate the answers if you think that would be better. Feel free to edit. Your guidance is appreciated.

PS..In the first email that was "edit" not "diet"! Must have remorseful about that piece of rhubarb pie I just ate. Very good though.

Yvonne

---

From: Vaucher, Yvonne  
Sent: Sunday, June 24, 2012 7:02 PM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik';  
[mgantz@rti.org](mailto:mgantz@rti.org)  
Subject: RE: SUPPORT FU PAPER

Consort figure

---

From: Vaucher, Yvonne  
Sent: Sunday, June 24, 2012 7:01 PM  
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; 'Myriam Peralta, M.D.'; 'Das, Abhik';  
[mgantz@rti.org](mailto:mgantz@rti.org)

Subject: RE: SUPPORT FU PAPER

---

From: Vaucher, Yvonne  
Sent: Sunday, June 24, 2012 7:00 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik';  
mgantz@rti.org  
Subject: RE: SUPPORT FU PAPER

The reply to reviewers is attached as are the highlighted combined paper and tables and the review letters from the NEJM for each paper. Please comment, diet. Marie and Abhik...be sure our replied re the sensitivity analyses and multiple imputations are stated correctly.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Friday, June 22, 2012 5:59 AM  
To: Vaucher, Yvonne  
Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik';  
mgantz@rti.org  
Subject: SUPPORT FU PAPER

Yvonne  
Are we close on submitting the SUPPORT FU paper?  
Thanks  
Rose

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



## Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Formatted: Highlight

Yvonne E. Vaucher, MD MPH<sup>1</sup>; \* Myriam Peralta-Carcelen, MD MPH<sup>2</sup>; \* Neil N. Finer, MD<sup>1</sup>; Waldemar A. Carlo, MD<sup>2</sup>; Michele C. Walsh, MD MS<sup>3</sup>; Marie G. Gantz, PhD<sup>4</sup>; Abbot R. Lupton, MD<sup>5</sup>; Bradley A. Yoder, MD<sup>6</sup>; Roger G. Faix, MD<sup>6</sup>; Abhik Das, PhD<sup>7</sup>; Kurt Schibler, MD<sup>8</sup>; Wade Rich, RRT<sup>2</sup>; Nancy S. Newman, RN<sup>4</sup>; Betty R. Vohr, MD<sup>5</sup>; Kimberly Yolton, PhD<sup>8</sup>; Roy J. Heyne, MD<sup>9</sup>; Deanne E. Wilson-Costello, MD<sup>5</sup>; Patricia W. Evans, MD<sup>10</sup>; Ricki F. Goldstein, MD<sup>11</sup>; Michael J. Acarregui, MD<sup>12</sup>; Ira Adams-Chapman, MD<sup>13</sup>; Athina Pappas, MD<sup>14</sup>; Susan R. Hintz, MD MS Epi<sup>15</sup>; Anna M. Dusick, MD FAAP<sup>16</sup>; Elisabeth C. McGowan, MD<sup>17</sup>; Richard A. Ehrenkranz, MD<sup>18</sup>; Anna Bodnar, MD<sup>6</sup>; Charles R. Bauer, MD<sup>19</sup>; Janell Fuller, MD<sup>20</sup>; T. Michael O'Shea, MD MPH<sup>21</sup>; Gary J. Myers, MD<sup>22</sup>; Rosemary D. Higgins, MD<sup>23</sup> for the SUPPORT Study Group of the *Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

\*Both authors contributed equally to the manuscript

<sup>1</sup> Department of Pediatrics, University of California at San Diego, San Diego, CA

<sup>2</sup> Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

<sup>3</sup> Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

<sup>4</sup> Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC

<sup>5</sup> Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

<sup>6</sup> Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT

<sup>7</sup> Statistics and Epidemiology Unit, RTI International, Rockville, MD

<sup>8</sup> Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH

<sup>9</sup> Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

<sup>10</sup> Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX

<sup>11</sup> Department of Pediatrics, Duke University, Durham, NC

<sup>12</sup> Department of Pediatrics, University of Iowa, Iowa City, IA (current affiliation Children's Hospital at Providence, Anchorage, AK)

<sup>13</sup> Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

<sup>14</sup> Department of Pediatrics, Wayne State University, Detroit, MI

<sup>15</sup> Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

<sup>16</sup> Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

<sup>17</sup> Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA

<sup>18</sup> Department of Pediatrics, Yale University School of Medicine, New Haven, CT

<sup>19</sup> University of Miami Miller School of Medicine, Miami, FL

<sup>20</sup> University of New Mexico Health Sciences Center, Albuquerque, NM

<sup>21</sup> Wake Forest University School of Medicine, Winston-Salem, NC

<sup>22</sup> Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

<sup>23</sup> *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD*

Corresponding author and reprints:

Yvonne E. Vaucher, M.D., M.P.H.

Telephone: 619-543-3759

University of California, San Diego

Fax: 619-543-3812

Division of Neonatology

Email: yvaucher@ucsd.edu

200 West Arbor Drive

San Diego, CA, 92013

Text: MeSH terms:

Cerebral palsy  
Infant, Newborn  
Infant, Low Birth Weight  
Infant, Extremely Low Birth Weight  
Infant, Premature  
Infant, Extremely Low Gestational Age  
Infant mortality  
Intellectual disability  
Intensive care, neonatal  
Neurodevelopmental outcome  
Oximetry  
Randomized controlled trial  
Continuous Positive Airway Pressure  
Intubation, intratracheal  
Pulmonary surfactants/therapeutic use  
Oxygen inhalation therapy/methods  
Oxygen administration & dosage  
Retinopathy of prematurity, epidemiology  
Child development  
Developmental disabilities, epidemiology  
Psychomotor disorders, epidemiology  
Follow-up studies

## ABSTRACT

**BACKGROUND:** The SUPPORT trial showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS:** Infants born at 24 0/7 to ~~through~~ 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP with a limited ventilation strategy vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months CA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants; 93.6% (990/1058) of survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [29.9% (183/613)] groups (RR 0.93, 95% CI 0.78 to 1.1, p=0.38) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)] oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality remained greater in the lower [22.1% (140/633)] compared to the higher [18.2% (118/648)] oxygen saturation group (RR 1.25, 95% CI 1.004 to 1.55, p=0.046).

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**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

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## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

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Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between the lower oxygen saturation target group (85-89%) vs. higher oxygen saturation target group (91-95%). However, the risk of ROP among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73; p<0.001) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60; p=0.04) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

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The pre-specified follow-up hypotheses of SUPPORT were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age.

## METHODS

### Study Design

1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation<sup>18</sup>. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygen target group) using a specially designed blinded oximeters.<sup>24</sup> Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18,24</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

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### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment

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assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-II).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26,27</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>28</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification; and visual impairment, defined as vision  $< 20/200$ , were based upon examination and parental report.

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Certified research staff collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

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#### Outcome

The pre-specified primary composite outcome at follow up for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score < 70, GMFCS  $\geq$  2, moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality among the entire trial cohort and the individual components of NDI among survivors at follow up. Exploratory secondary outcomes at 18 to 22 months CA included comparisons between treatment arms of death or individual components of NDI, Bayley III cognitive composite scores, and levels of cognitive delay. The primary composite outcome (Death or NDI), and individual components of NDI were also compared for the higher and lower gestational age strata.

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Comment [MG1]: It seems confusing that this is listed as "exploratory" but also as "pre-specified" above.

#### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18,24</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in the composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

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Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed

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according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted <sup>28</sup> ~~M~~, where missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes.<sup>29</sup> Two-sided p values of < 0.05 were considered statistically significant for all analyses, with ~~N~~ no adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than ~~48~~ tests per treatment comparison (CPAP vs. surfactant and low vs. high saturation) to be significant at the 0.05 level on the basis of chance alone.

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## RESULTS



The pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children lost to follow up, 33 were known to be alive. A neurodevelopmental assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months corrected age mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers received antenatal steroids. At follow up there were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

Primary outcome: The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months corrected age (Table 2 a/b). Results from the sensitivity analysis using multiple imputations were virtually identical to the analysis of the non-missing cases, and are not displayed. Neither were there significant differences in the outcome of death or NDI between treatment groups in the higher and lower gestational age strata. (Appendix A) There was no difference in death between the CPAP and Surfactant arms. Mortality

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remained significantly higher in the lower compared to the higher saturation target group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all p values > 0.7).

Other outcomes: The incidences of individual components of NDI [cognitive impairment (BSID-III cognitive composite score < 70), gross motor function level  $\geq$  2, moderate/severe cerebral palsy, hearing impairment, and blindness] among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Table 2 a and b) or between the gestational age strata (Appendix A). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen saturation target group vs. the lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month visit. (Table 3) Neither were there differences between the CPAP and Surfactant arms or between the lower and higher saturation groups in the combined outcome of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix B). Sixty percent (583/977) of children evaluated at 18-22 months corrected age had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq$  85) evaluations.

**Comment [AD3]:** Don't you want to mention here the higher mortality in the lower GA group for suf vs CPAP?

## DISCUSSION

This trial tested critical outcome hypotheses related to both ventilatory and oxygenation strategies in a very high risk, extremely premature population. We found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant or between those randomized to the lower vs.

higher oxygen saturation target groups in the SUPPORT trial. Mortality remained significantly higher in the lower compared to the higher oxygen saturation target group. There were no significant differences among survivors in any of the treatment arms for NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq 2$ ), hearing impairment, and bilateral blindness. To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which include pre-specified neurodevelopmental outcome at two years of age will not be available until 2014.<sup>30</sup>

Recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>21,31</sup> In SUPPORT death ~~prior to discharge~~ during initial hospitalization was increased among neonates randomized to the lower-oxygen-saturation target group. As was published previously, causes of death ~~before discharge~~ between the lower and higher oxygen saturation groups were not different.<sup>24</sup> Mortality remained higher in the lower oxygen saturation target group at 18 to 22 months corrected age as well as in the most immature gestational age stratum of the surfactant administration group.

Comment [164]: Shouldn't this be mentioned in the results section?

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>32,33</sup> We previously reported that the lower oxygen saturation target was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) among survivors ~~to be~~ discharge.<sup>24</sup> Eye surgery was more frequent in the higher oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at the 18 to 22 months visit, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher saturation groups.

Comment [165]: The "at" made it sound as if ROP was measured at discharge -- instead we mean among those who survived to discharge.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had comprehensive, standardized neurodevelopmental evaluation at 18-22 months corrected age. As in most trials of interventions starting at birth, generalizability may be limited by requiring antenatal consent which is associated with enrollment bias.

<sup>34,35</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>36</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome.

In summary, there were no significant differences in the composite outcome of death or NDI or in the individual components of NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation targets. Mortality was lower in the higher oxygen saturation target group and in the most immature stratum of the Early CPAP group and in the higher oxygen saturation target group.

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Figure: Consort Diagram for SUPPORT

Table 1: Demographic and neonatal characteristics of follow-up cohorts

Table 2: Primary outcome (Death or NDI) and component outcomes: CPAP vs. Surfactant and Lower vs. Higher Oxygen Saturation Target groups

Table 3: Visual outcome: Lower vs. Higher Oxygen Saturation Target groups

Appendix A: Outcomes of SUPPORT treatment arms by gestational age strata

Appendix B: Comparison of cognitive outcomes for SUPPORT treatment arms

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.

11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennfather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkert RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.

23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8-14.
27. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
28. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
29. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
30. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
31. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
32. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
33. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
34. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
35. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
36. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.





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SANTA BARBARA • SANTA CRUZ

YVONNE VAUCHER, M.D., MPH  
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DEPARTMENT OF PEDIATRICS  
DIVISION OF NEONATOLOGY

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~~June 30, 2014~~ ~~June 26, 2012~~ ~~June 25, 2012~~

Dear Editor:

Thank you for your review of our companion manuscripts "Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Two Different Oxygen Saturation Targets" and "Early CPAP versus Surfactant in Extremely preterm Infants Neurodevelopmental Outcomes in Early Childhood." As recommended, we are resubmitting a single manuscript "Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)" which concisely combines our companion manuscripts. We have responded to the editors and reviewers' comments, which have strengthened our combined manuscript. As indicated below, we have addressed the issues concerning

(b)(4)

(b)(4)

The condensed manuscript does not exceed 2700 words, has a total of 3 tables, 1 figure and a supplemental web appendix.

Response to Reviewers 1 and 2 and Statistical Reviewer for "Early CPAP versus Surfactant in Extremely preterm Infants Neurodevelopmental Outcomes in Early Childhood." (12-01547)

**Response to Reviewer 1**

1) (b)(4)

2)

3)

(b)(4)

**Response to Reviewer 2**

1) (b)(4)  
2)  
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Comment [M61]: It is an abbreviation

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Comment [A23]: Please reword.

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**Response to Statistical Reviewer 1 (Reviewers comments were combined for both papers)**

**Response to General Comments for both manuscripts [12-01547 (Early CPAP vs.; Surfactant) and 12-01618(Levels of oxygen saturation)]**

1) The papers have been condensed and combined.

2) (b)(4)

3)

**Comments for 12-01547 (Early CPAP vs. Surfactant)**

1) The error in the Abstract has been corrected in the rewritten, combined abstract.

2) (b)(4)

3)

4)

**Comments for 12-01618 (Levels of oxygen saturation)**

1) (b)(4)

2)

(b)(4)

**Anonymous Review**

The manuscripts have been combined as suggested.

Recommendations for the clinician with regards to the use of early CPAP vs. intubation and lower vs. higher oxygen saturation ranges are contained in the summary of each primary paper ("Early CPAP versus Surfactant in Extremely Preterm Infants." NEJM 2010;362:1970-9; "Target Ranges of Oxygen Saturation in Extremely Preterm Infants." NEJM 2010;362:1959-69) Since the (b)(4)

(b)(4)

**Response to Reviewers 1 and 2 and Statistical Reviewer for  
"Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of  
Two Different Oxygen Saturation Targets"**

**Response to Reviewer 1**

(b)(4)

**Response to Reviewer 2**

(b)(4)

(b)(4)



(b)(4)

**Response to Statistical Reviewer Reviewer 1:  
Comments pertaining to both manuscripts:**

1) The papers have been combined.

2) (b)(4)

2)

3)

**Comment [MG3]:** Number placement seems to be messed up.

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**Comments for 12-01547 (Early CPAP vs. Surfactant)**

1) (b)(4)

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4) (b)(4)

(b)(4)

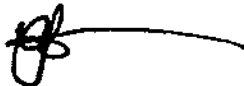
**Comments for 12-01618 (Levels of oxygen saturation)**

1) (b)(4)

2)

**Thank you for the opportunity to resubmit our manuscript. We believe that we have responded satisfactorily to the reviewers' questions, comments and suggestions.**

Sincerely,



Yvonne Vaucher, M.D., MPH  
Professor of Pediatrics,  
Division of Neonatology

**Table 1: Demographics and Characteristics of Follow-up (FUP) Cohorts**

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	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)



Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < 12 <sup>th</sup> grade/high school degree-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%) ‡	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language -no./total no.(%) ‡	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%) ‡	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	174/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months, Mean ± SD)	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7
Follow up-no./total no.(%)	511/545(93.8)	479/513(93.4)	479/2514(93.2)	551/544(93.9)

**Comment [MG1]:** <HS degree is actually what the category is -- <12 grade is different  
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**Comment [MG2]:** All were survivors in this table - I don't think you need this footnote

**Comment [MG3]:** Probably don't need this one either

**Comment [MG4]:** Need footnote explaining what this denominator is since it's bigger than the N in the column headers. Or, this row can be removed - it seems out of place in this table.

**Comment [MG5]:** All were survivors in this table

\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

¶ Among survivors to At 36 weeks postmenstrual age

‡ Only available at 18-22 months corrected age

‡ Among survivors to discharge or transfer

**Comparisons of neonatal outcomes are adjusted for stratification by center and gestational age and for familial clustering**

**From:** Ehrenkranz, Richard  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: PAS 2013 abstract with SUPPORT growth data  
**Date:** Monday, June 25, 2012 2:38:31 PM

---

Thanks for this reference Rose. Yes, this study would demonstrate that saturation targets do not influence WINROP's ability to detect high risk infants.

Richard

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, June 25, 2012 12:45 PM  
**To:** Ehrenkranz, Richard  
**Subject:** RE: PAS 2013 abstract with SUPPORT growth data

Richard

My understanding is that the algorithm will provide an "alarm" based on poor growth, correct? There is a 1700 infants study just published in Arch of Ophthalmology (*Arch Ophthalmol.* 2012;():1-8. doi:10.1001/archophthalmol.2012.243) using a US population. We needs to be very clear as to what the study will add (saturation targets and similar results I am assuming, correct).

You should likely add this new reference

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]  
**Sent:** Friday, June 22, 2012 3:46 PM  
**To:** Navarrete Cristina; Shahnaz Duara; Poindexter, Brenda B  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** PAS 2013 abstract with SUPPORT growth data

Hi:

I have attached a rough draft of a PAS 2013 abstract proposal to use a modification of the WINROP algorithm to examine the SUPPORT Growth secondary data. Please review/edit/critique/revise and let me know what you think. The proposals are due by July 2<sup>nd</sup>. I had discussed a this idea with Lois Smith at a symposium in Boston in March 2011 at which we were both speaking. Unfortunately, it had to wait until after the results were presented this year. Lois and Ann will provide the algorithm;

I have sent them this same draft. Thanks and sorry for the short notice.

Richard

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
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**From:** Ehrenkranz, Richard  
**To:** Duara, Shahnaz  
**Cc:** Navarrete, Cristina; Shahnaz Duara; Poindexter, Brenda B; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: PAS 2013 abstract with SUPPORT growth data  
**Date:** Monday, June 25, 2012 9:27:01 AM

---

Thanks Shahnaz. Good suggestion.  
Richard

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

**From:** Duara, Shahnaz [mailto:SDuara@med.miami.edu]  
**Sent:** Saturday, June 23, 2012 9:39 AM  
**To:** Ehrenkranz, Richard  
**Cc:** Navarrete, Cristina; Shahnaz Duara; Poindexter, Brenda B; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: PAS 2013 abstract with SUPPORT growth data

Hi Rich,  
Nice use of data. Wonder if a couple of data tables should be developed, so Abhik has an idea of what analysis is being requested.  
Shahnaz

Sent from my iPad

On Jun 22, 2012, at 2:46 PM, "Ehrenkranz, Richard"  
<richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>> wrote:

Hi:  
I have attached a rough draft of a PAS 2013 abstract proposal to use a modification of the WINROP algorithm to examine the SUPPORT Growth secondary data. Please review/edit/critique/revise and let me know what you think. The proposals are due by July 2nd. I had discussed a this idea with Lois Smith at a symposium in Boston in March 2011 at which we were both speaking. Unfortunately, it had to wait until after the results were presented this year. Lois and Ann will provide the algorithm; I have sent them this same draft. Thanks and sorry for the short notice.

Richard

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<Abstract proposal 22Jun12.docx>

**From:** Finer, Neil  
**To:** Wally Carlo, M.D.  
**Cc:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) (E); Myriam Peralta, M.D.; Das, Abhik; mgantz@rti.org  
**Subject:** Re: SUPPORT FU PAPER  
**Date:** Monday, June 25, 2012 9:15:30 AM

---

I am totally supportive of Wally's addition  
I agree that we are responding to the reviewers suggestions and previous publications  
Neil

On Jun 25, 2012, at 2:55 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

- > Dear Yvonne, Rose, Neil, Myriam, Abhik, and Marie:
- >
- > I believe we have not addressed well two comments made by two different reviewers. These comments are related and address our interpretation of the results.
- >
- > I think this is an important issue. I have reviewed our two NEJM papers and the BOOST II trials NEJM paper. These are below.
- >
- > I provide at the end of the comments two sentences to add to the paper at the end of the Discussion.
- >
- >
- > Reviewer: "A remarkable finding with broad implications for families and physicians is not fully addressed by the authors. Even though infants exposed to higher oxygen have much higher rates of eye surgery for retinopathy of prematurity (13.2 vs. 6.5 p <0.0001), they do not have higher rates of blindness as defined by the complete loss of mono or diocular vision. In light of the mortality advantage in the higher saturation group, this is a critical finding which is not sufficiently emphasized."
- >
- > Reviewer: "The conclusion summarizes the study findings - it would be important for the authors to provide some thoughts on how these results may affect the future management of these patients, in the context of current evidence."
- >
- >
- > We said before in the O2 sat NEJM paper: "At the present time, caution should be exercised regarding a strategy of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality".
- >
- > Ben Stenson et al (BOOST II) said in their NEJM meta-analysis: "Until longer-term data on survival and morbidity are available, we consider it prudent not to target an SpO2 of 85 to 89% in infants born earlier than 28 weeks of gestation. Final recommendations await information on the primary outcomes of disability-free survival, anticipated in 2014 (Current Controlled Trials number, ISRCTN00842661 [U.K. trial]; and Australian New Zealand Clinical Trials Registry numbers, ACTRN12605000055606 [Australian trial] and ACTRN12605000253606 [New Zealand trial])."
- >
- >
- > I think we need to move the field forward and add at the end of the Conclusion something like this:
- >
- > "As mortality remained lower in the higher oxygen saturation group at the time of follow up and there were no

adverse visual or neurodevelopmental problems, lower oxygen saturation targets cannot be recommended in these extremely preterm infants. Early CPAP with a limited ventilation strategy can be considered an alternative to early surfactant even in infants as immature as 24 weeks as mortality was lower in the most immature infants."

>  
>  
> I think it would be great to have something like this. It is not a strong recommendation, yet it provides interpretation of the results and putting them into clinical perspective.

> Wally

>  
> Wally Carlo, M.D.  
> Edwin M. Dixon Professor of Pediatrics  
> University of Alabama at Birmingham  
> Director, Division of Neonatology  
> Director, Newborn Nurseries  
> 1700 6th Avenue South  
> 176F Suite 9380R  
> Birmingham, AL 35233-7335  
> Phone: 205 934 4680  
> FAX: 205 934 3100  
> Cell: 205 (b)(6)

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

> From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
> Sent: Sunday, June 24, 2012 9:00 PM  
> To: Higgins, Rosemary (NIH/NICHD) [E]  
> Cc: Finer, Neil; Wally Carlo, M.D.; Myriam Peralta, M.D.; 'Das, Abhik'; mgantz@rti.org  
> Subject: RE: SUPPORT FU PAPER

> The reply to reviewers is attached as are the highlighted combined paper and tables and the review letters from the NEJM for each paper. Please comment, diet. Marie and Abhik...be sure our replied re the sensitivity analyses and multiple imputations are stated correctly.

> -----  
> From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
> Sent: Friday, June 22, 2012 5:59 AM  
> To: Vaucher, Yvonne  
> Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; mgantz@rti.org  
> Subject: SUPPORT FU PAPER

> Yvonne  
> Are we close on submitting the SUPPORT FU paper?  
> Thanks  
> Rose

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



**From:** [Wally Carlo, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT FU PAPER  
**Date:** Monday, June 25, 2012 9:03:54 AM

---

THANKS. I spent some time going over the 3 papers carefully so we can now as a group, improve on the sentences I suggested.

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, June 25, 2012 7:59 AM  
**To:** Wally Carlo, M.D.; Vaucher, Yvonne  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)  
**Subject:** RE: SUPPORT FU PAPER

Wally is correct - we need to fix this also.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, June 25, 2012 8:56 AM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
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I provide at the end of the comments two sentences to add to the paper at the end of the Discussion.

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Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology

Director, Newborn Nurseries  
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Birmingham, AL 35233-7335  
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Cc: Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; mgantz@rti.org  
Subject: SUPPORT FU PAPER

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**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT FU PAPER  
**Date:** Monday, June 25, 2012 8:57:17 AM

---

Rose:

I think what I wrote in the email I just sent you is an important issue.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
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Subject: SUPPORT FU PAPER

Yvonne

Are we close on submitting the SUPPORT FU paper?

Thanks

Rose

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Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852

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**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally; Myriam Peralta, M.D.](#); [Das, Abhik; mgantz@rti.org](#)  
**Subject:** Re: SUPPORT FU PAPER  
**Date:** Monday, June 25, 2012 2:54:21 AM

---

Yvonne and Myriam

I have reviewed each response and think that we have addressed every issue appropriately.

I trust that the Journal will agree

Great effort Yvonne and Myriam -congratulations!

The paper reads very well

Neil

On Jun 25, 2012, at 4:13 AM, "Vaucher, Yvonne" <[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)<<mailto:yvaucher@ucsd.edu>>> wrote:

All,

Sorry, first email sent off too soon by mistaken click before I reread and attached Table 3 and consort diagram.

There is considerable overlap in the reviewers comments and the statistical reviewer was the same for both papers.

However, this reply answers specifically all questions in the order they were given by each reviewer for each paper.

I can consolidate the answers if you think that would be better. Feel free to edit. Your guidance is appreciated.

PS..In the first email that was "edit" not "diet"! Must have remorseful about that piece of rhubarb pie I just ate. Very good though.

Yvonne

---

**From:** Vaucher, Yvonne  
**Sent:** Sunday, June 24, 2012 7:02 PM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Finer, Neil; Wally; 'Myriam Peralta, M.D.'; 'Das, Abhik'; [mgantz@rti.org](mailto:mgantz@rti.org)<<mailto:mgantz@rti.org>>  
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Consort figure

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**Subject:** RE: SUPPORT FU PAPER  
**Date:** Sunday, June 24, 2012 10:03:10 PM  
**Attachments:** [Consort Figure CombinedFinal062012.doc](#)

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Consort figure

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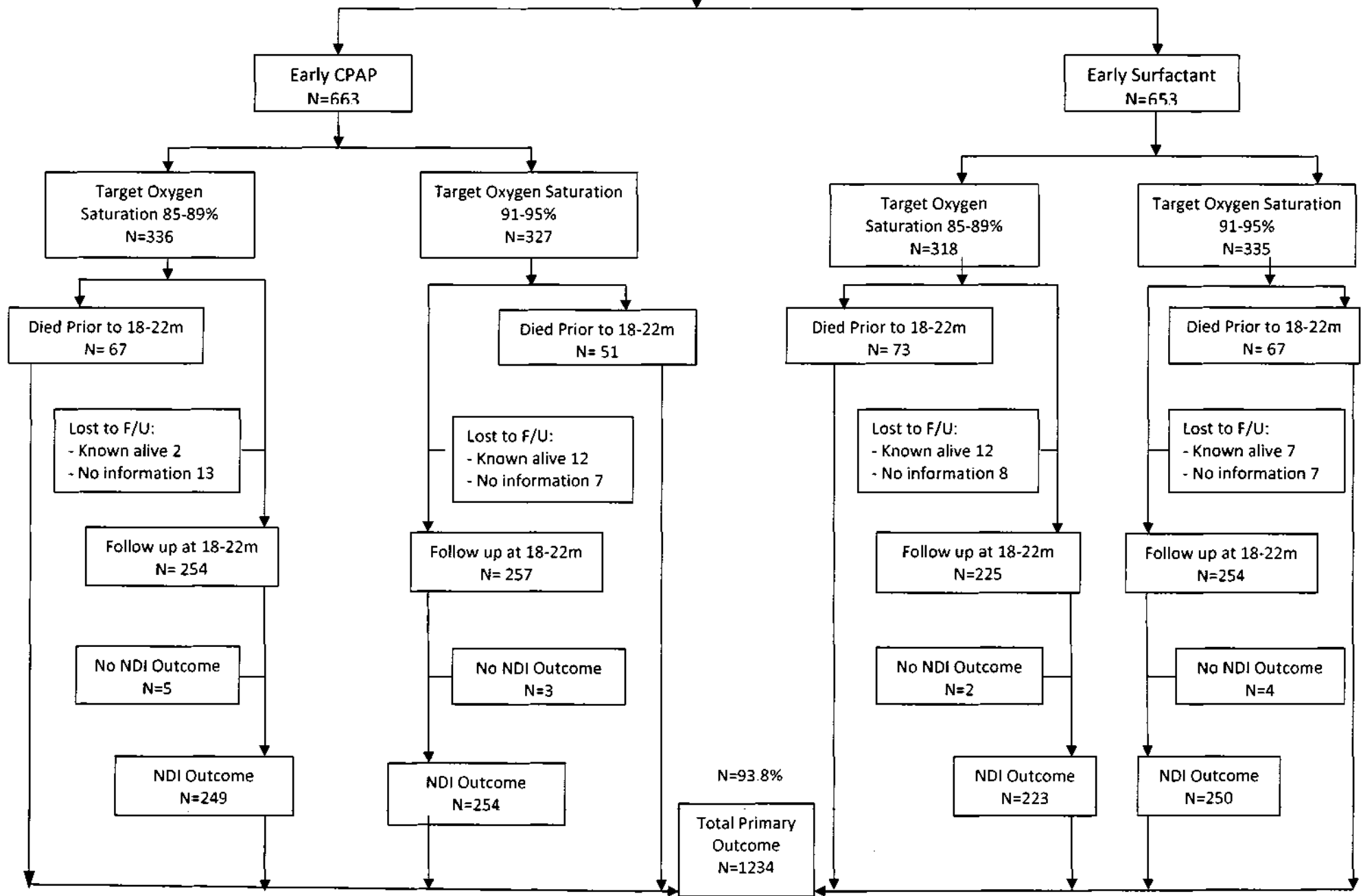
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**SUPPORT TRIAL**  
N=1316



Primary Outcome

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**Subject:** RE: SUPPORT FU PAPER  
**Date:** Sunday, June 24, 2012 10:00:17 PM  
**Attachments:** [CombinedSUPPORT\\_NDOutcome\\_YVFinal062012Double spacedHighlighted062412.docx](#)  
[NEJMCombinedSUPPORTResubmissionReply062412.doc](#)  
[NEJMReview0312CPAP.htm](#)  
[NEJMReview0312Oximeter.txt](#)  
[Table 1Combined\\_Final062012Highlighted062412.docx](#)  
[Table 2Combined\\_Final062012Highlighted062412.docx](#)  
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## Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

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Yvonne E. Vaucher, MD MPH<sup>1</sup>; \* Myriam Peralta-Carcelen, MD MPH<sup>2</sup>; \* Neil N. Finer, MD<sup>1</sup>; Waldemar A. Carlo, MD<sup>2</sup>; Michele C. Walsh, MD MS<sup>3</sup>; Marie G. Gantz, PhD<sup>4</sup>; Abbot R. Lupton, MD<sup>5</sup>; Bradley A. Yoder, MD<sup>6</sup>; Roger G. Faix, MD<sup>6</sup>; Abhik Das, PhD<sup>7</sup>; Kurt Schibler, MD<sup>8</sup>; Wade Rich, RRT<sup>2</sup>; Nancy S. Newman, RN<sup>4</sup>; Betty R. Vohr, MD<sup>5</sup>; Kimberly Yoltan, PhD<sup>8</sup>; Roy J. Heyne, MD<sup>9</sup>; Deanne E. Wilson-Costello, MD<sup>3</sup>; Patricia W. Evans, MD<sup>10</sup>; Ricki F. Goldstein, MD<sup>11</sup>; Michael J. Acarregui, MD<sup>12</sup>; Ira Adams-Chapman, MD<sup>13</sup>; Athina Pappas, MD<sup>14</sup>; Susan R. Hintz, MD MS Epi<sup>15</sup>; Anna M. Dusick, MD FAAP<sup>16</sup>; Elisabeth C. McGowan, MD<sup>17</sup>; Richard A. Ehrenkranz, MD<sup>18</sup>; Anna Bodnar, MD<sup>6</sup>; Charles R. Bauer, MD<sup>19</sup>; Janell Fuller, MD<sup>20</sup>; T. Michael O'Shea, MD MPH<sup>21</sup>; Gary J. Myers, MD<sup>22</sup>; Rosemary D. Higgins, MD<sup>23</sup> for the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

\*Both authors contributed equally to the manuscript

<sup>1</sup> Department of Pediatrics, University of California at San Diego, San Diego, CA

<sup>2</sup> Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

<sup>3</sup> Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

<sup>4</sup> Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC

<sup>5</sup> Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

<sup>6</sup> Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT

<sup>7</sup> Statistics and Epidemiology Unit, RTI International, Rockville, MD

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<sup>10</sup> Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX

<sup>11</sup> Department of Pediatrics, Duke University, Durham, NC

<sup>12</sup> Department of Pediatrics, University of Iowa, Iowa City, IA (current affiliation Children's Hospital at Providence, Anchorage, AK)

<sup>13</sup> Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

<sup>14</sup> Department of Pediatrics, Wayne State University, Detroit, MI

<sup>15</sup> Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

<sup>16</sup> Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

<sup>17</sup> Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA

<sup>18</sup> Department of Pediatrics, Yale University School of Medicine, New Haven, CT

<sup>19</sup> University of Miami Miller School of Medicine, Miami, FL

<sup>20</sup> University of New Mexico Health Sciences Center, Albuquerque, NM

<sup>21</sup> Wake Forest University School of Medicine, Winston-Salem, NC

<sup>22</sup> Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

<sup>23</sup> Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Corresponding author and reprints:

Yvonne E. Vaucher, M.D., M.P.H.

Telephone: 619-543-3759

University of California, San Diego

Fax: 619-543-3812

Division of Neonatology

Email: yvaucher@ucsd.edu

200 West Arbor Drive

San Diego, CA, 92013

Text: MeSH terms:

Cerebral palsy

Infant, Newborn

Infant, Low Birth Weight

Infant, Extremely Low Birth Weight

Infant, Premature

Infant, Extremely Low Gestational Age

Infant mortality

Intellectual disability

Intensive care, neonatal

Neurodevelopmental outcome

Oximetry

Randomized controlled trial

Continuous Positive Airway Pressure

Intubation, intratracheal

Pulmonary surfactants/therapeutic use

Oxygen inhalation therapy/methods

Oxygen administration & dosage

Retinopathy of prematurity, epidemiology

Child development

Developmental disabilities, epidemiology

Psychomotor disorders, epidemiology

Follow-up studies

## ABSTRACT

**BACKGROUND:** The SUPPORT trial showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS:** Infants born at 24 0/7 to ~~through~~ 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP with a limited ventilation strategy vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months CA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants; 93.6% (990/1058) of survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [29.9% (183/613)] groups (RR 0.93, 95% CI 0.78 to 1.1, p=0.38) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)] oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality remained greater in the lower [22.1% (140/633)] compared to the higher [18.2% (118/648)] oxygen saturation group (RR 1.25, 95% CI 1.004 to 1.55, p=0.046).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

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## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

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Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between the lower oxygen saturation target group (85-89%) vs. higher oxygen saturation target group (91-95%). However, the risk of ROP among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

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The pre-specified follow-up hypotheses of SUPPORT were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age.

## METHODS

### Study Design

1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation<sup>18</sup>. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygen target group) using a specially designed blinded oximeter.<sup>24</sup> Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18,24</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

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### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment

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assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26,27</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>28</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification; and visual impairment, defined as vision < 20/200), were based upon examination and parental report.

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Certified research staff collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

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#### Outcome

The pre-specified primary composite outcome at follow up for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score < 70, GMFCS  $\geq$  2, moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality among the entire trial cohort and the individual components of NDI among survivors at follow up. Exploratory secondary outcomes at 18 to 22 months CA included comparisons between treatment arms of death or individual components of NDI, Bayley III cognitive composite scores, and levels of cognitive delay. The primary composite outcome (Death or NDI), and individual components of NDI were also compared for the higher and lower gestational age strata.

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#### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18,24</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

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Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed

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according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted.<sup>29</sup> Missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes. Two-sided p values of < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 8 tests to be significant at the 0.05 level on the basis of chance alone.

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## RESULTS

The pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children lost to follow up, 33 were known to be alive. A neurodevelopmental assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean corrected age at neurodevelopmental assessment were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months corrected age mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers received antenatal steroids. At follow up there were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

Primary outcome: The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months corrected age (Table 2 a/b). Results from the sensitivity analysis using multiple imputations were virtually identical to the analysis of the non-missing cases. Neither were there significant differences in the outcome of death or NDI between treatment groups in the higher and lower gestational age strata. (Appendix A) There was no difference in death between the CPAP and Surfactant arms. Mortality remained significantly higher in

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the lower compared to the higher saturation target group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all p values > 0.7).

Other outcomes: The incidences of individual components of NDI [cognitive impairment (BSID-III cognitive composite score < 70), gross motor function level  $\geq 2$ , moderate/severe cerebral palsy, and blindness] among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Table 2 a and b) or between the gestational age strata.(Appendix A). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen saturation target group vs. the lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month visit. (Table 3) Neither were there differences between the CPAP and Surfactant arms or between the lower and higher saturation groups in the combined outcome of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix B). Sixty percent (583/977) of children evaluated at 18-22 months corrected age had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations.

## DISCUSSION

This trial tested critical outcome hypotheses related to both ventilatory and oxygenation strategies in a very high risk, extremely premature population. We found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant or between those randomized to the lower vs. higher oxygen saturation target groups in the SUPPORT trial. Mortality remained significantly higher in the

lower compared to the higher oxygen saturation target group. There were no significant differences among survivors in any of the treatment arms for NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq 2$ ), hearing impairment, and bilateral blindness. To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which include pre-specified neurodevelopmental outcome at two years of age will not be available until 2014.<sup>30</sup>

Recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>21,31</sup> In SUPPORT death prior to discharge was increased among neonates randomized to the lower-oxygen-saturation target group. As was published previously, causes of death before discharge between the lower and higher oxygen saturation groups were not different.<sup>24</sup> Mortality remained higher in the lower oxygen saturation target group at 18 to 22 months corrected age as well as in the most immature gestational age stratum of the surfactant administration group.

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>32,33</sup> We previously reported that the lower oxygen saturation target was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) among survivors at discharge.<sup>24</sup> Eye surgery was more frequent in the higher oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at the 18 to 22 months visit, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher saturation groups.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had comprehensive, standardized neurodevelopmental evaluation at 18-22 months corrected age. As in most trials of interventions starting at birth, generalizability may be limited by requiring antenatal consent which is associated with enrollment bias.<sup>34,35</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>36</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome.

In summary, there were no significant differences in the composite outcome of death or NDI or in the individual components of NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation targets. Mortality was lower in the most immature stratum of the Early CPAP group and in the higher oxygen saturation target group.

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Figure: Consort Diagram for SUPPORT

Table 1: Demographic and neonatal characteristics of follow-up cohorts

Table 2: Primary outcome (Death or NDI) and component outcomes: CPAP vs. Surfactant and Lower vs. Higher Oxygen Saturation Target groups

Table 3: Visual outcome: Lower vs. Higher Oxygen Saturation Target groups

Appendix A: Outcomes of SUPPORT treatment arms by gestational age strata

Appendix B: Comparison of cognitive outcomes for SUPPORT treatment arms

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.



11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkherth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.

23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007;109:8-14.
27. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
28. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
29. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
30. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
31. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
32. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
33. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
34. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
35. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
36. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.



YVONNE VAUCHER, M.D., MPH  
PROFESSOR OF PEDIATRICS  
DEPARTMENT OF PEDIATRICS  
DIVISION OF NEONATOLOGY

200 WEST ARBOR DRIVE, MC 8774  
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**August 11, 2014**

**Dear Editor:**

**Thank you for your review of our companion manuscripts “Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Two Different Oxygen Saturation Targets” and “Early CPAP versus Surfactant in Extremely preterm Infants Neurodevelopmental Outcomes in Early Childhood.” As recommended, are resubmitting a single manuscript “Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)” which concisely combines our companion manuscripts. We have responded to the editors and reviewers’ comments which has strengthened our combined manuscript. As indicated below, we have addressed the issues concerning**

(b)(4)

(b)(4) **The condensed manuscript does not exceed 2700 words, has a total of 3 tables, 1 figure and a supplemental web appendix.**

**Response to Reviewers 1 and 2 and Statistical Reviewer for “Early CPAP versus Surfactant in Extremely preterm Infants Neurodevelopmental Outcomes in Early Childhood.” (12-01547)**

**Response to Reviewer 1**

- 1) (b)(4)
- 2)
- 3)

(b)(4)

4)

5)

6)

**Response to Reviewer 2**

(b)(4)

1)

2)

3)

4)

5)

6)

7)

**Response to Statistical Reviewer 1 (Reviewers comments were combined for both papers)**

**Response to General Comments for both manuscripts [12-01547 (Early CPAP vs, Surfactant) and 12-01618(Levels of oxygensautration)]**

**1) The papers have been condensed and combined.**

2) (b)(4)

3)

**Comments for 12-01547 (Early CPAP vs. Surfactant)**

**1) The error in the Abstract has been corrected in the rewritten, combined abstract**

2) (b)(4)

3)

4)

**Comments for 12-01618 (Levels of oxygen saturation)**

1) (b)(4)

2)

**Anonymous Review**

**The manuscripts have been combined as suggested.**

**Recommendations for the clinician with regards to the use of early CPAP vs. intubation and lower vs. higher oxygen saturation ranges are contained in the summary of each primary paper (“Early CPAP versus Surfactant in Extremely Preterm Infants.” NEJM 2010;362:1970-9; “Target Ranges of Oxygen Saturation in Extremely Preterm Infants.” NEJM 2010;362:1959-69.) Since the** (b)(4)

(b)(4)

**Response to Reviewers 1 and 2 and Statistical Reviewer for  
“Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of  
Two Different Oxygen Saturation Targets”**

**Response to Reviewer 1**

(b)(4)

**Response to Reviewer 2**

(b)(4)

(b)(4)



**Response to Statistical Reviewer Reviewer 1:**  
**Comments pertaining to both manuscripts:**

**1) The papers have been combined.**

(b)(4)



**Comments for 12-01547 (Early CPAP vs. Surfactant)**

1) (b)(4)

2)

3)

(b)(4)

4) (b)(4)

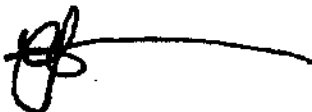
**Comments for 12-01618 (Levels of oxygen saturation)**

1) (b)(4)

2)

**Thank you for the opportunity to resubmit our manuscript. We believe that we have responded satisfactorily to the reviewers questions, comments and suggestions.**

Sincerely,





**Yvonne Vaucher, M.D., MPH**  
**Professor of Pediatrics,**  
**Division of Neonatology**

**From:** Finer, Neil  
**Sent:** Monday, March 26, 2012 6:59 AM  
**To:** Wally Carlo; rose higgins  
**Cc:** Vaucher, Yvonne  
**Subject:** Fwd: New England Journal of Medicine 12-01547

I know you guys are at a Network meeting and I would guess that you have got the same response to the Marions paper  
Can we arrange a phone call to discuss these and whether we want a combined paper in NEJM?  
I am OK with that  
be well  
Neil

Begin forwarded message:

**From:** "editorial@nejm.org" <editorial@nejm.org>  
**Date:** March 26, 2012 6:46:45 AM PDT  
**To:** "Finer, Neil" <nfiner@ucsd.edu>  
**Subject:** New England Journal of Medicine 12-01547

Dear Dr. Finer:

I am writing about your manuscript, "Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood." We found your study interesting but do not consider it acceptable for publication in the Journal in its present form. We would be interested, however, in receiving a single manuscript that combines the results in this paper with those currently included in your companion manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets." We believe the results of these two reports are best presented as a single manuscript.

As raised by the statistician, whose comments on both manuscripts are included below, it is important to address (b)(4)

(b)(4)

If you choose to resubmit, as we hope that you will, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy.

We ask that the final version of your manuscript not exceed 2700 words (text) and that there be no more than 5 tables or figures in the print version. It is fine to include additional material (methodologic, and other tables or figures as needed) in a supplemental web appendix.

To resubmit your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter "For Authors." Under "My Manuscripts," click on "Manuscripts with Decisions." Your manuscript will appear at the bottom of the screen under "Manuscripts with Decisions."

Click on "Create a Resubmission," and follow the instructions for resubmitting your manuscript. When your manuscript has been submitted, a new manuscript ID will be assigned.

Thank you for submitting your work to the Journal.

Sincerely,

Caren G. Solomon, MD  
Deputy Editor

Michael F. Greene, MD  
Associate Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Reviewer: 1

<b>Comments for the Author</b>

(b)(4)

Reviewer: 2

**<b>Comments for the Author</b>**

This manuscript is a follow up on the intent to treat (ITT) article that was published in the NEJM 2010;362:1970-9. The ITT findings continue to be hotly contested because (b)(4)

(b)(4)

A few clarifications/modifications would improve the manuscript:

1. Change the title to reflect the entire article. Consider - (b)(4)

(b)(4)

Statistical Reviewer: 1

Comments for the Author:

These manuscripts report longer follow-up for death and/or neurological impairment in the SUPPORT trial where a factorial design was used to examine early CPAP vs surfactant and two target ranges of oxygen saturation. Both manuscripts have several strengths, including the relatively (b)(4)

(b)(4)

**This review combines comments for both papers, since the papers have so much in common.**

**There are some issues that must be addressed in a revision.**

**General comments for the two manuscripts:**

(b)(4)

**Comments for 12-01547, early CPAP vs surfactant**

(b)(4)

**Comments for 12-01618, two target levels of oxygen saturation.**

(b)(4)

(b)(4)



NEJMReview0312Oximeter

From: **Finer, Neil**  
Sent: **Tuesday, March 27, 2012 7:02 AM**  
To: **Vaucher, Yvonne**  
Subject: **Fw: New England Journal of Medicine 12-01618**

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

From: **Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]**  
Sent: **Monday, March 26, 2012 3:15 PM**  
To: **'wcarlo@peds.uab.edu'; Finer, Neil; 'adas@rti.org'; 'mgantz@rti.org'**  
Subject: **Fw: New England Journal of Medicine 12-01618**

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

From: **Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]**  
Sent: **Monday, March 26, 2012 06:01 PM**  
To: **Higgins, Rosemary (NIH/NICHD) [E]**  
Subject: **Fw: New England Journal of Medicine 12-01618**

Here are the reviews, sorry I could not forward it before, my phone was not working.

I am traveling to the meeting tomorrow, I should arrive around 11:30 am or so I hope we can talk then. thanks \_\_\_\_\_

From: **onbehalfof+editorial+nejm.org@manuscriptcentral.com**  
[onbehalfof+editorial+nejm.org@manuscriptcentral.com] on behalf of  
**editorial@nejm.org [editorial@nejm.org]**  
Sent: **Monday, March 26, 2012 8:40 AM**  
To: **Myriam Peralta, M.D.**  
Subject: **New England Journal of Medicine 12-01618**

Dear Dr. Peralta Carcelen:

I am writing about your manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets." We found your study interesting but do not consider it acceptable for publication in the Journal in its present form. We would be interested, however, in receiving a single manuscript that combines the results in this paper with those currently included in your companion manuscript, "Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood." We believe that the results of these 2 reports are best presented as a single manuscript.

As raised by the statistician, whose comments on both manuscripts are included below, it is important to address whether there is a (b)(6)

(b)(6)

If you choose to resubmit, as we hope that you will, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy.

We ask that the final version of your manuscript not exceed 2700 words (text) and that there be no more than 5 tables or figures in the print version. It is fine to include additional material (methodologic, and other tables or figures as needed) in a supplemental web appendix.

To resubmit your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter "For Authors." Under "My Manuscripts," click on "Manuscripts with

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Decisions." Your manuscript will appear at the bottom of the screen under "Manuscripts with Decisions." Click on "Create a Resubmission," and follow the instructions for resubmitting your manuscript. When your manuscript has been submitted, a new manuscript ID will be assigned.

Thank you for submitting your work to the Journal.

Sincerely,

Caren G. Solomon, MD  
Deputy Editor

Michael F. Greene, MD  
Associate Editor

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<http://www.nejm.org>

Reviewer: 1

**<b>Comments for the Author</b>**

(b)(4)



Reviewer: 2

**<b>Comments for the Author</b>**

This manuscript by the investigators in the NICHD Neonatal Network addresses the central questions remaining following the initial publication of the



NEJMReview0312Oximeter

SUPPORT trial which reported the rather unexpected increase in NICU mortality associated with randomization of extremely preterm infants to a relatively narrow range of lower versus higher oxygen saturations targets

(b)(4)



Minor Comment: The manuscript has several grammatical and typographical errors  
Page 3

NEJMReview0312Oximeter  
and would benefit from careful editing.

Statistical Reviewer: 1  
Comments for the Author:

(b)(4)



**NE1MReview0312oximeter**

(b)(4)



**Table 1: Demographics and Characteristics of Follow-up (FUP) Cohorts**

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	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)

Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education $\leq$ 12 <sup>th</sup> grade-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%) †	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language -no./total no.(%) ‡	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%)†	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	117/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months, Mean $\pm$ SD)	19.9 $\pm$ 2.4	20.1 $\pm$ 2.7	19.9 $\pm$ 2.4	20.2 $\pm$ 2.7
Follow up-no./total no.(%)	511/545(93.8)	479/513(93.4)	479/514(93.2)	551/544(93.9)

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\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

¶ Among survivors to 36 weeks postmenstrual age

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‡ Only available at 18-22 months corrected age

† Among survivors to discharge or transfer

Comparisons of neonatal outcomes are adjusted for stratification by center and gestational age and for familial clustering

**Table 2: Death or NDI: CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups\***

<u>a. CPAP vs. Surfactant</u>	<u>CPAP</u>	<u>Surfactant</u>	<u>ARR*</u>	<u>p</u>
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

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<b><u>b. Lower vs. Higher Oxygen Saturation</u></b>	<b><u>Lower</u></b>	<b><u>Higher</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA-no./total no.(%)	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined-no./total no.(%)	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI-no./total no.(%)	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70-no./total no.(%)	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2-no./total no.(%)	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy-no./total no.(%)	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral-no./total no.(%)	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment-no./total no.(%)	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

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\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower	Higher	ARR*	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness and other abnormal eye findings were not adjusted for study center due to small N)



**From:** [Ehrenkranz, Richard](#)  
**To:** [Navarrete Cristina](#); [Shahnaz Duara](#); [Poindexter, Brenda B](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** PAS 2013 abstract with SUPPORT growth data  
**Date:** Friday, June 22, 2012 3:46:24 PM  
**Attachments:** [Abstract proposal 22Jun12.docx](#)

---

Hi:

I have attached a rough draft of a PAS 2013 abstract proposal to use a modification of the WINROP algorithm to examine the SUPPORT Growth secondary data. Please review/edit/critique/revise and let me know what you think. The proposals are due by July 2<sup>nd</sup>. I had discussed a this idea with Lois Smith at a symposium in Boston in March 2011 at which we were both speaking. Unfortunately, it had to wait until after the results were presented this year. Lois and Ann will provide the algorithm; I have sent them this same draft. Thanks and sorry for the short notice.

Richard

Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
PO Box 208064  
New Haven, CT 06520-8064  
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The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

## **Interaction of Early Weight Gain and Oxygen Saturation Target on the Development of Retinopathy of Prematurity in Extremely Preterm Infants**

Richard A. Ehrenkranz, MD, Lois E. H. Smith, MD, PhD, Ann Hellström, MD, PhD, Cristina Navarrette, MD, Shahnaz Duara, MD, and Brenda B. Poindexter, MD

### **Abstract/Synopsis:**

Several years ago, Löfqvist and colleagues (1, 2) described and validated the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm that was developed to identify infants < 32 weeks' gestation who were highly likely to develop severe ROP. This group has also demonstrated that a modification of the WINROP algorithm that used postnatal weight gain changes alone could accurately identify infants at risk (3).

We propose to test the accuracy of the modified WINROP algorithm to identify severe ROP in infants who participated in the NICHD NRN SUPPORT Growth secondary study (4, 5).

Objective: To use the modified WINROP algorithm to examine the interaction of early postnatal weight gain and oxygen saturation target on the development of ROP.

Hypothesis: We hypothesize that the modified WINROP algorithm will accurately identify infants at risk of severe ROP regardless of the oxygen saturation range targeted.

Methods: This will be a secondary analysis of infants whom were enrolled in the NICHD NRN SUPPORT Growth secondary study. The modified WINROP algorithm will be used to identify infants at risk of severe ROP and its accuracy will be determined by comparing the list of infants identified with the final ROP outcomes.

### **Statement of the problem:**

Availability of experienced ophthalmologists to perform the recommended ROP screening exams and ablative retinal treatment is limited. Therefore, accurate methods, such as WINROP, of identifying patients at greatest risk of severe ROP and of the need for ablative therapy would be beneficial. Furthermore, since lower oxygen saturation target ranges are being used to reduce the risk of severe ROP, it is important to ensure that the accuracy of these methods are not influenced by the targeted oxygen saturation range.

### **Objective:**

To use the modified WINROP algorithm to examine the interaction of early postnatal weight gain and oxygen saturation target on the development of ROP.

### **Hypothesis:**

We hypothesize that the modified WINROP algorithm will accurately identify infants at risk of severe ROP regardless of the oxygen saturation range targeted.

## **Background/previous studies:**

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that is associated with preterm infants and is a major cause of visual impairment and blindness (6). Routine retinal screening examinations for ROP are recommended for infants with preterm infants with a birth weight (BW) < 1500 g or a gestational age (GA)  $\leq$  32 weeks and selected infants with a BW between 1500-2000 g or a GA > 32 weeks with an unstable course (6). Extremely preterm (EPT) infants, especially those less than 28 weeks' gestation, have the greatest risk of developing severe ROP and the need for ablative treatment according to the recommendations of the Early Treatment for Retinopathy of Prematurity Trial (ETROP) study (7). Several years ago, Löfqvist and colleagues (1, 2) described and validated the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm that was developed to identify infants < 32 weeks' gestation who were highly likely to develop severe ROP. This group has also demonstrated that a modification of the WINROP algorithm that used postnatal weight gain changes alone could accurately identify infants at risk (3). A clinical prediction model to predict risk of severe ROP was described by Binenbaum and co-workers (8) following a secondary analysis of the Premature Infants in Need of Transfusion (PINT) study data; their birth weight-gestational age-weight model was also found to accurately identify infants at high risk of requiring ablative therapy.

The NICHD NRN SUPPORT trial (5) reported that the rates of severe retinopathy or death did not differ significantly between the lower oxygen saturation (85-89%) group and the higher oxygen saturation (91-95%) 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). However, 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), while 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).

The NICHD NRN SUPPORT Growth secondary study (6) was performed to investigate whether infants would have better growth and better growth trajectories at 36 weeks post-menstrual age (PMA) and at 18-22 months corrected age (CA), in the group with the lower oxygen saturation target. The analyses found that oxygen saturation target assignment did not cause a difference in the combined outcome of death or growth failure at 36wks PMA, or at 18-22mos CA.

We propose to test the accuracy of the modified WINROP algorithm to identify severe ROP in SUPPORT Growth secondary study participants.

## **Methods/Analyses:**

This will be a secondary analysis of infants whom were enrolled in the NICHD NRN SUPPORT Growth secondary study (5). Of 1316 infants 24 0/7 to 27 6/7 weeks' gestation enrolled into the SUPPORT main trial (4), 810 participated in the Growth secondary study; 402 in the LOW oxygen saturation (85-89%) group and 408 in the HIGH oxygen saturation (91-95%) group. Of those infants, 333 and 348 respectively, survived to 36 weeks' PMA.

For this study, infants will be separated into the oxygen saturation arm into which they were randomized in the SUPPORT trial [LOW saturation (85-89%) vs HIGH saturation (91-95%)]. The

dataset for the SUPPORT Growth secondary study includes body weight measurements on day of life 1, 7, 14, 21, and 28 and at 32 and 36 weeks' PMA (or discharge, whichever came first). Final ROP outcomes were collected as part of the SUPPORT trial. The modified WINROP algorithm will be used to identify infants at risk of severe ROP and its accuracy will be determined by comparing the list of infants identified with the final ROP outcomes.

The primary outcome will be the percentage of infants identified by the modified WINROP algorithm to have severe ROP who experienced a final outcome of severe ROP in the SUPPORT trial. Although severe ROP was defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab in the SUPPORT trial (4), for this secondary study, severe ROP will be defined as Stage 3 ROP or worse.

### References:

1. Löfqvist C, Andersson E, Sigurdsson, Engström E, Härd A, Niklasson A, Smith LEH, Hellström A. Longitudinal postnatal weight and insulin-like growth factor I measurements in the prediction of retinopathy of prematurity. *Arch Ophthalmol* 2006; 124:1711-1718.
2. Löfqvist C, Hansen-Pupp I, Andersson E, Holm K, Smith LEH, Ley D, Hellström A. Validation of a new retinopathy of prematurity screening method monitoring longitudinal postnatal weight and insulin-like growth factor 1. *Arch Ophthalmol* 2009; 127:622-627.
3. Hellström A, Härd A, Engström E, Niklasson A, Smith L, Löfqvist C. Early weight gain predicts retinopathy in preterm infants: New, simple, efficient approach to screening. *Pediatr* 2009; 123:e638-e645.
4. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network (Ehrenkranz RA). Targets Ranges of Oxygen Saturation in Extremely Preterm Infants. *N Engl J Med* 2010; 362:1959-1969. Epub 2010 May 16.
5. Navarrete CT, Wrage LA, Duara Shahnaz, on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network. Growth outcomes of preterm infants exposed to different oxygen saturation target ranges from birth. *E-PAS2012:2755.5*.
6. AAP Policy Statement. Screening Examination of Premature Infants for Retinopathy of Prematurity. *Pediatrics*. 2006; 117:572-576.
7. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003; 121:1684-94.
8. Binenbaum G, Ying G, Quinn GE, Dreiseitl S, Karp K, Roberts RS, Karpalani H and the Premature Infants in Need of Transfusion Study Group. A clinical prediction model to stratify retinopathy of prematurity risk using postnatal weight gain. *Pediatr* 2011; 127:e607-e614.

**From:** [Luc Brion](#)  
**To:** [Wally Carlo, M.D.](#); [Finer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Cc:** [JACLYN LEVAN](#)  
**Subject:** RE: Question about the SUPPORT trial protocol  
**Date:** Friday, June 22, 2012 8:37:16 AM

---

Thanks a lot!

Luc

Luc P. Brion, MD  
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**From:** [Wally Carlo, M.D.](mailto:WCarlo@peds.uab.edu) [mailto:WCarlo@peds.uab.edu]  
**Sent:** Friday, June 22, 2012 6:54 AM  
**To:** [Luc Brion](#); [Finer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Cc:** [JACLYN LEVAN](#)  
**Subject:** RE: Question about the SUPPORT trial protocol

Luc.

The level if evidence is physiological and really expert opinion and practice. We wanted a low mean and a physiological reason for less than 2x is to get below the chocking point but this has not been tested with babies.

Wally

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

**From:** [Luc Brion](mailto:Luc.Brion@UTSouthwestern.edu) <[Luc.Brion@UTSouthwestern.edu](mailto:Luc.Brion@UTSouthwestern.edu)>  
**To:** "Finer, Neil" <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
**Cc:** "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>, [JACLYN LEVAN](#) <[JACLYN.LEVAN@phhs.org](mailto:JACLYN.LEVAN@phhs.org)>  
**Sent:** Fri, Jun 22, 2012 11:39:28 GMT+00:00  
**Subject:** RE: Question about the SUPPORT trial protocol

Neil:

Thanks a lot for your response  
Best regards,  
Luc

Luc P. Brion, MD  
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-----Original Message-----

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]  
Sent: Friday, June 22, 2012 3:52 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Luc Brion; Wally Carlo, M.D.; JACLYN LEVAN  
Subject: Re: Question about the SUPPORT trial protocol

I believe that this was the criteria some NRN units were using for infants on HFOV at the time Neil

On Jun 20, 2012, at 10:26 PM, "Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>> wrote:

Luc

I am not sure so have included Wally and Neil on the email.

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and  
Perinatology Branch CDBPM, NIH  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
Sent: Wednesday, June 20, 2012 3:53 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]

Cc: JACLYN LEVAN  
Subject: Question about the SUPPORT trial protocol

Rosc:

I have a question about the protocol of the SUPPORT trial.  
Could you please let me know the rationale for using an amplitude  $< 2x$  MAP as criterion for extubation in the following statement?

"An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but MUST have Extubation attempted within 24 hours of fulfilling ALL of the following criteria documented on a single blood gas.

A mean airway pressure (MAP)  $< 8$  cm H<sub>2</sub>O, ventilator rate  $< 20$  bpm, an amplitude  $< 2X$  MAP if on high frequency ventilation (HFO)"

Thanks a lot  
Luc

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---

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**From:** [Wally Carlo, M.D.](mailto:Wally_Carlo_M.D.)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins_Rosemary_NIH_NICHD); "Shankaran, Seetha"  
**Subject:** RE: Another Cytokine proposal for 2012??  
**Date:** Thursday, June 21, 2012 9:43:01 PM

---

Hi Seetha and Rose.

Yes. CP was one of the major outcomes in the primary paper.

Wally

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

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
**To:** "&apos;Shankaran, Seetha&apos;"; <[sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu)>, "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>  
**Sent:** Thu, Jun 21, 2012 19:12:11 GMT+00:00  
**Subject:** RE: Another Cytokine proposal for 2012??

Seetha

I think the primary paper addressed CP (Carlo et al 2011 Journal of Pediatrics)\_

Wally - is this correct?

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

**From:** Shankaran, Seetha [<mailto:sshankar@med.wayne.edu>]  
**Sent:** Thursday, June 21, 2012 2:55 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally  
**Cc:** Shankaran, Seetha  
**Subject:** Another Cytokine proposal for 2012??

Rose and Wally

One of my colleagues wants to look at "Clinical utility of evaluation of anti-inflammatory cytokines and growth factors in Extremely low birth weight newborns at risk of cerebral palsy" and before he proceeded further I wanted to make sure this was not done before. Looking at my list/cytokine folder I see the following:

1) DEVELOPMENT OF A PREDICTIVE MODEL OF NEUROLOGIC HANDICAP USING A



**COMBINED CLINICAL AND LABORATORY APPROACH: AN ANCILLARY STUDY TO THE NICHD CYTOKINE PROTOCOL** Namasivayam Ambalavanan MD and Waldemar Carlo MD

2) Association of inflammatory cytokine gene polymorphisms with brain injury, neurologic recovery and neurodevelopmental outcome in extremely low birth weight (ELBW) infants A secondary study for the Cytokine Study, Ricki F. Goldstein M.D., Duke University Medical Center, Daniel Laskowitz, MD, Division of Neurology, Ellen Bennett, MD, Department of Pathology

3) The association of cytokines with adverse neurocognitive outcome and neurodevelopmental impairment at 18-22 months in the NICHD Cytokine Study: Susan Hintz, Ambal and Wally Carlo

I believe all 3 are approved secondary studies. Should my colleague not proceed further?

Let me know

Thanks

Seetha

Seetha Shankaran, MD  
Professor of Pediatrics  
Wayne State University School of Medicine  
Director, Division of Neonatal/Perinatal Medicine  
Children's Hospital of Michigan and  
Hutzel Women's Hospital  
313-745-1436 (o)  
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sshankar@med.wayne.edu

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Wednesday, July 11, 2007 3:36 PM

To: Wally Carlo, M.D.; Shankaran, Seetha; Ronald N Goldberg; Ehrenkranz Richard (E-mail); Tyson, Jon E; Barbara Stoll; Das, Abhik; Poole Kenneth (E-mail); McDonald, Scott A.

Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg

Subject: HintzCytoMDIProposal

To the cytokines subcommittee  
- here is another proposal

Thanks

Rose

<<HintzCytoMDIProposal.doc>>

**From:** Luc Brion  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo, M.D."; "Finer, Neil"  
**Cc:** JACLYN LEVAN  
**Subject:** RE: Question about the SUPPORT trial protocol  
**Date:** Wednesday, June 20, 2012 5:28:30 PM

---

Thanks

Luc

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, June 20, 2012 3:25 PM  
**To:** Luc Brion; 'Wally Carlo, M.D.'; 'Finer, Neil'  
**Cc:** JACLYN LEVAN  
**Subject:** RE: Question about the SUPPORT trial protocol

Luc

I am not sure so have included Wally and Neil on the email.

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](mailto:higginsr@mail.nih.gov)

---

**From:** Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]

**Sent:** Wednesday, June 20, 2012 3:53 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** JACLYN LEVAN  
**Subject:** Question about the SUPPORT trial protocol

Rose:

I have a question about the protocol of the SUPPORT trial.  
Could you please let me know the rationale for using an amplitude < 2x MAP as criterion for extubation in the following statement?

"An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have Extubation attempted within 24 hours of fulfilling **ALL** of the following criteria documented on a single blood gas. A mean airway pressure (MAP) < 8 cm H<sub>2</sub>O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)"

Thanks a lot  
Luc

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**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Preemie hypothermia  
**Date:** Wednesday, June 20, 2012 2:58:04 PM

---

yes

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, June 20, 2012 2:55 PM  
**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 (KIRPALANI@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarfo@uab.edu)  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'ROGER.FAIX@HSC.UTAH.EDU'  
**Subject:** Preemie hypothermia

RTI has an internal initiative to further develop biostatistical skills in emerging areas of clinical trials biostatistics. As part of that, there is a possibility of using the preemie hypothermia trial as a model Bayesian trial that this initiative can use to enhance RTI's skills in designing trials from a Bayesian perspective. This will all be done by RTI statisticians and perhaps one external consultant who will sign any necessary confidentiality agreements with RTI. Abhik thinks this is a great opportunity to get some 'free' statistical support for this trial, which will require a lot of preparatory work because Bayesian trials do need a lot more groundwork than traditionally designed trials.

**Please send me a yes/no vote by *July 2* to allow RTI to pursue this endeavor.**

**This protocol will be on the list for the next budget vote.**

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**From:** Luc Brion  
**To:** Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Dennis Wallace (dwallace@rti.org); Wally Carlo (wacarlo@uab.edu) (wacarlo@uab.edu); 'ambal@uab.edu'; Kristi Watterberg (KWatterberg@salud.unm.edu)  
**Subject:** RE: "Final" Sodium Diuretic Proposal  
**Date:** Sunday, June 17, 2012 4:13:25 PM  
**Attachments:** Sodium Diuretic Factorial (Final for External Review) LPB comments 061712.docx

---

Kathleen:

This is great!

Congratulations on your patience to move this forward.

I have only a few suggestions in the text.

Best regards,

Luc

Luc P. Brion, MD  
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Director, Fellowship Training Program in Neonatal-Perinatal Medicine The  
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**Subject:** "Final" Sodium Diuretic Proposal

I've attached a "final" version of the Sodium Diuretic Proposal. I think it's ready to be forwarded it to the FDA, advisory board, and external reviewers.

Thanks to everyone who has helped bring this together.

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**Sodium and Diuretic (SAND) Trial -**  
**A Randomized Factorial Design Trial of Sodium Supplementation and Diuretics**  
**in Extremely Preterm Infants**

Kathleen Kennedy MD MPH, Kristi Watterberg MD, Waldemar Carlo MD, Namasivayam  
Ambalavanan MD, Brenda Poindexter MD, Luc Brion, MD, Dennis Wallace, PhD

**INTRODUCTION**

Diuretic therapy is commonly used in neonatal practice; although short-term pulmonary benefits have been demonstrated, longer term effects on bronchopulmonary dysplasia and potential adverse effects are unknown. Sodium supplementation might be essential for optimal neurodevelopment. There is compelling rationale for determining the effects of diuretic therapy and sodium supplementation in a large multicenter randomized trial. They are being proposed as a factorial design for the following reasons:

- 1) If done sequentially, regardless of which study is one first, the findings of the first study will be hard to interpret and generalize, and could be misleading, without careful control or time-consuming monitoring of the other practice. The factorial design will yield generalizable results in the shortest period of time.
- 2) The findings of the first study might become irrelevant (no longer generalizable) if the second study finds an advantage for the practice that was less prevalent in clinical practice during the first study.
- 3) Some of the study monitoring measurements are labor-intensive, but using them for both studies will optimize efficiency since both studies need more or less the same information.
- 4) Even if we don't have high power to look for an interaction, we may well be able to identify an interaction if it is large enough. We would have no ability to identify interaction without using a factorial design.

Because we have limited existing data from randomized trials about the magnitude of benefit for either study arm, and we have no existing information about the presence or magnitude of an interaction, this study is designed with a fixed sample size. If the data are not concerning for a clinically important interaction between the two interventions, the findings will be reported as main effects and the study will have high power to identify even relatively small effect sizes. If there is a confirmed or suggested clinically important interaction that renders a main effects conclusion inappropriate for either arm, the findings in that arm will be reported as subgroup (by strata for the other arm) findings. In this case, it is possible that we will not have adequate power within the subgroups to identify small but clinically important differences and the study findings will be reported as inconclusive. This approach is an application of the recommendation in a recent commentary that concluded "every RCT (should) follow testing the primary and secondary hypotheses with exploratory moderator analyses and ... report, as hypotheses to be tested in future studies, (factors) that modify treatment effects."<sup>1</sup>

**HYPOTHESES**

**Sodium Supplementation**

Provision of 4-5 mEq/kg sodium intake daily, as compared to 2-3 mEq/kg/day, to preterm infants <29 weeks gestation or < 1000g birth weight from the 14<sup>th</sup> postnatal day until 34 weeks postmenstrual age (or discharge, if discharged earlier) will result in improved cognitive development at 18-22 months corrected age (primary outcome). Secondary outcomes include somatic growth (weight, length, mid-arm and head circumference) at 36 weeks postmenstrual age, death or neurodevelopmental impairment (NDI – 2011 Network Follow-up definition),



somatic growth at 18-22 months adjusted age, and the safety of this intervention [by monitoring adverse events including hypernatremia, hypertension, non-protocol diuretic use, and adverse outcomes of prematurity including patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), late onset sepsis, bronchopulmonary dysplasia (BPD), and death].

#### Diuretics

Among infants < 29 weeks gestation or < 1000g at birth, liberal use of diuretic (as needed based on support) to infants who are on supplemental oxygen or mechanical ventilation for at least 48 hrs in the interval from 14 days after birth to 31 6/7 weeks postmenstrual age will reduce the incidence of death or BPD at 36 weeks postmenstrual age (using the physiologic definition) among all enrolled infants by a relative risk reduction of least 20% (primary outcome). It is also hypothesized (secondary outcomes) that liberal use of diuretic will reduce death or NDI (2011 Network Follow-up definition). Other secondary outcomes include the use of postnatal systemic steroids, inhaled steroids, bronchodilators, and nitric oxide, incidence of death or severe BPD<sup>2</sup> at 36 weeks postmenstrual age, weight, length, mid-arm and head circumference at 36 weeks postmenstrual age and 18-22 months adjusted age, and the safety of this intervention by monitoring adverse events including hyponatremia, hypochloremia, non-protocol NaCl supplementation, KCl supplementation, arginine Cl supplementation, hypercalcemia, hypocalcemia, renal calcifications, fractures (clinically diagnosed), and adverse outcomes of prematurity including PDA, IVH, PVL, NEC, ROP, and death before discharge, hearing screen at 3 months of age or discharge, and hearing loss at 18-22 months adjusted age.

### **BACKGROUND AND RATIONALE**

#### Sodium Supplementation

Despite advances in nutritional support for preterm infants, postnatal growth restriction remains quite common.<sup>3</sup> A Network cohort study of growth velocity and outcomes found that the majority of extremely low birth weight infants had weight for gestational age below the 10<sup>th</sup> percentile of expected intrauterine growth at hospital discharge.<sup>4</sup> Growth deficits persisted at 18-22 months, with over half of the infants' weights remaining below the 10<sup>th</sup> percentile; in addition, 37% and 22% of these infants had length and head circumference, respectively, below the 10<sup>th</sup> percentile.<sup>5</sup> These deficits were associated with neurodevelopmental impairments, with a significant relationship between in-hospital growth velocity and the likelihood of cerebral palsy, a Mental or Psychomotor Developmental Index (MDI, PDI) <70 on the BSID-II, and neurodevelopmental impairment.<sup>25</sup>

Targeted nutritional interventions have led to increases in protein, fat and carbohydrate intake provided to extremely preterm infants,<sup>6</sup> however, dietary intake of one key element necessary for growth – sodium – may be inadequate. Sodium is essential for adequate growth and development in both animal models<sup>7,8,9,10</sup> and in humans.<sup>11,12</sup> Juvenile rats fed diets with insufficient sodium show decreased weight and length gain, as well as reduced protein synthesis and accretion of lean body mass,<sup>27,28</sup> while maintaining relatively normal serum sodium. In one experiment, for example, sodium-restricted rat pups gained < ½ the weight and only 70% of the length of the control group, with only a mild decrease in serum sodium (134 mEq/L vs 139 mEq/L).<sup>7</sup> Thus, serum sodium concentration is a poor measure of total body sodium depletion. Repletion of sodium resulted in improved weight and length, but incomplete catch-up growth.<sup>27,28</sup> Lung growth following pneumonectomy is also specifically impaired in sodium-deficient juvenile rats.<sup>10,16</sup>

Diuretic therapy may be detrimental to growth due to sodium wasting. Figures 1 and 2, below, show the effect of furosemide on growth in weanling rats fed a normal diet.<sup>13</sup> Increasing

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doses of furosemide were associated with progressive restriction of body weight growth (Figure 1). This was not due to changes in body water composition. Extracellular water decreased, but only accounted for 4% of the difference in body weights (inulin method). Subsequently, these investigators supplied potassium and/or sodium to replace the amount documented to be lost in balance studies of the previous experiment. Repletion of potassium did not improve weight gain; however, restoration of the amount of sodium lost with the diuretic therapy resulted in normalization of weight gain (Figure 2). While these observations in rats may not be directly applicable to human nutrition, they support the biologic plausibility of sodium as a limiting factor for growth. Chronic salt depletion has also been associated with diminished linear growth in humans.<sup>14</sup>

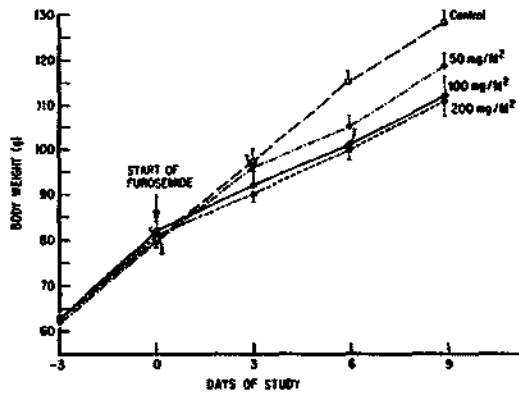


Figure 1

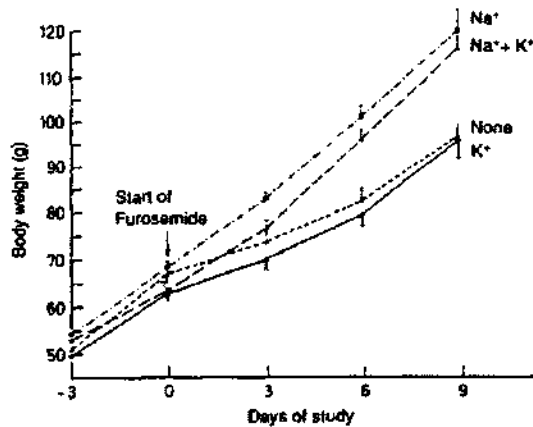


Figure 2

Four small randomized controlled trials (RCTs) of sodium supplementation in preterm infants have been reported. Two of those RCTs evaluated supplementation with NaHCO<sub>3</sub> or NaCl vs. placebo for late metabolic acidosis and found that both treatments resulted in improved weight

gain.<sup>15</sup> A third RCT (Figure 3, below) evaluated the effects of supplementing dietary sodium to a total of 4-5 mEq/kg/day from postnatal day 4-14 in 46 infants 27-34 weeks gestation. The investigators found that the sodium-supplemented infants had significantly improved weight gain which was sustained after the treatment period, indicating that the weight gain did not represent fluid retention from the additional sodium; a fourth study confirmed this finding.<sup>16,17</sup> Infants were monitored for adverse effects including edema, circulatory overload, hyponatremia, and IVH; none were seen. In a follow-up of the first study, investigators evaluated neurodevelopment in 37 of the 46 children at 10-13 years of age, and found that the treated infants performed significantly better in motor function, performance IQ, general memory and behavior.<sup>18</sup> Observational studies in preterm infants have shown associations between hyponatremia and hearing deficits in very-low-birth-weight infants<sup>19</sup> and cerebral palsy in infants <32 weeks gestation.<sup>20</sup>

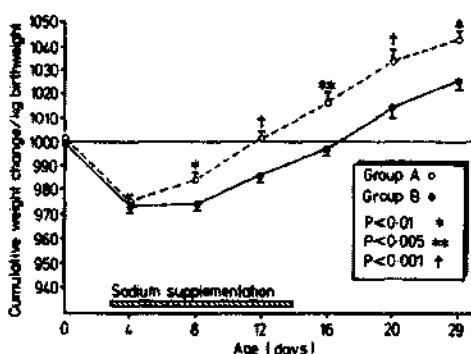


Figure 3

Sodium requirements for preterm infants change greatly during the first and second postnatal weeks. Infants are born with excess total body water and sodium that are normally lost during the first postnatal week.<sup>21</sup> RCTs have shown that giving additional sodium during the first week is associated with failure of appropriate diuresis and increased risk for adverse outcomes, including BPD.<sup>22,23</sup> However, after the first postnatal week, calculation of adequate dietary sodium must incorporate (1) sodium need for growth; (2) sodium loss through the kidney; and (3) incomplete gastrointestinal absorption.

The amount of sodium needed for growth has been calculated from the reference fetus of Ziegler et al.<sup>24</sup> At 24-28 weeks, estimated weight gain is about 17 g/kg/day. The fetus contains 9.5 mEq Na/100g body weight, resulting in an approximate need for retained sodium of 1.6 mEq/kg/day Na for growth. One sodium balance study showed that low birth weight infants fed supplemented human milk retained less sodium than this (1.2-1.5 mEq/kg/day),<sup>25</sup> and another showed that despite lower GFR, the most immature infants had the highest sodium losses, attributed to limited tubular sodium reabsorption capacity.<sup>26</sup> Urinary sodium losses have been studied by several investigators. In one group of 34 stable formula-fed infants <32 weeks gestation, urinary losses were reported to average 2.8 mEq/kg/day at 7-10 days, 1.5 mEq/kg/day at 14-17 days, and 1.6 mEq/kg/day at 21-26 days.<sup>27</sup> Although the urinary losses at 7-10 days may still represent loss of excess body water and salt following birth, significant sodium losses were documented throughout the study. Urinary losses may be even higher in more immature infants. Sodium malabsorption has also been reported in preterm infants; it is inversely related to postmenstrual age and adds a small amount to the daily sodium need.<sup>28</sup> The

minimum daily need calculated from the accretion and retention studies would be more than 3 mEq/kg/day, even with 100% efficiency of use and without complicating factors such as diuretic or caffeine use.<sup>29</sup> Combining the studies of urinary and fecal losses with the estimated intrauterine sodium accretion rate, Al-Dahhan et al recommended that infants born before 30 weeks gestation receive 5 mEq/kg/day of sodium.<sup>25,26</sup>

In the absence of clinical trials comparing the long-term effects of different sodium intakes, the currently recommended sodium intake for growing preterm infants, based on the above observational data, is 3-5 mEq/kg/day.<sup>30</sup> Most parenteral nutrition solutions for preterm infants provide about 3 mEq/kg/day. Preterm formulas (24 cal/oz) contain 1.4 -1.5 mEq Na/100ml.<sup>30,30a</sup> Early human milk contains 1.3-1.7 mEq Na/100ml, but after the first week it drops to 0.5-1.1 mEq/100ml.<sup>31</sup> Powdered fortifiers add 0.7mEq Na/100ml of milk.<sup>30,30a</sup> Thus, with 150 ml/kg/day enteral feedings, a preterm infant will receive an estimated 1.8 to 2.7 mEq Na/kg/day. Even though total body sodium depletion occurs without hyponatremia,<sup>7, 8, 11, 41</sup> enteral sodium chloride supplementation for preterm infants is uncommon in the absence of hyponatremia (survey of Network sites, included as Appendix 1). Given these current nutritional practices, extremely low gestational age infants are likely to experience sodium deficiency after the first postnatal weeks, which may adversely affect short-term growth and long-term neurodevelopment. This RCT will study the effect of increased sodium intake that is still within the AAP recommended range (4-5 mEq/kg/day) as compared to typical sodium intake (2-3 mEq/kg/day) on growth and cognitive outcomes.

While there is limited data on sodium supplementation in preterm infants, there is even less known about the relative benefits of sodium as NaCl vs other anions. One small RCT showed no difference between NaCl and NaHCO<sub>3</sub>.<sup>43,45</sup> One observational study suggested that Cl deficiency also may be associated with poor growth and neurodevelopment,<sup>32</sup> a finding supported by data from juvenile rats.<sup>33</sup> Therefore, sodium will be given as NaCl, to additionally increase intake of chloride, which may also promote optimal growth.<sup>34</sup>

#### Diuretics

Bronchopulmonary dysplasia (BPD) is a common cause of morbidity and a contributor to late mortality in preterm infants. BPD affects 25% of infants 501-1249g birth weight as defined by the new physiologic definition developed in the NICHD NRN.<sup>35</sup> In the NICHD Network from 2003-2007, for infants born at < 29 weeks who survived to 36 wks postmenstrual age, the prevalence of moderate or severe BPD (oxygen use at 36 wks) was 42%; the prevalence of severe BPD (>30% oxygen or positive pressure at 36 wks) was 18%.<sup>36</sup> BPD is associated with worse cognitive outcomes at school age,<sup>37</sup> and with abnormal pulmonary function in adolescent survivors,<sup>38</sup> and can result in pulmonary dysfunction that persists into adulthood.<sup>39</sup>

The pathogenesis of BPD is multifactorial.<sup>40</sup> Interstitial edema is often seen in acute lung injury that precedes BPD; pulmonary edema may also result from a patent ductus arteriosus or fluid overload.<sup>41,42</sup> Adams et al<sup>43</sup> observed that infants with BPD had higher lung water content and more gravity-dependent atelectasis and alveolar flooding. Interstitial edema reduces lung compliance and increases airway resistance by causing narrowing of terminal airways. The rationale for the use of diuretics is that they reduce interstitial lung fluid by increasing lung fluid reabsorption by a diuresis-independent mechanism (loop diuretics)<sup>44</sup> as well as by increasing urine output.<sup>45</sup> The reduction in interstitial lung fluid may improve lung compliance and reduce resistance, thereby reducing ventilator and oxygen requirements, which in turn may reduce volutrauma or barotrauma and oxygen toxicity that contribute to the development of BPD.

Diuretics are commonly used for the prevention and/or treatment of BPD despite limited data on their safety or their effectiveness for the prevention of mortality, BPD, or other long-term outcomes. In the STOP-ROP trial, diuretics were used in 54% of the enrolled infants.<sup>46</sup> A recently published survey of 151 US neonatologists (39% response rate) reported that clinicians

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Comment [lpb1]: Diuresis-independent mechanism has been reported for loop diuretics only.

presented with various clinical scenarios would use prn or regularly scheduled diuretics in 31% of the scenario responses. This treatment choice increased when scenarios involved increased respiratory support (supplemental oxygen, CPAP, or ventilator) and with increasing postnatal age (from 7 to 28 days).<sup>47</sup> An accompanying editorial emphasized the discrepancy between clinicians' optimism regarding therapeutic benefit and the paucity of evidence for benefit from randomized clinical trials.<sup>48</sup> The NRN database does not have information on use of diuretics during hospitalization. However, during the GDB year 2010 (most recent available), 11% of infants < 29 weeks were discharged home on diuretics.

Systematic reviews of loop and distal diuretics for preterm infants with developing or established BPD<sup>45,49,50</sup> indicate that chronic administration (1-4 weeks) of diuretics improves lung mechanics. The Cochrane systematic review of diuretics acting on the distal tubule<sup>45,48</sup> considered a total of 17 studies. Six studies fulfilled entry criteria. Distal tubule diuretics improved lung mechanics in preterm infants >3 weeks of age. Data from two small studies<sup>51,52</sup> with a combined sample size of 77 and significant heterogeneity indicated that chronic administration of thiazide-spironolactone reduced mortality (RR 0.30, CI 0.09 to 0.93; RD -0.17, CI -0.031 to -0.02) and tended to shorten the intubation period. If proven to reduce mortality by the reported risk reduction, this would be the most effective therapy for infants with or at risk for BPD. The Cochrane systematic review of loop diuretics found that the only diuretic meeting selection criteria was furosemide; administration of furosemide improved both oxygenation and lung compliance, but there are no studies of furosemide reporting important clinical outcomes.<sup>45,49</sup> Although the chronic administration of diuretics in infants remains prevalent, there have been no randomized controlled trials of diuretics for BPD in the post-surfactant era or since the increase in antenatal steroid administration in the 1990s.

The proposed trial will address whether chronic administration of diuretics (chlorothiazide if on feedings, furosemide if NPO) in high-risk preterm infants reduces death or BPD at 36 weeks postmenstrual age and leads to improvements in other outcomes including NDI or death at 18-22 months corrected age. Spironolactone will not be used because it has potential adverse effects and has not been shown to provide incremental benefit.<sup>53</sup>

In summary, there is strong evidence that diuretics improve pulmonary mechanics and some suggestion of benefit on mortality and BPD at 36 weeks postmenstrual age. If proven to be as effective as in the two previous trials, this treatment could have a larger impact than other therapies for prevention of BPD (e.g., vitamin A had a relative risk reduction of BPD or death of 11%).

#### **Additional Rationale for Factorial Design:**

As with previous factorial designs undertaken by the Network (SAVE and SUPPORT trials), this study has multiple compelling reasons to justify a design that would allow us to consider interaction between the two study arms. In this proposal, study "arm" refers to either the sodium supplementation or diuretic comparison. Within each arm, "group" refers to the treatment assignment (drug vs placebo). Hyponatremia is common in diuretic-treated preterm infants. If sodium deficiency is harmful for preterm infants, it is likely that those treated with diuretics will be more deficient, and more likely to benefit from supplementation, than those not treated with diuretics. If fluid retention is part of the pathogenesis of BPD, it is plausible that sodium supplementation could exacerbate BPD. This effect might or might not be ameliorated with diuretic treatment. If diuretics are beneficial for BPD, it is plausible that the beneficial effect would be mitigated by sodium supplementation. If diuretics have a deleterious effect on neurodevelopment, this effect might be ameliorated with sodium supplementation. None of these potential relationships can be evaluated in trials evaluating single interventions. Even if the study is not adequately powered to definitively investigate these interactions, this factorial design will provide the best feasible information about the magnitude and direction of these

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potential interactions, and it will be much more informative than conducting one or both trials independently.

## **METHODS**

**Study Design:** randomized, masked, placebo-controlled 2x2 factorial design clinical trial

### **Population:**

#### **Inclusion criteria:**

Inborn and outborn infants <29 weeks gestation OR <1000 grams birth weight. Infants must be enrolled into the trial early enough that the sodium supplementation intervention can be started in the window of 12-16 days postnatal age. The diuretic intervention will only be started for infants requiring supplemental oxygen (>21% by hood or cannula (any type, any flow) or CPAP) or mechanical ventilation with any FiO<sub>2</sub> for at least 48 continuous hours between 12-16 days after birth and 31 6/7 weeks postmenstrual age. (Infants on CPAP with 21% oxygen will not be eligible for diuretic study drug administration.)

**Exclusion criteria:** major life-threatening congenital anomaly, a permanent neuromuscular condition that affects respiration, terminal illness (heart rate < 100 per minute, unresponsiveness to resuscitation), decision to withhold or limit support, hypernatremia >145 mEq/L at the time of enrollment, oliguria (< 1 ml/kg/hr over 24 hrs prior to enrollment) or renal dysfunction (elevated creatinine above 1.5 at the time of enrollment). If hypernatremia, oliguria, or elevated creatinine resolves such that the infant can be enrolled and begin study sodium by 16 days of age, the infant would be eligible for inclusion.

### **Randomization:**

After parental consent is obtained, infants will be randomized 1:1 to the two sodium supplementation groups, and within each of these groups, randomized 1:1 into the two diuretic groups, using a stratified, permuted block design with a centralized telephone procedure. Randomization will be stratified by study center and by gestational age (<26 weeks; ≥26 weeks). Treatment allocation will be revealed to the pharmacy staff only. Multiple gestations (if more than one is eligible) will be randomized independently. Although consent may be obtained in advance, infants should not be randomized until just prior to the plan to begin study drug (sodium). "Enrollment" will be used synonymously with randomization and beginning study drug (sodium) in the remainder of the protocol.

### **Interventions:**

All study drugs will be prepared by the investigational pharmacy at each study center after randomization assignment by the Data Coordinating Center.

### **Sodium Supplementation:**

Beginning on postnatal day 14 (window from 12-16 days) and continuing until 34 weeks postmenstrual age, either placebo or 2 mEq/kg/day of NaCl will be provided as follows:

- a. **Intravenous administration:** while the infant is receiving <100 ml/kg of enteral feedings, 4 ml/kg of a 3% NaCl solution (0.5 mEq/ml) or the same volume of placebo [ $\frac{1}{4}$  normal saline; 4 ml/kg=0.14 mEq/kg Na] will be given IV once/day as a 24 hr infusion.
- b. **Enteral administration:** when the infant is receiving ≥100 ml/kg enteral feedings, study drug will be added to the feedings, as 0.25 ml/kg/dose of a 4 mEq/ml solution of NaCl (preparation used at UNM) or the same volume of

placebo [ $\frac{1}{4}$  normal saline; 0.25 ml/kg=0.01 mEq/kg Na] every 12 hours.

Sodium supplementation or placebo dose will be weight-adjusted weekly; administration will be continued until the infant reaches 34 weeks postmenstrual age. If a serum sodium of  $>145$  is identified on either routine clinical or study-mandated laboratory testing, sodium study drug will be held. Repeat testing will be done in one week or sooner if clinically indicated. Study drug will be resumed when the serum sodium is  $\leq 140$ .

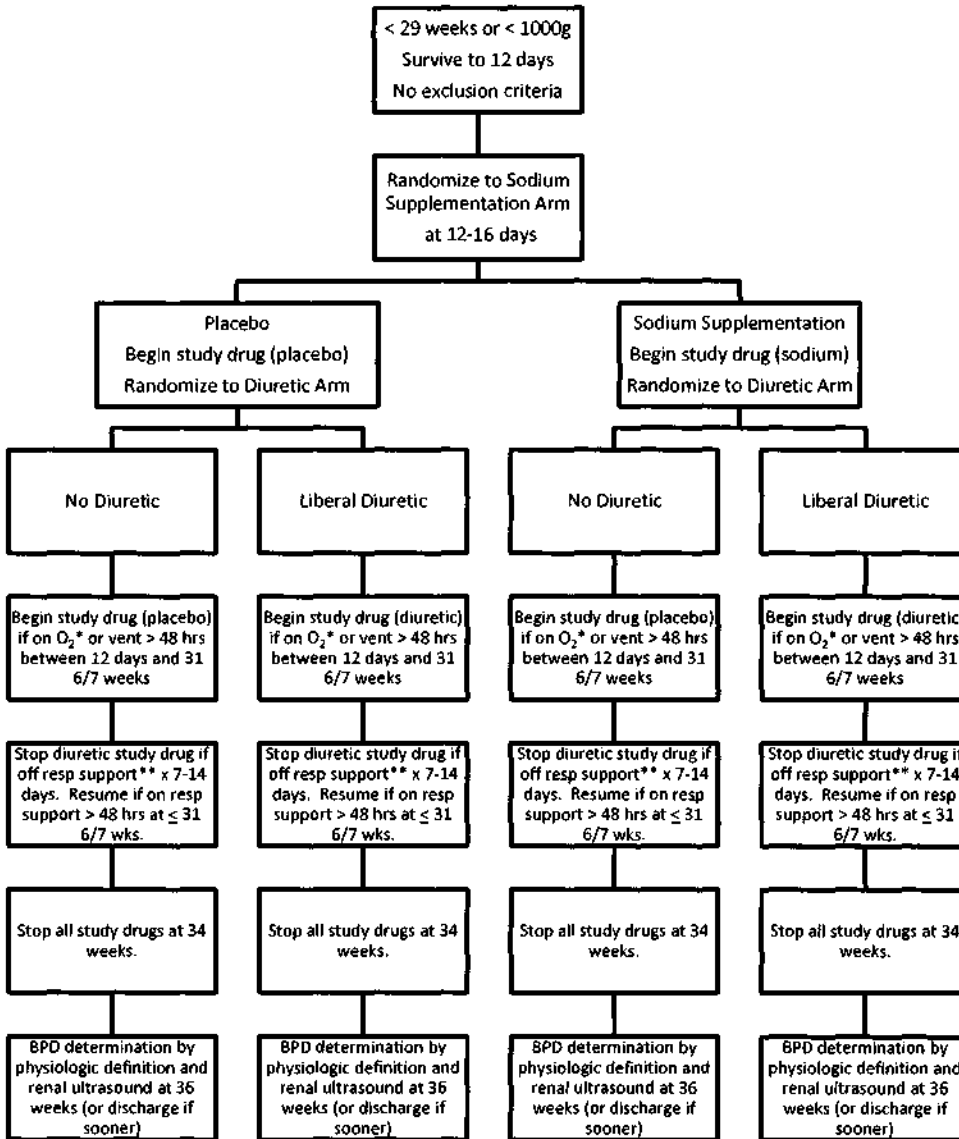
**Diuretics:**

In the diuretic arm, study drug will be initiated for infants requiring supplemental oxygen ( $>21\%$ ) or mechanical ventilation for at least 48 consecutive hours between 12-16 days after birth (when the infant is enrolled into the trial) and 31 6/7 weeks postmenstrual age.

- a. **Intravenous administration:** Infants randomized to the "liberal diuretic" group will be treated with furosemide 1 mg/kg twice a day IV if not on feedings. The IV placebo (0.1 ml/kg  $\frac{1}{4}$  normal saline) will provide 0.004 mEq/kg of sodium.
- b. **Enteral administration:** Infants randomized to the "liberal diuretic" group will be treated with chlorothiazide 10 mg/kg twice a day PO if being fed enterally. The chlorothiazide is available as a pale yellow suspension (250 mg/5 ml) with labeling for pediatric use from Salix Pharmaceuticals. A similar-appearing placebo has been formulated and will be provided for all study sites by Hope Compounding Pharmacy, Katy, TX. The ingredients (National Drug Code numbers) in the placebo are as follows:

Sucrose Octaacetate NF	(51927-2246-00)
Benzoic Acid USP	(51927-1114-00)
Flavor Creme Dementhe	(51927-2327-00)
Flavor Marshmallow	(51927-2699-00)
Glycerin	(51927-2865-00)
Saccharin	(51927-1466-00)
Xanthan Gum	(51927-1637-00)
Calcium Carbonate prec Heavy	(51927-1044-00)
Food Color, Yellow (liquid)	(51927-1424-00)
Base, PCCA Syrup Vehicle	(51927-3521-00)

The diuretic study drug will be continued at the same dose (weight-adjusted weekly) until a postmenstrual age of 34 weeks or until off all respiratory support (not on supplemental oxygen  $>21\%$  or mechanical ventilation) for 7-14 consecutive days (whichever is earlier). The infant may have study diuretic drug discontinued after 7 consecutive days and must have study diuretic drug discontinued by 14 consecutive days. (For this study, CPAP will not be considered as "respiratory support".) If the infant is off study drug and meets criteria again (at least 48 consecutive hrs of  $>21\%$   $FiO_2$  or mechanical ventilation) before 31 6/7 weeks postmenstrual age, study drug will be resumed. Diuretic study drug administration will be withheld if the infant develops hypotension or hypovolemia requiring fluid resuscitation or inotropes. If the infant develops a creatinine  $>1.5$  (routine clinical labs or study-mandate labs) after study enrollment and meets the criteria for diuretic study drug administration, furosemide/placebo (1 mg/kg/dose IV q 12 hr if NPO or 2 mg/kg/dose PO q 12 hr if on feedings) will be used instead of chlorothiazide/placebo until the creatinine decreased to  $<1.5$ . Diuretic treatment based on clinician preference can be used after 36 weeks (only after the physiologic challenge for the BPD outcome has been determined).



\* "on O<sub>2</sub>" includes nasal cannula only if FiO<sub>2</sub> is > 21%

\*\* "resp support" for this study includes supplemental oxygen >21% or mechanical ventilation (does not include CPAP with 21% O<sub>2</sub>)



**Co-interventions:**

As is recommended for management trials, clinical care including fluid and nutritional management and ventilator/oxygen therapy will be at the discretion of the attending clinician but will be monitored for the study. Randomization within centers and masking of both study arms should minimize bias in co-interventions between the drug and placebo groups. The use of caffeine will be recommended for "prevention or treatment of apnea" as reported in the only large randomized trial of methylxanthines.<sup>54</sup>

**Non-protocol Use of Sodium Supplements and Diuretics:**

The use of non-protocol sodium supplements and diuretics will be restricted and monitored by the study. Additional sodium may be ordered by clinicians, but educational efforts will be directed at encouraging replacement of Cl with KCl or arginine Cl (or increasing Cl vs acetate in TPN) and discouraging Na supplements (above the site's standard TPN concentrations or the amount in fortified human milk or preterm formula) if the serum Na is  $\geq 130$ . Returning to standard TPN sodium or discontinuing supplements to feedings will be encouraged when the serum Na is  $> 135$ . Courses of Na supplements to feedings (not TPN or IV fluid) will be recorded as start and stop dates.

Contamination in the diuretic arm will be minimized by limiting non-protocol diuretic use before 36 weeks and by prospectively monitoring center performance for compliance. All non-study diuretic use is strongly discouraged. Thiazides are not allowed and will be tracked as a protocol violation. The use of furosemide (all doses) will be recorded. If one or more doses are given within 48 hrs of a 10% absolute increase in FiO<sub>2</sub> (averaged over at least 6 hrs) with a 5% relative increase in weight over an interval of  $< 48$  hrs, they will be recorded but not counted as a protocol violation. If these conditions are not met, the doses(s) will be considered protocol violations. Each center will be required to establish site-specific mechanisms to maintain equipoise and minimize non-protocol diuretic use (eg requiring attending or local PI approval for non-study diuretics). All doses of "non-protocol diuretic use" will be recorded. Non-protocol treatments will not result in exit from the study for individual patients; differences in these treatments between randomized masked treatment groups will be interpreted as effects of study drug treatment. Site-specific and overall compliance with the protocol will be sequentially monitored by the study subcommittee and DSMC with corrective measures to be taken as deemed necessary.

**Primary Outcomes:**

**Sodium Supplementation:**

The primary outcome will be the Bayley BSID-III Cognitive Score as determined at 18-22 months adjusted age (assessed among all enrolled infants by assigning a low score for infants who die before assessment).

**Diuretics:**

The primary outcome of death or BPD (by physiologic definition) will be determined at a postmenstrual age of 36 weeks (window of 36 0/7 to 36 6/7 weeks).

**Secondary Outcomes (for both arms unless specified):**

1) Daily weights for the first 7 days after sodium supplementation study drug is initiated, then weekly weight and head circumference (secondary outcomes for sodium supplementation arm).

2) Postnatal systemic steroids, inhaled steroids, bronchodilators, and nitric oxide (first and last dates of scheduled administration, whether continuous or not, not including prn doses) (secondary outcomes for diuretic arm, safety outcomes for sodium supplementation arm)

3) Weight, length, mid-upper arm and head circumference at 36 weeks postmenstrual age (window of 36 0/7 to 36 6/7 weeks), done by research nurse using a length board for length. Infants transferred or discharged at <36 weeks will return to clinic if feasible, otherwise data will be sought from continuing care providers.

4) Weight, length, waist, mid-upper arm and head circumference at 18-22 months adjusted age (done by research nurse, using length board for length)

5) Death or NDI (Bayley III Cognitive score <70, Motor score < 70, GMFCS  $\geq$ 2; Moderate to Severe CP with GMFCS  $\geq$ 2, vision < 20-200 bilateral, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate  $\pm$  amplification with cochlear implant or hearing aid (2011 Network FU definition)

#### **Safety Monitoring:**

No adverse events were reported in two previous small randomized trials of sodium supplementation<sup>1616,1747</sup> or in the two small randomized trials of diuretics.<sup>5154,5252</sup> A variety of known or suspected effects on electrolyte balance have been observed in observational reports of diuretic use in preterm infants.<sup>4848</sup> Hyponatremia, hyponatremia, hypokalemia, hypochloremia, hypercalcemia, hypocalcemia, hypertension, and non-protocol diuretic use will be monitored, as will adverse outcomes of prematurity including PDA, IVH, PVL, NEC, ROP, late-onset sepsis, BPD, and death. Summary tables of these events will be provided to the Network Data Safety Monitoring Committee when 25, 50 and 75% of subjects have reached 36 weeks postmenstrual age. Hypertension, defined as treatment with antihypertensive medication during study drug administration, will be compared between the two sodium supplementation groups. Monitoring will be performed for possible diuretic risks including nephrocalcinosis (renal ultrasound at 35-37 weeks or discharge, whichever occurs first), fractures (by x-ray if clinical suspicion) due to osteopenia of prematurity, hearing screen at 3 months or discharge (whichever occurs first), and follow-up of abnormal hearing screens.

#### **Safety Outcomes:**

1) Hyponatremia (Na>145), hyponatremia (Na<135), hypokalemia (K <3.6) and hypochloremia (Cl <95), hypercalcemia (total >11 mg/dL or ionized >1.5 mmol/L), hypocalcemia (total < 7 mg/dL or ionized <1.2 mmol/L)<sup>55</sup> after enrollment using study recorded labs only (see Laboratory Testing below)

2) NaCl, KCl, arginine Cl supplementation to feedings - first and last date for each course (safety outcome for diuretic arm, adherence monitoring for sodium supplementation arm)

3) Hypertension treated with antihypertensive medication (yes/no). We will also collect all blood pressures recorded during the 24 hr period at 14 days after initiating sodium supplementation study drug, at 36 weeks adjusted age, and at 18-22 months.

4) Non-protocol diuretic use - all doses (safety outcome for sodium supplementation arm, compliance monitoring for diuretic arm)

5) Patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), late onset sepsis, bronchopulmonary dysplasia (BPD) by physiologic definition and death – all using GDB definitions. Each morbidity outcome will be expressed as a proportion of survivors and as “death or \_\_\_” among all enrolled.

6) Renal calcifications by renal ultrasound at 36 weeks or discharge, whichever is sooner

7) Fractures of long bones or ribs (diagnosed by x-ray if clinical suspicion)

8) Hearing screen at 3 months or discharge (whichever is sooner); hearing impairment (permanent hearing loss that does not permit the child to understand directions of the examiner)

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**Comment [(pb2):** I would specify that blood pressure will be measured when the baby is calm. This is an important to avoid falsely high values (Duncan et al. Pediatrics. 2008 Sep;122(3):e590-4). I would also mention that we will compare blood pressure between groups. Any statistical difference may become a starting point for longer term follow-up study and could potentially be the first sign of later developing hypertension.

or amplification with a cochlear implant or hearing aid) at follow-up by maternal report or medical record at 18-22 months

9) Laboratory testing: Clinically performed chemistries (Na, K, Cl, HCO<sub>3</sub>, Ca, Ph, Alk Phos) will be recorded no more than once daily for 14 days after study drug (sodium) is started then weekly (nearest to 21, 28,... days after enrollment). If no serum chemistries (at least electrolytes and Ca) are ordered by the clinicians in the 7-14 day and 14-28 day windows after study drug is started, these labs (Na, K, Cl, HCO<sub>3</sub>, Ca) will be ordered for study safety monitoring at 14 days and again at 28 days after the first study drug is begun. If diuretic study drug is started or resumed more than 1 week after sodium study drug, another set of labs will be ordered (if not ordered by clinicians) 7-14 days after diuretic study drug is initiated.

10) 18-22 month follow-up blood pressure

#### **Compliance Monitoring:**

1) Methylxanthines (first and last dates of scheduled administration, whether continuous or not)

2) Diuretic use and electrolyte supplements as detailed under Secondary Outcomes

3) Sodium and calorie intake: Monitoring will be performed weekly (nearest to 7, 14, 21... days after enrollment) during the study drug administration period. (The specific hours of the 24 hr period may be decided by centers based on how nursing documentation is done.) The ordered parenteral sodium will be recorded. Actual 24-hr fluid and caloric intake will be recorded/calculated from the nursing record. In addition, the type(s) of enteral feeding (formula, human milk, fortifier use) will be recorded.

#### **Statistical Analysis:**

All analyses will be by intention to treat. Death will be included in all negative outcome categories. All analyses will be stratified by center, gestational age strata, and the strata for the other study intervention.

For the sodium supplementation arm, the primary outcome of BSID-III Cognitive Scale score will be analyzed as a continuous variable, using regression analysis including center, gestational age, and diuretic group stratifications. Because the study will not begin until postnatal day 14, mortality after enrollment is likely to be low; however, if the inclusion of lowest BSID-III scores for infants who died significantly skews the distribution, a non-parametric test will be used. Secondary outcomes will be analyzed with linear regression for continuous variables or logistic regression for dichotomous variables. After analysis of unadjusted risk differences, other factors known to affect neurodevelopmental outcomes (e.g., gender, maternal education, family income, NEC, late-onset sepsis) may be evaluated as confounders in a multivariable analysis of outcome (secondary analysis).

For the diuretic arm, the primary outcome will be BPD defined as need for supplemental oxygen using the physiologic definition<sup>33,35</sup> at a postmenstrual age (using the best obstetrical estimate) of 36 weeks (window of 36 0/7 to 36 6/7 weeks) or death prior to BPD determination. The primary outcome will be assessed by comparing the proportion of infants who died or had BPD by Mantel-Haenszel chi-square analysis with center, gestational age strata, and sodium supplementation group as stratification factors.

The proposed protocol has two primary hypotheses; these hypotheses are designed to address two distinct treatment regimens and a distinct primary outcome is being used to test the benefit of the individual treatments (with cognitive development being used to test the benefit of sodium supplementation and reduction in death or BPD being used to test the benefit of liberal use of diuretics). As such, protection of the Type I error rate at the hypothesis rather than at the study level is appropriate, and the study has been powered to test each of these primary hypotheses based on tests of marginal differences, at the 0.05 level. As recommended by

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many experts<sup>56</sup>, the number of planned comparisons is clearly articulated in the protocol and will be acknowledged in the manuscripts.

Formal testing of interaction is planned. Before the trial begins, we will develop pre-specified criteria for the decisions regarding whether main effects or subgroup findings will be used for the primary analyses.

**Power Calculations:**

Because there is essentially no information, beyond biologic plausibility, on which to base speculation about the magnitude or direction of interaction we might observe, we have elected to propose a study of the largest feasible sample size (1200) that might be considered by the Network. In the table below, we calculate the anticipated power to identify clinically important main treatment effects as well as the power to identify clinically important interactions and treatment effects by subgroup (as would be deemed appropriate if an important interaction was identified). We can assume that there will be 50:50 allocation in each arm of the study so each cell in the 2x2 factorial will have 300 subjects.

**Assumptions for Diuretics Arm:**

Using the NRN's Generic Data Base and the physiologic definition of BPD, it is estimated that BPD/death at 36 weeks will occur in 0.58 of the infants<sup>35,36, GDB 2009, 57</sup>. It doesn't matter for the baseline event rate that not all infants will receive the diuretic intervention because the control event rate is based on all enrolled infants. We have calculated the power to identify a 20% relative risk reduction; this is considerably smaller than the (likely unrealistic) 70% relative risk reduction in mortality reported in the Cochrane review<sup>45,46</sup> of the only prior randomized trials. It should allow for some mitigation of the effect size because of cross-contamination (some infants in the liberal diuretic group who do not meet criteria for diuretics, some infants in the no diuretic group who are given open label diuretics). We have also calculated the power to identify a smaller effect size of 10% relative risk reduction.

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**Sodium Supplementation:**

We hypothesize that sodium supplementation will improve cognitive outcome; therefore, the primary outcome for this trial will be cognitive development at 18-22 months adjusted age as measured by the BSID-III Cognitive Score. Because the groups will be compared to each other, any change in scores between the BSID-II and BSID-III will not affect the primary outcome. To include death as a competing outcome, infants who die prior to study completion will be included and assigned the lowest score on the BSID-III Cognitive Scale ("untestable"=54). This scale has a standard deviation of 15 points in the Network.<sup>58</sup>

**Power Calculations for BPD/Death Outcome\*:**

Premise	Postulated "True" Event Rates for Death or BPD	Power to Identify Main Effects Difference for Diuretics	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Diuretic Effect within Sodium Subgroups	Power to Identify Effect of Sodium on Death/BPD
No Interaction; 20% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.464	0.98 (0.97)	NA	NA	NA	NA
No Interaction; 10% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.522 Na/Di = 0.522	0.52 (0.48)	NA	NA	NA	NA

Sodium increases Death/BPD by 10%; No Interaction; (20% RR Reduction with Diuretics)	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.510	0.98 (0.98)	NA	NA	NA	0.44 (0.41)
Interaction [Diuretic effect reduced by 50% (RRR=0.10) with Na]	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.522	0.85 (0.81)	0.17 (0.15)	0.39 (0.37)	Within Placebo 0.82 (0.78) Within Na 0.31 (0.28)	NA
Sodium increases Death/BPD by 10%; Interaction [Diuretic effect increased by 50% (RRR=0.30) with Na]	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.447	>0.99 (>0.99)	0.12 (0.12)	0.33 (0.33)	Within Placebo 0.82 (0.77) Within Na >0.97 (>0.96)	0.24 (0.22)

\*PI/PI = Placebo/Placebo; Na/PI = Sodium/Placebo; PI/Di = Placebo/Diuretic; Na/Di = Sodium/Diuretic

Initial value assume that 1200 subjects (300 per treatment combination) are available for analysis. Numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up.

**Power Calculations for Cognitive Score Outcome (assuming 12% mortality)\*:**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.86 (0.83)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.37 (0.32)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.86 (0.83)	NA	NA	NA	0.86 (0.83)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.62 (0.58)	0.12 (0.12)	0.33 (0.32)	Within Placebo 0.60 (0.54) Within Diuretic 0.18 (0.17)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.33 (0.31)	0.60 (0.57)	Within Either 0.18 (0.17)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.33 (0.31)	0.33 (0.31)	0.60 (0.57)	Within Placebo 0.05 (0.05) Within Diuretic 0.60 (0.54)	Within Either 0.21 (0.20)

\*PI/PI = Placebo/Placebo; Na/PI = Sodium/Placebo; PI/Di = Placebo/Diuretic; Na/Di = Sodium/Diuretic

Initial values assume that 1200 subjects (300 per treatment combination) are available for analysis. Numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19.8 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54).

Please see Appendix 2 for the summary calculations used to select a sample size of 1200. (The detailed power calculations for all sample sizes considered are in Appendix 3). This seemed like the best compromise for achieving additional power without creating a budget that would be cost-prohibitive. The budget calculations are at the top of the spreadsheet (totals in green). The power calculations for each sample size considered (580, 1000, 1200, 1600, 2000) are below the budget with the main effects analyses of the primary hypotheses in bold. The first and second power calculation tables represent the range of power expected for different assumptions that might be made about deaths, loss to follow-up, multiples, etc. The sample of 1200 allows for a minimum of 80% power (in red) for both primary hypotheses when allowances are made for deaths, loss to FU, etc. That would also achieve >80% power to identify a main diuretic effect if sodium supplementation makes diuretics 50% less effective. If diuretics make sodium supplementation less effective (it could easily go the other way with sodium being more effective in the presence of diuretics), we might not have good power to identify the sodium supplementation main effect, but increasing the sample size further for this purpose would greatly increase the cost. As expected, our power to identify moderate magnitude interactions is not high with any of the proposed sample sizes. If there were a very large interaction, we might be able to identify it. Of note, the most important type of interaction that we would want to detect (a beneficial effect of sodium with diuretics and a harmful effect without diuretics, or vice versa) can be identified with 57-60% power if we use an alpha error of 0.20 for the test of interaction.

#### **Available Population:**

In 2009, 1840 infants in this gestational age group were born in Network centers; 1603 survived >12 hours. Estimating eligibility at 80% and a consent rate of 60%,  $\approx$ 770 inborn infants could be enrolled in one year from the 16 sites in the 2006-2011 Network. If the number of available subjects were increased by 25% for outborn infants not included in the GDB, and by 12% for the increase to 18 centers, there could be 1078 available subjects per year. (Study duration and budget calculations were based on 960 enrolled per year.)

Based on our questionnaire, 15/18 of the current Network centers do not routinely or frequently supplement sodium. Most of the respondents in 17/18 centers would be willing to frequently or routinely withhold diuretics from infants with BPD and mild-moderate respiratory support. Depending on how many of the current centers are able to participate in the trial, patient enrollment could be completed within 2-3 years. Note: Current Network practice regarding routine sodium supplementation will be ascertained as in Appendix 1 prior to finalizing the protocol.

#### **Competing Studies:**

This study will be compatible with INS and NEST. Depending on how the Concurrent Research Committee evaluates what constitutes a conflict, this study may be viewed as compatible with the hydrocortisone and MILK trials (same primary endpoints, but all are interventions that are common in clinical practice) and may not be considered compatible with the PDA study (same primary endpoints, potential objections by clinicians to "withholding both aggressive treatment of PDA and diuretics).

#### **Human Subjects Considerations:**

Both genders and all racial and ethnic groups will be eligible. IRB approval will be obtained prior to study implementation, and parental consent will be obtained prior to individual randomization. Confidentiality will be maintained with standard Network practices. Safety monitoring will be performed as outlined above. Because the amount of study sodium to be provided is within the recommendations of the AAP,<sup>45,49</sup> no ethical issues arise from this intervention arm. The possible risks associated with diuretics are known but their clinical significance is uncertain. Diuretics have been used for decades in neonates with some evidence of benefit and little evidence of harm. Known adverse effects of diuretics include electrolyte imbalance and dehydration. Potential adverse effects include nephrocalcinosis and hearing loss (with furosemide). Common use of diuretics in clinical practice suggests that clinicians believe that the potential benefits of diuretic therapy, including improved pulmonary mechanics<sup>49,49</sup> and possibly lower mortality,<sup>45,46</sup> override the concerns for adverse effects. This trial has been designed to minimize the clinical use of furosemide, and it will be the first randomized trial large enough to reliably ascertain the side effects of diuretics in these infants.

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#### LIMITATIONS

A potential downside of the factorial design is that either intervention might diminish the effectiveness of the other intervention (diuretics might be less beneficial on BPD with sodium supplementation; the benefits of sodium supplementation on NDI might be reduced by diuretics). On the other hand, the baseline rate of BPD might be higher when some infants are supplemented with sodium, the risk of NDI might be higher when some infants are treated with diuretics. There is no way to predict how this will play out without doing the study. The power calculations are an attempt to anticipate how these various scenarios might affect the analysis and conclusions.

#### **BUDGET (based on 1200 patients enrolled)**

Coordinator time (\$35/hr):	
Consent/enrollment (3 hrs x 1200 pts; 2 hrs x 800 pts who decline)	\$ 182,028
Data collection 17 hrs/patient (2 hrs/wk x 2, 1 hr/week x 8, 2 hrs at 36 wks, 3 hrs for forms) x 1200 patients	\$ 714,000
3 hrs per patient for GDB forms on non-GDB patients (est 400)	\$ 41,958
Pharmacy:	
Start-up (\$2000/center)	\$ 36,000
Yearly fee (\$500/year x 3 years x 18 centers)	\$ 27,000
Medication (\$6/dose x 4/day, avg 56 days = \$1344/pt x 1200)	\$ 1,612,800
Placebo Formulation Fee	\$ 400
Placebo (\$40/120ml x 600 patients)	\$ 24,000
Study chemistries (Na, K, Cl, HCO <sub>3</sub> , Ca x 2 x \$50 x 1200)	\$ 120,000
Renal ultrasound: 1 per patient at \$110/test x 1200	\$ 132,000
Follow up (assume 90% FU):	
\$75/pt for tracking 120 lost pts	\$ 4,500
\$400/pt extra for ≤ 26 6/7 wks (est 360 pts)	\$ 151,848
\$700/pt for others (est 720 pts)	\$ 532,266
	<u>\$ 3,578,800</u>

<sup>1</sup> Kramer HC, Frank E, Kupfer DJ. Moderators of treatment outcomes: clinical, research, and policy importance. JAMA 2006; 296:1286-1289.

<sup>2</sup> Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001; 163: 1723-1729.

- <sup>3</sup> Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? *Semin Perinatol*. 2003; 27:302-310.
- <sup>4</sup> Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL, Katsikiotis V, Tyson JE, Oh W, Shankaran S, Bauer CR, Korones SB, Stoll BJ, Stevenson DK, Papile LA. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics*. 1999; 104:280-289.
- <sup>5</sup> Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006; 117:1253-1261.
- <sup>6</sup> Hans DM, Pylipow M, Long JD, Thureen PJ, Georgieff MK. Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey. *Pediatrics* 2009; 123:51-57.
- <sup>7</sup> Wassner SJ. Altered growth and protein turnover in rats fed sodium-deficient diets. *Pediatr Res* 1989; 26:608-613.
- <sup>8</sup> Wassner SJ. The effect of sodium repletion on growth and protein turnover in sodium-depleted rats. *Pediatr Nephrol* 1994; 8:501-504.
- <sup>9</sup> Aviv A, Kobayashi T, Higashino H, Bauman JW Jr, Yu SS. Chronic sodium deficit in the immature rat: its effect on adaptation to sodium excess. *Am J Physiol* 1982; 242 (Endocrinol Metab 5): E241-E247.
- <sup>10</sup> Gallaher KJ, Wolpert E, Wassner S, Rannels DE. Effect of diet-induced sodium deficiency on normal and compensatory growth of the lung in young rats. *Pediatr Res* 1990; 28:455-459.
- <sup>11</sup> Haycock GB. The influence of sodium on growth in infancy. *Pediatr Nephrol* 1993; 7:871-875.
- <sup>12</sup> Bower TR, Pringle KC, Soper RT. Sodium deficit causing decreased weight gain and metabolic acidosis in infants with ileostomy. *J Pediatr Surg*. 1988; 23:567-572.
- <sup>13</sup> Fine BP, Ty A, Lestrangle N, Maher E, Levine OR. Diuretic-induced growth failure in rats and its reversal by sodium repletion. *J Pharmacol Exp Ther* 1987; 242:85-89.
- <sup>14</sup> Wassner SA, Kulin HE. Diminished linear growth associated with chronic salt depletion. *Clin Pediatr* 1990; 29: 719-721.
- <sup>15</sup> Kalhoff H, Manz F. Nutrition, acid-base status and growth in early childhood. *Eur J Nutr* 2001; 40:221-230.
- <sup>16</sup> Al-Dahhan J, Haycock GB, Nichol B, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. III. Effect of salt supplementation. *Arch Dis Child* 1984; 59:945-950.
- <sup>17</sup> Vanpee M, Herin P, Broberger U, Aperia A. Sodium supplementation optimizes weight gain in preterm infants. *Acta Paediatr* 1995; 84:1312-1314.
- <sup>18</sup> Al-Dahhan J, Jannoun L, Haycock GB. Effect of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10-13 years of age. *Arch Dis Child Fetal Neonatal Ed* 2002; 86:F120-123.
- <sup>19</sup> Bergman I, Hirsch RP, Fria TJ, Shapiro SM, Holzman I, Painter MJ. Cause of hearing loss in the high-risk premature infant. *J Pediatr* 1985; 106:95-101.
- <sup>20</sup> Murphy DJ, Hope PL, Johnson A. Neonatal risk factors for cerebral palsy in very preterm babies: case-control study. *BMJ* 1997; 314:404-408.
- <sup>21</sup> Lorenz JM, Kleinman LI, Ahmed G, Markarian K. Phases of fluid and electrolyte homeostasis in the extremely low birth weight infant. *Pediatrics* 1995; 96:484-989.
- <sup>22</sup> Costarino AT Jr, Gruskay JA, Corcoran L, Polin RA, Baumgart S. Sodium restriction versus daily maintenance replacement in very low birth weight premature neonates: a randomized, blind therapeutic trial. *J Pediatr* 1992; 120:99-106.
- <sup>23</sup> Hartnoll G, Bétrémieux P, Modi N. Randomised controlled trial of postnatal sodium supplementation on body composition in 25 to 30 week gestational age infants. *Arch Dis Child Fetal Neonatal Ed* 2000; 82:F24-28.
- <sup>24</sup> Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. *Growth* 1976; 40:329-341.
- <sup>25</sup> Kashyap S, Schulze KF, Forsyth M, Dell RB, Ramakrishnan R, Heird WC. Growth, nutrient retention, and metabolic response of low-birth-weight infants fed supplemented and unsupplemented preterm human milk. *Am J Clin Nutr* 1990; 52:254-262.
- <sup>26</sup> Al-Dahhan J, Haycock GB, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. I. Renal aspects. *Arch Dis Child* 1983; 58:335-342.



- <sup>27</sup> Giapros VI, Papaloukas AL, Andronikou SK. Urinary mineral excretion in preterm neonates during the first month of life. *Neonatology* 2007; 91:180-185.
- <sup>28</sup> Al-Dahhan J, Haycock GB, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. II. Gastrointestinal aspects. *Arch Dis Child*.1983; 58:343-345.
- <sup>29</sup> Shirley DG, Walter SJ, Noormohamed FH. Natriuretic effect of caffeine: assessment of segmental sodium reabsorption in humans. *Clin Sci* 2002; 103:461-466.
- <sup>30</sup> American Academy of Pediatrics. *Pediatric Nutrition Handbook*. Kleinman RE ed.2009.
- <sup>31</sup> Schanler RJ, Oh W. Composition of breast milk obtained from mothers of premature infants as compared to breast milk obtained from donors. *J Pediatr* 1980; 96:679-681.
- <sup>32</sup> Malloy MH, Graubard B, Moss H et al. Hypochloremic metabolic alkalosis from ingestion of a chloride-deficient infant formula: outcome 9 and 10 years later. *Pediatrics* 87: 811-822, 1991.
- <sup>33</sup> Heinly MM, Wassner SJ. The effect of isolated chloride depletion on growth and protein turnover in young rats. *Pediatr Nephrol* 1994; 8: 555-560.
- <sup>34</sup> Heinly MM, Wassner SJ. The effect of isolated chloride depletion on growth and protein turnover in young rats. *Pediatr Nephrol* 1994; 8:555-560.
- <sup>35</sup> Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, et al; National Institute of Child Health and Human Development Neonatal Research Network. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics* 2004; 114:1305-1311.
- <sup>36</sup> Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sanchez PJ, O'Shea M, Goldberg RN, Van Meurs KP, Faix RG, Phelps DL, Frantz ID, Watterberg KL, Saha S, Das A, Higgins RD for the National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010; 126:443-456.
- <sup>37</sup> Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kerckmar C, et al. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. *Pediatrics* 2003; 112:e359.
- <sup>38</sup> Halvorsen T, Skadberg BT, Eide GE, Roksund OD, Carlsen KH, Bakke P. Pulmonary outcome in adolescents of extreme preterm birth: a regional cohort study. *Acta Paediatr* 2004; 93:1294-1300.
- <sup>39</sup> Northway WH, Jr, Moss RB, Carlisle KB, Parker BR, Popp RL, Pitlick PT, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med* 1990; 323:1793-1799
- <sup>40</sup> Ambalavanan N, Carlo WA. Bronchopulmonary dysplasia: new insights. *Clin Perinatol* 2004; 31:613-628.
- <sup>41</sup> Brown ER, Stark A, Sosenko I, Lawson EE, Avery ME. Bronchopulmonary dysplasia: possible relationship to pulmonary edema. *J Pediatr* 1978; 92:982-984
- <sup>42</sup> Tammela OK. Appropriate fluid regimens to prevent bronchopulmonary dysplasia. *Eur J Pediatr* 1995; 154:S15-18.
- <sup>43</sup> Adams EW, Harrison MC, Counsell SJ, Ailsop JM, Kennea NL, Hajnal JV, et al. Increased lung water and tissue damage in bronchopulmonary dysplasia. *J Pediatr* 2004; 145:503-507.
- <sup>44</sup> Thom J, Perks AM. The effects of furosemide and bumetanide on lung liquid production by in vitro lungs from fetal guinea pigs. *Can J Physiol Pharmacol* 1990; 68:1131-1135.
- <sup>45</sup> Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. *Cochrane Database Syst Rev*. 2011; 9:CD001817.
- <sup>46</sup> The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics* 2000; 105:295-310.
- <sup>47</sup> Hagadorn JI, Sanders MR, Staves C, Herson VC, Daigle K. Diuretics for very low birth weight infants in the first 28 days: a survey of the US neonatologists. *J Perinatol* 2011; [Epub ahead of print]
- <sup>48</sup> Stewart AL, Brion LP. Routine use of diuretics in very low birth weight infants in the absence of supporting evidence. *J Perinatol* 2011; 31:633-634.
- <sup>49</sup> Stewart A, Brion LP. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. *Cochrane Database Syst Rev*. 2011; 9:CD001453.
- <sup>50</sup> Brion LP, Soll RF. Diuretics for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev*. 2008;(1):CD001454.

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- <sup>51</sup> Albersheim SG, Solimano AJ, Shama AK, Smyth JA, Rotschild A, Wood BJ, et al. Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989; 115:615-620.
- <sup>52</sup> Kao LC, Durand DJ, McCrea RC, Birch M, Powers RJ, Nickerson BG. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. *J Pediatr* 1994; 124:772-781.
- <sup>53</sup> Hoffman DJ, Gerdes JS, Abbasi S. Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomized trial. *J Perinatol* 2000; 1: 41-45.
- <sup>54</sup> Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007; 357:1893-1902.
- <sup>55</sup> Lorenz JM. Assessing fluid and electrolyte status in the newborn. *Clinical Chemistry* 1997; 43:205-210.
- <sup>56</sup> Rothman KJ. No adjustments needed for multiple comparisons. *Epidemiology* 1990; 1: 43-46.
- <sup>57</sup> Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, Stoll BJ, Buchter S, Laptook AR, Ehrenkranz RA, Cotten CM, Wilson-Costello DE, Shankaran SA, Van Meurs KP, Davis A, Gantz MG, Finer NN, Yoder BA, Faix RG, Carlo WA, Schibler KR, Newman NS, Das A, Higgins RD, Walsh MC; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Prediction of Bronchopulmonary Dysplasia by Postnatal Age in Extremely Premature Infants. *Am J Respir Crit Care Med* 2011 Mar 4. [Epub ahead of print]
- <sup>58</sup> Lowe J, Duncan A, Nolen T, Vohr B, Adams-Chapman I, Watterberg K, NICHD Neonatal Research Network. Effect of Ethnicity/Race on Cognitive and Language Testing at 18-22 Months in Extremely Low Birth Weight Infants. E-PAS20101360.6 (abstract)

### Appendix 1 – Current NICHD Center Practices

The following questionnaire was sent to the PIs of the participating Network sites in Nov-Dec 2010. Eleven of the current centers responded. Responses were received from the remaining 2 centers and the 5 new centers in Aug 2011:

In planning of a factorial trial of Na supplementation and diuretics, the study working group would like to get responses to the following from your clinical practice group. We understand that practice may vary widely within centers, so we would appreciate it if you could briefly discuss these questions at a division meeting and provide the number of practitioners in your site who would select each response for the following questions: (Please feel free to add comments if needed to fully answer the questions.)

For ELBW infants who are not on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 130-135 (assuming the infant is not believed to be fluid overloaded)?

Never     Infrequently     Sometimes     Frequently     Routinely

For ELBW infants who are not on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 125-130 (assuming the infant is not believed to be fluid overloaded)?

Never     Infrequently     Sometimes     Frequently     Routinely

For ELBW infants who are not on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 120-125 (assuming the infant is not believed to be fluid overloaded)?

Never     Infrequently     Sometimes     Frequently     Routinely

For ELBW infants who are on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 130-135 (assuming the infant is not believed to be fluid overloaded)?

Never     Infrequently     Sometimes     Frequently     Routinely

For ELBW infants who are on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 125-130 (assuming the infant is not believed to be fluid overloaded)?

Never     Infrequently     Sometimes     Frequently     Routinely

For ELBW infants who are on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 120-125 (assuming the infant is not believed to be fluid overloaded)?

Never     Infrequently     Sometimes     Frequently     Routinely

For ELBW infants who are not hyponatremic, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) as a "nutrition" supplement?

Never     Infrequently     Sometimes     Frequently     Routinely

In the setting of an RCT of diuretics vs no diuretics, how often would you have sufficient equipment to withhold all diuretics from ELBW infants until 36 wks PMA in the following situations?

On CPAP and FiO2 30-40%

Never     Infrequently     Sometimes     Frequently     Routinely

On moderate vent support (MAP of 6) and FiO2 30-40%

Never     Infrequently     Sometimes     Frequently     Routinely

On high vent support and (MAP of 10) FiO2 >40%

Never     Infrequently     Sometimes     Frequently     Routinely

Survey results are summarized as follows (modal response for each site is green):

	03 Case	04 Dallas	05 Wayne	09 Emory	11 Cincinnati	12 Indiana	14 Brown	15 Stanford	16 Alabama	18 Houston	19 Duke	24 Iowa	26 New Mexico	27 Penn	28 Rochester	29 UCLA	30 Ohio State	31 Missouri	
For ELBW infants who are not on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 130-135 (assuming the infant is not believed to be fluid overloaded)?																			
Never																			
Infrequently	2				1														
Sometimes					2			2		3									
Frequently																			
Routinely																			
Missouri: Infrequently for 130; frequently for 135																			
For ELBW infants who are not on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 125-130 (assuming the infant is not believed to be fluid overloaded)?																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
For ELBW infants who are not on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 120-125 (assuming the infant is not believed to be fluid overloaded)?																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
For ELBW infants who are on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 130-135 (assuming the infant is not believed to be fluid overloaded)?																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
For ELBW infants who are on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 125-130 (assuming the infant is not believed to be fluid overloaded)?																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
For ELBW infants who are on diuretics, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) when serum Na is 120-125 (assuming the infant is not believed to be fluid overloaded)?																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
For ELBW infants who are not hyponatremic, do you add Na supplements to enteral feedings (at 7 days to 36 weeks PMA) as a "nutrition" supplement?																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
In the setting of an RCT of diuretics vs no diuretics, how often would you have sufficient equipment to withhold all diuretics from ELBW infants until 36 wks PMA in the following situations?																			
On CPAP and FiO2 30-40%																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
On moderate vent support (MAP of 6) and FiO2 30-40%																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
On high vent support and (MAP of 10) FiO2 >40%																			
Never																			
Infrequently																			
Sometimes																			
Frequently																			
Routinely																			
Comments	Most of the sites who responded to the first questionnaire submitted responses on individual facility, Iowa and Wayne submitted majority opinions; Cincinnati submitted a majority opinion for each practice site. In the second round, Dallas, UCLA, Ohio, and Penn submitted majority opinions. I'm not sure about Emory.																		
Penn	With the input of our medical directors I have completed the questionnaire as best I could. Local practice in this area is not very standardized and there will be quite a bit of variability in practice between attendings. All the more reason to study it!																		
Ohio	We do believe that we as a group would have equipment in withholding diuretics in an RCT - but clearly there will be occasions when diuretics will be given.																		

Prior to implementing this study, a formal query will be sent to all Network sites, asking: "of the last 10 babies who would have been eligible for this study, how many received sodium supplementation while on full enteral feedings, at <34 weeks postmenstrual age, while not receiving concomitant diuretic therapy?" This query will enable us to quickly ascertain, with a modest effort, whether any center routinely supplements stable growing preterm infants with sodium.

## Appendix 2 – Calculation of Projected Power vs Study Budget

	580	1000	1200	1600	2000
Number of patients					
Duration of enrollment (yrs)	0.60	1.04	1.25	1.67	2.08
Time to complete study (with follow-up)	2.44	2.88	3.08	3.50	3.92
<b>Budget</b>					
<b>Coordinator time</b>					
Consent	87,980	151,690	182,028	242,704	303,380
Data collection	345,100	595,000	714,000	952,000	1,190,000
Addtl GDB data collection	20,280	34,965	41,958	55,944	69,930
<b>Medication</b>					
Start-up	36,000	36,000	36,000	36,000	36,000
Yearly fee	18,000	27,000	27,000	27,000	36,000
Medication	779,520	1,344,000	1,612,800	2,150,400	2,688,000
Chemistries	58,000	100,000	120,000	160,000	200,000
Ultrasound	63,800	110,000	132,000	176,000	220,000
<b>Follow-up</b>					
Tracking lost to FU	2,175	3,750	4,500	6,000	7,500
For GDB pts	73,393	126,540	151,848	202,464	253,080
For nonGDB pts	257,262	443,555	532,266	709,688	887,110
<b>Total</b>	<b>1,741,510</b>	<b>2,972,500</b>	<b>3,554,400</b>	<b>4,718,200</b>	<b>5,891,000</b>
<b>Power Calculations (upper end of estimated range)</b>					
Main effects (BPD/Death; RR= 8)	<b>~0.80</b>	<b>0.95</b>	<b>0.98</b>	<b>&gt;0.99</b>	<b>&gt;0.99</b> (primary hypothesis for diuretic arm)
Main effects (BPD/Death; RR= 9)		0.45	0.52	0.64	0.75
Main effects (CogSc/Death; 12% mortality, mean diff =4)	<b>~0.80</b>	<b>0.80</b>	<b>0.86</b>	<b>0.94</b>	<b>0.98</b> (primary hypothesis for Na arm)
Main effects (CogSc/Death; 12% mortality, mean diff =2)		0.27	0.37	0.40	0.48
Main diuretic effect if less beneficial in Na arm (RR=0.8)		0.80	0.85	0.93	0.96
Main Na effect if less beneficial in diuretic arm (mean diff =4)		0.55	0.62	0.75	0.83
Identify interaction for MDI/Death at p=0.20		0.36	0.39	0.46	0.51
Identify interaction for BPD/Death at p=0.21		0.31	0.33	0.37	0.41
<b>Power Calculations (lower end of estimated range)</b>					
Main effects (BPD/Death; RR= 8)		<b>0.94</b>	<b>0.97</b>	<b>&gt;0.99</b>	<b>&gt;0.99</b> (primary hypothesis for diuretic arm)
Main effects (BPD/Death; RR= 9)		0.41	0.48	0.60	0.69
Main effects (CogSc/Death; 12% mortality, mean diff =4)		<b>0.76</b>	<b>0.83</b>	<b>0.92</b>	<b>0.96</b> (primary hypothesis for Na arm)
Main effects (CogSc/Death; 12% mortality, mean diff =2)		0.25	0.32	0.37	0.45
Main diuretic effect if diuretic less effective in Na arm (RR=0.8)		0.75	0.81	0.91	0.97
Main Na effect if Na less effective in diuretic arm (mean diff =4)		0.50	0.58	0.70	0.79
Identify interaction for BPD/Death at p=0.20		0.35	0.37	0.43	0.47
Identify interaction for CogSc/Death at p=0.20		0.30	0.32	0.35	0.39

**Appendix 3 – Power Calculations for Sample Sizes Considered**

**Table 1-1: Power for the Death/BPD Outcome (2000 Subject Version)**

Premise	Postulated "True" Event Rates for Death or BPD	Power to Identify Main Effects Difference for Diuretics	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Diuretic Effect within Sodium Subgroups	Power to Identify Effect of Sodium on Death/BPD
No Interaction; 20% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.464	>0.99 (>0.99)	NA	NA	NA	NA
No Interaction; 10% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.522 Na/Di = 0.522	0.75 (0.69)	NA	NA	NA	NA
Sodium increases Death/BPD by 10%; No Interaction; (20% RR Reduction with Diuretics)	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.510	>0.99 (>0.99)	NA	NA	NA	0.65 (0.61)
Interaction [Diuretic effect reduced by 50% (RRR=0.10) with Na]	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.522	0.97 (0.96)	0.25 (0.24)	0.51 (0.47)	W/in Placebo 0.96 (0.93) W/in Na 0.46 (0.42)	NA
Sodium increases Death/BPD by 10%; Interaction [Diuretic effect increased by 50% (RRR=0.30) with Na]	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.447	>0.99 (>0.99)	0.19 (0.16)	0.42 (0.39)	W/in Placebo 0.96 (0.94) W/in Na >0.99 (>0.99)	0.36 (0.34)

Initial values assume that 2000 subjects or 500 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up.

**Table 1-2a: Power Estimates for the Cognitive Outcome (2000 Subject Version):**

**Assume 10% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.99 (0.98)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.56 (0.52)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.99 (0.98)	NA	NA	NA	0.99 (0.98)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.88 (0.85)	0.18 (0.17)	0.42 (0.40)	W/in Placebo 0.85 (0.81) W/in Diuretic 0.32 (0.30)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.55 (0.51)	0.79 (0.76)	W/in Either 0.32 (0.30)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.55 (0.51)	0.55 (0.51)	0.79 (0.76)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.85 (0.81)	W/in Either 0.32 (0.30)

Initial values assume that 2000 subjects or 500 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)



**Table 1-2b: Power Estimates for the Cognitive Outcome (2000 Subject Version)**

**Assume 12% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.98 (0.96)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.48 (0.45)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.98 (0.96)	NA	NA	NA	0.98 (0.96)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.83 (0.79)	0.17 (0.16)	0.41 (0.39)	W/in Placebo 0.80 (0.76) W/in Diuretic 0.25 (0.27)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.51 (0.47)	0.76 (0.72)	W/in Either 0.25 (0.27)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.51 (0.47)	0.51 (0.47)	0.76 (0.72)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.80 (0.76)	W/in Either 0.25 (0.27)

Initial values assume that 2000 subjects or 500 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19.8 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)

**Table 2-1: Power for the Death/BPD Outcome (1000 Subject Version)**

Premise	Postulated "True" Event Rates for Death or BPD	Power to Identify Main Effects Difference for Diuretics	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Diuretic Effect within Sodium Subgroups	Power to Identify Effect of Sodium on Death/BPD
No Interaction; 20% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.464	0.95 (0.94)	NA	NA	NA	NA
No Interaction; 10% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.522 Na/Di = 0.522	0.45 (0.41)	NA	NA	NA	NA
Sodium increases Death/BPD by 10%; No Interaction; (20% RR Reduction with Diuretics)	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.510	0.97 (0.95)	NA	NA	NA	0.38 (0.34)
Interaction [Diuretic effect reduced by 50% (RRR=0.10) with Na]	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.522	0.80 (0.75)	0.15 (0.13)	0.36 (0.35)	W/in Placebo 0.75 (0.70) W/in Na 0.26 (0.24)	NA
Sodium increases Death/BPD by 10%; Interaction [Diuretic effect increased by 50% (RRR=0.30) with Na]	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.447	>0.99 (0.98)	0.12 (0.11)	0.32 (0.31)	W/in Placebo 0.75 (0.70) W/in Na 0.96 (0.93)	0.36 (0.34)

Initial values assume that 1000 subjects or 250 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up.

**Table 2-2a: Power Estimates for the NDI Outcome (1000 Subject Version):**

**Assume 10% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.85 (0.81)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.30 (0.28)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.85 (0.81)	NA	NA	NA	0.99 (0.98)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.81 (0.77)	0.12 (0.11)	0.32 (0.31)	W/in Placebo 0.56 (0.52) W/in Diuretic 0.18 (0.17)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.55 (0.51)	0.79 (0.76)	W/in Either 0.18 (0.17)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.32 (0.29)	0.32 (0.29)	0.59 (0.56)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.56 (0.52)	W/in Either 0.18 (0.17)

Initial values assume that 1000 subjects or 250 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)

**Table 2-2b: Power Estimates for the NDI Outcome (1000 Subject Version)**

**Assume 12% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.80 (0.76)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.27 (0.25)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.80 (0.75)	NA	NA	NA	0.80 (0.75)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.55 (0.50)	0.11 (0.10)	0.31 (0.30)	W/in Placebo 0.51 (0.46) W/in Diuretic 0.16 (0.15)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.29 (0.26)	0.55 (0.52)	W/in Either 0.16 (0.15)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.29 (0.26)	0.29 (0.26)	0.55 (0.52)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.51 (0.46)	W/in Either 0.16 (0.15)

Initial values assume that 1000 subjects or 250 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19.8 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)

**Table 3-1: Power for the Death/BPD Outcome (1200 Subject Version)**

Premise	Postulated "True" Event Rates for Death or BPD	Power to Identify Main Effects Difference for Diuretics	Power to Identify Interaction at $p=0.05$	Power to Identify Interaction at $p=0.20$	Power to Identify Diuretic Effect within Sodium Subgroups	Power to Identify Effect of Sodium on Death/BPD
No Interaction; 20% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.464	0.98 (0.97)	NA	NA	NA	NA
No Interaction; 10% RR Reduction	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.522 Na/Di = 0.522	0.52 (0.48)	NA	NA	NA	NA
Sodium increases Death/BPD by 10%; No Interaction; (20% RR Reduction with Diuretics)	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.510	0.98 (0.98)	NA	NA	NA	0.44 (0.41)
Interaction [Diuretic effect reduced by 50% (RRR=0.10) with Na]	PI/PI = 0.580 Na/PI = 0.580 PI/Di = 0.464 Na/Di = 0.522	0.85 (0.81)	0.17 (0.15)	0.39 (0.37)	W/in Placebo 0.82 (0.78) W/in Na 0.31 (0.28)	NA
Sodium increases Death/BPD by 10%; interaction [Diuretic effect increased by 50% (RRR=0.30) with Na]	PI/PI = 0.580 Na/PI = 0.638 PI/Di = 0.464 Na/Di = 0.447	>0.99 (>0.99)	0.12 (0.12)	0.33 (0.33)	W/in Placebo 0.82 (0.77) W/in Na 0.97 (0.96)	0.24 (0.22)

Initial values assume that 1200 subjects or 300 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up.

**Table 3-2a: Power Estimates for the NDI Outcome (1200 Subject Version):**

**Assume 10% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at $p=0.05$	Power to Identify Interaction at $p=0.20$	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	Pi/Pi = 95 Na/Pi = 99 Pi/Di = 95 Na/Di = 99	0.91 (0.87)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	Pi/Pi = 95 Na/Pi = 97 Pi/Di = 95 Na/Di = 97	0.35 (0.32)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	Pi/Pi = 95 Na/Pi = 99 Pi/Di = 91 Na/Di = 95	0.91 (0.88)	NA	NA	NA	0.91 (0.88)
Na is less beneficial with diuretics	Pi/Pi = 95 Na/Pi = 99 Pi/Di = 95 Na/Di = 97	0.77 (0.69)	0.13 (0.12)	0.34 (0.33)	W/in Placebo 0.64 (0.59) W/in Diuretic 0.21 (0.20)	NA
Interaction: Na is beneficial with diuretics, harmful without	Pi/Pi = 95 Na/Pi = 93 Pi/Di = 95 Na/Di = 97	NA	0.37 (0.34)	0.64 (0.61)	W/in Either 0.32 (0.30)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	Pi/Pi = 95 Na/Pi = 95 Pi/Di = 93 Na/Di = 97	0.37 (0.34)	0.37 (0.34)	0.64 (0.61)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.64 (0.59)	W/in Either 0.21 (0.20)

Initial values assume that 1200 subjects or 300 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)

**Table 3-2b: Power Estimates for the NDI Outcome (1200 Subject Version)**

**Assume 12% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.86 (0.83)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.37 (0.32)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.86 (0.83)	NA	NA	NA	0.86 (0.83)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.62 (0.58)	0.12 (0.12)	0.33 (0.32)	W/in Placebo 0.60 (0.54) W/in Diuretic 0.18 (0.17)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.33 (0.31)	0.60 (0.57)	W/in Either 0.18 (0.17)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.33 (0.31)	0.33 (0.31)	0.60 (0.57)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.60 (0.54)	W/in Either 0.21 (0.20)

Initial values assume that 1200 subjects or 300 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19.8 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)

**Table 4-1: Power for the Death/BPD Outcome (1600 Subject Version)**

Premise	Postulated "True" Event Rates for Death or BPD	Power to Identify Main Effects Difference for Diuretics	Power to Identify Interaction at $p=0.05$	Power to Identify Interaction at $p=0.20$	Power to Identify Diuretic Effect within Sodium Subgroups	Power to Identify Effect of Sodium on Death/BPD
No Interaction; 20% RR Reduction	P/PI = 0.580 Na/PI = 0.580 P/Di = 0.464 Na/Di = 0.464	>0.99 (>0.99)	NA	NA	NA	NA
No Interaction; 10% RR Reduction	P/PI = 0.580 Na/PI = 0.580 P/Di = 0.522 Na/Di = 0.522	0.64 (0.60)	NA	NA	NA	NA
Sodium increases Death/BPD by 10%; No Interaction; (20% RR Reduction with Diuretics)	P/PI = 0.580 Na/PI = 0.638 P/Di = 0.464 Na/Di = 0.510	>0.99 (>0.99)	NA	NA	NA	0.56 (0.52)
Interaction [Diuretic effect reduced by 50% (RRR=0.10) with Na]	P/PI = 0.580 Na/PI = 0.580 P/Di = 0.464 Na/Di = 0.522	0.93 (0.91)	0.20 (0.19)	0.46 (0.43)	W/in Placebo 0.91 (0.87) W/in Na 0.37 (0.34)	NA
Sodium increases Death/BPD by 10%; Interaction [Diuretic effect increased by 50% (RRR=0.30) with Na]	P/PI = 0.580 Na/PI = 0.638 P/Di = 0.464 Na/Di = 0.447	>0.99 (>0.99)	0.15 (0.14)	0.38 (0.36)	W/in Placebo 0.91 (0.87) W/in Na >0.99 (>0.99)	0.30 (0.28)

Initial values assume that 1600 subjects or 400 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up.



**Table 4-2a: Power Estimates for the NDI Outcome (1600 Subject Version):**

**Assume 10% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.95 (0.97)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.44 (0.41)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.97 (0.95)	NA	NA	NA	0.97 (0.95)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.81 (0.77)	0.16 (0.15)	0.38 (0.37)	W/in Placebo 0.76 (0.72) W/in Diuretic 0.27 (0.25)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.47 (0.44)	0.73 (0.76)	W/in Either 0.27 (0.25)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.47 (0.44)	0.47 (0.44)	0.73 (0.76)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.76 (0.72)	W/in Either 0.27 (0.25)

Initial values assume that 1600 subjects or 400 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)

**Table 4-2b: Power Estimates for the NDI Outcome (1600 Subject Version)**

**Assume 12% Mortality**

Premise	Postulated "True" Mean Cognitive Score	Power to Identify Main Effects Difference for Sodium	Power to Identify Interaction at p=0.05	Power to Identify Interaction at p=0.20	Power to Identify Sodium Effect within Diuretic Subgroups	Power to Identify Effect of Diuretics on Cognitive Score
No Interaction; Mean Difference = 4	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 99	0.94 (0.92)	NA	NA	NA	NA
No Interaction; Mean Difference of 2	PI/PI = 95 Na/PI = 97 PI/Di = 95 Na/Di = 97	0.40 (0.37)	NA	NA	NA	NA
Diuretics decrease Cognitive Score by 4; No Interaction (Mean Difference of 4 with Sodium)	PI/PI = 95 Na/PI = 99 PI/Di = 91 Na/Di = 95	0.94 (0.92)	NA	NA	NA	0.94 (0.92)
Na is less beneficial with diuretics	PI/PI = 95 Na/PI = 99 PI/Di = 95 Na/Di = 97	0.75 (0.70)	0.15 (0.14)	0.37 (0.35)	W/in Placebo 0.71 (0.66) W/in Diuretic 0.23 (0.21)	NA
Interaction: Na is beneficial with diuretics, harmful without	PI/PI = 95 Na/PI = 93 PI/Di = 95 Na/Di = 97	NA	0.47 (0.42)	0.69 (0.66)	W/in Either 0.25 (0.27)	NA
Interaction: Diuretics are harmful without Na, beneficial with Na	PI/PI = 95 Na/PI = 95 PI/Di = 93 Na/Di = 97	0.47 (0.42)	0.47 (0.42)	0.69 (0.66)	W/in Placebo 0.05 (0.05) W/in Diuretic 0.71 (0.66)	W/in Either 0.23 (0.21)

Initial values assume that 1600 subjects or 400 per treatment combination are available for analysis while numbers in parentheses assume that only 90% of the subjects are available for analyses. Given other uncertainties in the analyses, the range is likely to account for any uncertainty in outcome assessment or loss to follow-up. Note that these calculations assume that the within cell standard deviation is 19.8 (as computed from the mixture of measured outcomes and unmeasured individuals fixed at 54)

**From:** Buchanan, Lisa (HHS/OASH)  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)  
**Date:** Thursday, June 14, 2012 10:01:53 AM

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Thanks!

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, June 12, 2012 10:22 AM  
**To:** Buchanan, Lisa (HHS/OASH)  
**Cc:** Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi,

To address the questions:

1. Dr. Finer was the principal investigator on the CPAP/surfactant portion of the study. Since this was a factorial design, Dr. Wally Carlo was the principal investigator on the oxygen saturation arm of the study. Both Drs. Finer and Carlo were the lead investigators for the study.
2. Each IRB reviewed and approved the trial. There was no central IRB for the study.

Let me know if you need additional information

Rose

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

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**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Monday, June 11, 2012 5:26 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hello Dr. Higgins,

I'm finishing up my review of the SUPPORT trial and I have a couple quick questions:

1. I noted that Dr. Finer's name and institution (UCSD) is on the template consent. The DSMC minutes list him as the lead investigator for the study. What is (was) Dr. Finer's (UCSD) role in the SUPPORT trial? Is UCSD the lead site?
2. Also, did each of the 21 IRBs review and oversee the trial their institution or did any

of the institutions rely on the review of another institution's IRB?

Thanks in advance!  
Lisa Buchanan  
240-453-8298

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, April 13, 2012 2:53 PM  
**To:** Buchanan, Lisa (HHS/OASH)  
**Subject:** Re: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi

There were no sites outside of the US. Recruitment is complete. However, there is a sub cohort of approximately 500-550 infants enrolled who had neuroimaging who are part of a school age Follow up (FU) study at 6.5-7.5 years of age. The windows are open for FU and will continue through 2016. Data analyses from the 18-22 month FU are in process.

Let me know if you have other questions.

Regards,  
\$rose

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**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Friday, April 13, 2012 02:40 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good afternoon Rose,

I have two quick questions regarding the study referenced above. Did this trial involve any sites outside of the US? And are all study activities complete/close for all of the sites?

Thanks,  
Lisa

Lisa Buchanan, MAOM, CIP  
Public Health Analyst  
Division of Compliance Oversight  
Office for Human Research Protections  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852  
Ph: 240-453-8298  
Fax: 240-453-6909

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 01, 2012 1:31 PM

**To:** Buchanan, Lisa (HHS/OASH)  
**Cc:** Borrer, Kristina C (HHS/OASH)  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi,

These were sent and we have confirmed with FED EX that they were delivered – can you confirm that you have them??

Thanks

Rose

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

**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Monday, January 09, 2012 11:40 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Borrer, Kristina C (HHS/OASH)  
**Subject:** "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good morning Dr. Higgins.

I am reviewing responses to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. OHRP has only opened its investigation with the University of Alabama. However, we would like to review the informed consent documents for all of the sites (~20). The data coordinating center, RTI, recommended that we contact you for this information. (See email below.) Would it be possible for you to provide copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPORT study?

Please feel free to contact me if you have any questions regarding this request.

Thanks,  
Lisa

**Lisa Buchanan, MAOM**  
Public Health Analyst, Division of Compliance Oversight  
Office for Human Research Protections  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200

Rockville, MD 20852  
Ph: 240-453-8298  
Fax: 240-453-6909

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**From:** Borasky, David [mailto:dborasky@rti.org]  
**Sent:** Thursday, August 04, 2011 12:19 PM  
**To:** Borrer, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Hi Kristina –

We had a chance to discuss your request with the RTI DCC folks this morning and how RTI may be able to help facilitate this for OHRP.

As I mentioned this morning, the RTI IRB does not require the DCC to provide RTI IRB with copies of the approved informed consent documents for each site. I did confirm that the DCC requires sites to submit copies of study approval notices to the DCC, but they do not require submission of copies of site-level informed consent documents to the DCC. Some sites do include them with the approval notices, but this is not done consistently and may not be done every time a consent document is amended at the site level. Therefore, the DCC's records for site-level consent documents are incomplete.

The RTI IRB and the Neonatal Research Network DCC appreciate your desire to expeditiously obtain site-level informed consent documents for the SUPPORT Trial. We believe that the best way to facilitate this is to have OHRP submit a formal request to the Neonatal Research Network steering committee via the NICHD project officer Rosemary Higgins (contact information below) to have the RTI Data Coordinating Center collect copies of the final approved consent forms (as well as whether or not this is the initially approved documents or all versions that were used with participants for the duration of the study) for each of the SUPPORT Trial sites for transmittal to OHRP.

I hope this is a suitable approach.

Best,

Dave

Dr. Higgins contact information:

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

301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

\*\*\*\*\*

David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

Phone: 919-316-3903  
Fax: 919-316-3897  
E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

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**From:** Borrer, Kristina C (HHS/OASH) [<mailto:Kristina.Borrer@hhs.gov>]  
**Sent:** Friday, July 29, 2011 4:23 PM  
**To:** Borasky, David  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Dave,  
We were wondering if you would be able to get us copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPRT study. Is that possible?  
Thanks for your assistance.  
Kristina

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**From:** Borasky, David [<mailto:dborasky@rti.org>]  
**Sent:** Monday, July 25, 2011 1:13 PM  
**To:** Borrer, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Thank you for the quick response Kristina.

RTI was not engaged in the conduct of the SUPPORT clinical protocol nor would have been considered the IRB of record. RTI serves as the network data coordinating center for all sites, and in this role received coded data for analysis.

Therefore, as per your email, we will not submit a response to the letter dated July 18, 2011.

Regards,

Dave

\*\*\*\*\*

David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd

RTP, NC 27709  
USA

Phone: 919-316-3903  
Fax: 919-316-3897  
E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

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**From:** Borrer, Kristina C (HHS/OASH) [<mailto:Kristina.Borrer@hhs.gov>]  
**Sent:** Monday, July 25, 2011 1:00 PM  
**To:** Borasky, David  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Dave,  
If RTI is not engaged in the research, we do not require any additional information at this time. We'll let you know if we need anything else.

Kristina C. Borrer, Ph.D.  
Director  
Division of Compliance Oversight  
Office for Human Research Protections  
1101 Wootton Parkway, Suite 200  
The Tower Building  
Rockville, MD 20852  
email: [kristina.borrer@hhs.gov](mailto:kristina.borrer@hhs.gov)  
Phone: (240) 453-8132  
Fax: (240) 453-6909

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**From:** Borasky, David [<mailto:dborasky@rti.org>]  
**Sent:** Monday, July 25, 2011 11:10 AM  
**To:** Borrer, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** clarification requested

Good morning Kristina,

On Friday we (RTI) received a letter from you that was addressed to both our signatory official (Ward Sax) and the SO of UAB (Dr. Marchase) related to the SUPPORT trial. However, we noticed that the letter's salutation was only addressed to Dr. Marchase.

For the SUPPORT Trial (and for the entire Neonatal Research Network) RTI serves as the data coordinating center and we have no oversight of the clinical research. We receive and analyze coded data, and do not have access to the code linking subjects to identifiers.

Given our role and that we are not in the salutation, we assume that OHRP does not expect a formal response from RTI. Would you please confirm if our assumption is correct, and if not, provide guidance on what OHRP would want RTI to provide given our role with the SUPPORT Trial? I leave on vacation tomorrow, so if you could reply to all I would appreciate it. Juesta Caddell is the Director of our IRB office and is the HPA on our FWA.

Thank you.



Dave

\*\*\*\*\*

David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

Phone: 919-316-3903  
Fax: 919-316-3897  
E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

**From:** [Finer, Neil](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Vaucher, Yvonne](#); [Myriam Peralta-Carcelen \(MPeralta@peds.uab.edu\)](#)  
**Cc:** [Wally Carlo](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: Clearance | Vaucher, Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)  
**Date:** Tuesday, June 12, 2012 1:45:02 PM

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Fantastic  
Great job Myriam and Yvonne  
Neil

On 6/12/12 5:39 AM, "Archer, Stephanie (NIH/NICHD) [E]"  
<[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)> wrote:

>The revised SUPPORT FU paper has been cleared by NICHD for submission.

>

>Good luck!

>

>Stephanie

>

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>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](mailto:archerst@mail.nih.gov)

>

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

>From: NICHDWorkflow  
>Sent: Monday, June 11, 2012 7:09 PM  
>To: Archer, Stephanie (NIH/NICHD) [E]  
>Cc: NICHDWorkflow  
>Subject: Clearance Tracking: Journal Article/Scientific Manuscript  
>Clearance Request Approved

>

>The following request for clearance was approved:

>

>Request ID: 3496  
>Request Type: Journal Article/Scientific Manuscript  
>Title: Outcome at 18-22 months of the Surfactant Positive Airway  
>Pressure and Pulse Oximetry Randomized Trial (SUPPORT) (NRN)(Vaucher)  
>Requestor: NIH\archerst  
>Branch/Center/Division: PP/CDBPM  
>Status: Approved

>

>You may access the system at:

><http://insider.nichd.nih.gov/clearancetracking>

>

**From:** Vaucher, Yvonne  
**To:** Wally Carlo, M.D.; Archer, Stephanie (NIH/NICHD) [E]; Myriam Peralta, M.D.  
**Cc:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Clearance | Vaucher, Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)  
**Date:** Tuesday, June 12, 2012 12:39:44 PM

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Thanks to all. Your input really makes a difference!

Yvonne

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, June 12, 2012 6:21 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]; Vaucher, Yvonne; Myriam Peralta, M.D.  
**Cc:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Clearance | Vaucher, Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Congratulations. Great job, Yvonne and Myriam and everyone else for the excellent work.

Wally

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

**From:** "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>  
**To:** "'&apos;Vaucher, Yvonne&apos;," <yvaucher@ucsd.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu>  
**Cc:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, '&apos;Neil Finer&apos;,' <nfiner@ucsd.edu>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Sent:** Tue, Jun 12, 2012 12:40:58 GMT+00:00  
**Subject:** Clearance | Vaucher, Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

The revised SUPPORT FU paper has been cleared by NICHD for submission.

Good luck!

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](mailto:archerst@mail.nih.gov)

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

**From:** NICHDWorkflow  
**Sent:** Monday, June 11, 2012 7:09 PM

To: Archer, Stephanie (NIH/NICHD) [E]

Cc: NICHDWorkflow

Subject: Clearance Tracking: Journal Article/Scientific Manuscript Clearance Request Approved

The following request for clearance was approved:

Request ID: 3496

Request Type: Journal Article/Scientific Manuscript

Title: Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) (NRN)(Vaucher)

Requestor: NIH\archerst

Branch/Center/Division: PP/CDBPM

Status: Approved

You may access the system at: <http://insider.nichd.nih.gov/clearancetracking>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Spong, Catherine (NIH/NICHD) [E]  
**Subject:** FW: "SUPPORT Trial" (HHS Protocol 2U10HD034216)  
**Date:** Tuesday, June 12, 2012 9:54:00 AM

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Cathy

I intend to respond with the following:

1. Dr. Finer was the principal investigator on the CPAP/surfactant portion of the study. Since this was a factorial design, Dr. Wally Carlo was the principal investigator on the oxygen saturation arm of the study. Both Drs. Finer and Carlo were the lead investigators for the study.
2. Each IRB reviewed and approved the trial. There was no central IRB for the study.

Should I copy Yvonne?

Thanks

Rose

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

---

**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Monday, June 11, 2012 5:26 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hello Dr. Higgins,

I'm finishing up my review of the SUPPORT trial and I have a couple quick questions:

1. I noted that Dr. Finer's name and institution (UCSD) is on the template consent. The DSMC minutes list him as the lead investigator for the study. What is (was) Dr. Finer's (UCSD) role in the SUPPORT trial? Is UCSD the lead site?
2. Also, did each of the 21 IRBs review and oversee the trial their institution or did any of the institutions rely on the review of another institution's IRB?

Thanks in advance!  
Lisa Buchanan  
240-453-8298

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

**Sent:** Friday, April 13, 2012 2:53 PM  
**To:** Buchanan, Lisa (HHS/OASH)  
**Subject:** Re: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi

There were no sites outside of the US. Recruitment is complete. However, there is a sub cohort of approximately 500-550 infants enrolled who had neuroimaging who are part of a school age Follow up (FU) study at 6.5-7.5 years of age. The windows are open for FU and will continue through 2016. Data analyses from the 18-22 month FU are in process.

Let me know if you have other questions.

Regards,  
\$rose

---

**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Friday, April 13, 2012 02:40 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good afternoon Rose,

I have two quick questions regarding the study referenced above. Did this trial involve any sites outside of the US? And are all study activities complete/close for all of the sites?

Thanks,  
Lisa

Lisa Buchanan, MAOM, CIP  
Public Health Analyst  
Division of Compliance Oversight  
Office for Human Research Protections  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852  
Ph: 240-453-8298  
Fax: 240-453-6909

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 01, 2012 1:31 PM  
**To:** Buchanan, Lisa (HHS/OASH)  
**Cc:** Borrer, Kristina C (HHS/OASH)  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi,

These were sent and we have confirmed with FED EX that they were delivered – can you confirm that you have them??

Thanks  
Rose

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

---

**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Monday, January 09, 2012 11:40 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Borrer, Kristina C (HHS/OASH)  
**Subject:** "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good morning Dr. Higgins,

I am reviewing responses' to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. OHRP has only opened its investigation with the University of Alabama. However, we would like to review the informed consent documents for all of the sites (~20). The data coordinating center, RTI, recommended that we contact you for this information. (See email below.) Would it be possible for you to provide copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPORT study?

Please feel free to contact me if you have any questions regarding this request.

Thanks,  
Lisa

***Lisa Buchanan, MAOM***  
Public Health Analyst, Division of Compliance Oversight  
Office for Human Research Protections  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852  
Ph: 240-453-8298  
Fax: 240-453-6909

---

**From:** Borasky, David [mailto:[dborasky@rti.org](mailto:dborasky@rti.org)]  
**Sent:** Thursday, August 04, 2011 12:19 PM

**To:** Borrer, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Hi Kristina –

We had a chance to discuss your request with the RTI DCC folks this morning and how RTI may be able to help facilitate this for OHRP.

As I mentioned this morning, the RTI IRB does not require the DCC to provide RTI IRB with copies of the approved informed consent documents for each site. I did confirm that the DCC requires sites to submit copies of study approval notices to the DCC, but they do not require submission of copies of site-level informed consent documents to the DCC. Some sites do include them with the approval notices, but this is not done consistently and may not be done every time a consent document is amended at the site level. Therefore, the DCC's records for site-level consent documents are incomplete.

The RTI IRB and the Neonatal Research Network DCC appreciate your desire to expeditiously obtain site-level informed consent documents for the SUPPORT Trial. We believe that the best way to facilitate this is to have OHRP submit a formal request to the Neonatal Research Network steering committee via the NICHD project officer Rosemary Higgins (contact information below) to have the RTI Data Coordinating Center collect copies of the final approved consent forms (as well as whether or not this is the initially approved documents or all versions that were used with participants for the duration of the study) for each of the SUPPORT Trial sites for transmittal to OHRP.

I hope this is a suitable approach.

Best,

Dave

Dr. Higgins contact information:

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

\*\*\*\*\*



David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

Phone: 919-316-3903  
Fax: 919-316-3897  
E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

---

**From:** Borrer, Kristina C (HHS/OASH) [mailto:[Kristina.Borrer@hhs.gov](mailto:Kristina.Borrer@hhs.gov)]  
**Sent:** Friday, July 29, 2011 4:23 PM  
**To:** Borasky, David  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Dave,  
We were wondering if you would be able to get us copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPRT study. Is that possible?  
Thanks for your assistance.  
Kristina

---

**From:** Borasky, David [mailto:[dborasky@rti.org](mailto:dborasky@rti.org)]  
**Sent:** Monday, July 25, 2011 1:13 PM  
**To:** Borrer, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Thank you for the quick response Kristina.

RTI was not engaged in the conduct of the SUPPORT clinical protocol nor would have been considered the IRB of record. RTI serves as the network data coordinating center for all sites, and in this role received coded data for analysis.

Therefore, as per your email, we will not submit a response to the letter dated July 18, 2011.

Regards,

Dave

\*\*\*\*\*  
David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

Phone: 919-316-3903  
Fax: 919-316-3897  
E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

---

**From:** Borrer, Kristina C (HHS/OASH) [mailto:Kristina.Borrer@hhs.gov]  
**Sent:** Monday, July 25, 2011 1:00 PM  
**To:** Borasky, David  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Dave,

If RTI is not engaged in the research, we do not require any additional information at this time. We'll let you know if we need anything else.

Kristina C. Borrer, Ph.D.

Director

Division of Compliance Oversight

Office for Human Research Protections

1101 Wootton Parkway, Suite 200

The Tower Building

Rockville, MD 20852

email: [kristina.borrer@hhs.gov](mailto:kristina.borrer@hhs.gov)

Phone: (240) 453-8132

Fax: (240) 453-6909

---

**From:** Borasky, David [mailto:dborasky@rti.org]  
**Sent:** Monday, July 25, 2011 11:10 AM  
**To:** Borrer, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** clarification requested

Good morning Kristina,

On Friday we (RTI) received a letter from you that was addressed to both our signatory official (Ward Sax) and the SO of UAB (Dr. Marchase) related to the SUPPORT trial. However, we noticed that the letter's salutation was only addressed to Dr. Marchase.

For the SUPPORT Trial (and for the entire Neonatal Research Network) RTI serves as the data coordinating center and we have no oversight of the clinical research. We receive and analyze coded data, and do not have access to the code linking subjects to identifiers.

Given our role and that we are not in the salutation, we assume that OHRP does not expect a formal response from RTI. Would you please confirm if our assumption is correct, and if not, provide guidance on what OHRP would want RTI to provide given our role with the SUPPORT Trial? I leave on vacation tomorrow, so if you could reply to all I would appreciate it. Juesta Caddell is the Director of our IRB office and is the HPA on our FWA.

Thank you.

Dave

\*\*\*\*\*  
David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

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

**Phone:** 919-316-3903  
**Fax:** 919-316-3897  
**E-mail:** [dborasky@rti.org](mailto:dborasky@rti.org)

**From:** Pablo Sanchez  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Diana Vasil; Lijun Chen; Roy Heyne; Lizette Torres  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; "Gabrio, Jenna"  
**Subject:** RE: Consent and IRB approval  
**Date:** Saturday, June 09, 2012 2:00:48 AM  
**Attachments:** [consent form support follow-up.pdf](#)  
[HIPAA support follow-up.pdf](#)  
[approval letter--irb.docx](#)

---

Hi Rose--attached are the IRB-approved forms--pablo

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Wednesday, June 06, 2012 9:29 AM  
**To:** Pablo Sanchez; Diana Vasil; Lijun Chen; Roy Heyne  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; 'Gabrio, Jenna'  
**Subject:** Consent and IRB approval

Do you have the consent form and IRB approval for:

- SUPPORT Neuroimaging 6-7 Year FU

If so, please forward. If not, let us know your timeframe

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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UT Southwestern Medical Center  
The future of medicine, today.

The University of Texas Southwestern Medical Center at Dallas  
Parkland Health & Hospital System  
Children's Medical Center  
Texas Scottish Rite Hospital for Children

**CONSENT TO PARTICIPATE IN RESEARCH**

Title of Research: Neuroimaging and Neurodevelopmental Outcome: A  
Secondary to Surfactant Positive Airway Pressure and Pulse  
Oximetry Trial (SUPPORT)- Extended SUPPORT NEURO School  
Age Follow-up Study

Sponsor: National Institute of Child Health and Human Development  
(NICHD) Neonatal Research Network (NRN)

Study Doctors: Pablo J. Sánchez, MD  
Roy Heyne, M.D.

Research Personnel: Lizette Torres, RN  
Alicia Guzmán

You may call these study doctors or research personnel during regular office hours at 214-456-6000. At other times, you may call them at 214-456-7000.

Note: If you are a parent or guardian of a minor and have been asked to read and sign this form, the "you" in this document refers to the minor with regards to evaluations involving the child participation and to yourself with regards to evaluations involving you as a parent/guardian.

**Instructions:**

Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

**Why is this study being done?**

This study is being done to see how children, who participated in the earlier trial of neuroimaging and neurodevelopmental outcome: a secondary to surfactant positive airway pressure and pulse oximetry Trial (SUPPORT), are now doing at school age. The purpose of this phase of the study is to examine participants at school age and determine whether near-term MRI is better than ultrasound in predicting physical and developmental outcome. We will also be assessing how body size and growth relate to blood pressure at school age in premature born infants.



### **Why am I being asked to take part in this research study?**

You are being asked to take part in this study because your child participated in the brain imaging part of the SUPPORT study.

### **How many people will take part in this study?**

About 45 children (and their parents/caretakers) will take part in this study at Children's Medical Center. This study also is taking place at a number of other medical facilities around the country. There will be a total of about 370 children (and their parents/caretakers) participating in this research study throughout the United States and/or other countries.

### **What is involved in the study?**

If you agree to be in this study, you will be asked to sign this consent form and will have the following tests and procedures.

#### Procedures and Evaluations during the Research:

At the study visit, you, as parent/caretaker, will be asked to:

1. Provide general information like the child's age and birth date, medical history household makeup, and parent/caretaker education and occupation;
2. Answer questions concerning the child's health, observed behaviors, and the child's day to day activities, including questionnaires of health-related quality of life, specific motor behaviors that can be observed in an everyday setting,
3. Answer questions that assess: attention, problem solving, and planning difficulties, and related learning, behavior, and emotional problems in children,
4. If your child is unable to complete the Weschler Intelligence Scale for Children 4th Edition (WISC-IV), then you will be asked to complete the Pediatric Evaluation of Disability Inventory (PEDI) which includes questions about your child's ability to care for him/herself, to move about, and interact socially.

At the same study visit, your child will undergo the following examinations:

1. Growth measurements, skinfold measurements, blood pressure, and pulse;
2. A test of skills in English (only for Spanish speaking children)
3. A test of child abilities called the WISC-IV (in English or Spanish which involves doing problem solving with words, blocks and pictures;
4. A detailed neurological evaluation by a certified medical examiner, including tests of sensation, manual dexterity, aiming and catching, balance, strength, reflexes, coordination, and ability to walk;
5. The Neurological/Psychological test (NEPSY), a test of your child's ability to pay attention and to solve visual problems;
6. The Woodcock-Johnson III (in English) or the Bateria III Woodcock-Muñoz (in Spanish) a test designed to measure academic achievement.

During the clinic visit, the interviews for you as a parent will take about 1½-2 hours and the time to evaluate your child will take about 3½ hours, including breaks. Some children may take



longer. The interview with you will be at the same time your child is being tested so the whole visit will last about 3½ - 4 hours.

The above procedures are being done primarily for research, not for medical purposes. Even though the researchers are not looking at your results of these tests to find or treat a medical problem, you will be given a summary of how your child performed. You and your regular doctor can decide together whether to follow up with more tests or treatment.

**How long can I expect to be in this study?**

This study will only last for one visit, unless your child is not able to complete all the tests in one visit, in which case we will arrange with you another time to complete the evaluations.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

**What are the risks of the study?**

There are no known risks to the child or responsible adult to participating in the medical/neurological and developmental/psychological testing of this study, though testing may be tiring to some.

Psychological Stress

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break or stop your participation in this study at any time.

Loss of Confidentiality

Any time information is collected; there is a potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Other Risks

There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

**What are the possible benefits of this study?**

If you agree to take part in this study, there may be possible benefits to your child for taking part in this study are identification of possible neurological or developmental problems, and summary information about such, which you may share with the child's regular doctor or another doctor of choice. This may in turn lead to further evaluation and/or treatment as decided by the child's doctor/s. However, the researchers cannot guarantee that you will benefit from participation in this research.

We hope the information learned from this study will benefit others who are born prematurely and may help us treat infants in the future.



**What options are available if I decide not to take part in this research study?**

This is not a treatment study. You do not, have to be part of it to get treatment for your condition.

**Will I be paid if I take part in this research study?**

Yes. You will be given a \$150.00 at the end of the study visit if you take part in this research. If you stop taking part in this study or are withdrawn by the research team, you will not receive payment.

Your social security number (SSN) will be given to The University of Texas Southwestern Medical Center in order to process your payment as required by law. This information will remain confidential unless you give your permission to share it with others, or if we are required by law to release it.

If you are an employee of UT Southwestern, your payment will be added to your regular paycheck and income tax will be deducted.

UT Southwestern, as a State agency, will not be able to make any payments to you for your participation in this research if the State Comptroller has issued a "hold" on all State payments to you. Such a "hold" could result from your failure to make child support payments or pay student loans, etc. If this happens, UT Southwestern will be able to pay you for your taking part in this research 1) after you have made the outstanding payments and 2) the State Comptroller has issued a release of the "hold."

You will be reimbursed for transportation to and from the research center (for example cab or bus fare) if needed. In order to receive reimbursement you will need to turn in all your receipts to the research coordinator.

**Will my insurance provider or I be charged for the costs of any part of this research study?**

No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

**What will happen if I am harmed as a result of taking part in this study?**

It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center, Children's Medical Center, Parkland Health & Hospital System, and/or Texas Scottish Rite Hospital for Children.

You retain your legal rights during your participation in this research

**Can I stop taking part in this research study?**





Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor may be a research investigator in this study. He is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

**Will my information be kept confidential?**

Medical information collected during this study and the results of any test or procedure done may be included in your medical record and this information may be available to health care providers and authorized persons including your insurance company.

You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- National Institutes of Child Health and Human Development;
- Representatives of government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people, and
- The UT Southwestern Institutional Review Board.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Will I be contacted in the future?

You have the option to elect to be contacted in the future in order to obtain follow-up information or to ask you to take part in more research. (A "no" answer will not disqualify you from this research.)

Yes \_\_\_\_\_ initials

No \_\_\_\_\_ initials

If you elect "yes", please keep in touch with Dr. Sanchez and maintain a current address and telephone number on file. Please notify Dr. Sanchez if your legal name changes.

**Whom do I call if I have questions or problems?**

For questions about the study, contact Pablo Sanchez, M.D. or Roy Heyne, M.D. at 214-648-



3753 during regular business hours and at 214-456-7000 after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

**SIGNATURES:**

**YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.**

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

\_\_\_\_\_  
Participant's Name (printed)

\_\_\_\_\_  
Legally authorized representative's Name (printed)

\_\_\_\_\_  
Legally authorized representative's Signature

\_\_\_\_\_  
Date & Time

\_\_\_\_\_  
Name of person obtaining consent (printed)

\_\_\_\_\_  
Signature of person obtaining consent

\_\_\_\_\_  
Date & Time



**The University of Texas Southwestern Medical Center at Dallas  
Children's Medical Center of Dallas, Parkland Health & Hospital System  
Retina Foundation of the Southwest, Texas Scottish Rite Hospital for Children  
The University of Texas Southwestern Moncrief Cancer Center**

**Authorization for Use and Disclosure of  
Health Information for Research Purposes**

NAME OF RESEARCH PARTICIPANT: \_\_\_\_\_

**What is the purpose of this form?**

This authorization describes how information about you and your health will be used and shared by Dr. Roy Heyne and his staff when you participate in the research study: Neuroimaging and Neurodevelopmental Outcome: A Secondary to Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) - Health information is considered "protected health information" when it may directly identify you as an individual. By signing this form you are agreeing to permit the researchers and others (described in detail below) to have access to and share this information. If you have questions, please ask a member of the research team.

**Who will be able to use or share my health information?**

*Parkland Health & Hospital System & Children's Medical Center* may use or share your health information with Dr. Roy Heyne and his staff at UT Southwestern Medical Center for the purpose of this research study.

**Will my protected health information be shared with someone other than the Researchers?**

Yes, the Researchers may share your health information with others who may be working with the Researchers on the Research Project for purposes directly related to the conduct of this research study or as required by law. These other people or entities include:

- Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD) of the National Institute of Health (NIH). The sponsor includes any people, entities, groups or companies working for or with the sponsor or owned by the sponsor. The sponsor will receive written reports about your participation in the research. The sponsor may look at your health information to assure the quality of the information used in the research.
- Neonatal Research Network. These are other research facilities that are working with UT Southwestern on the Research Project.
- Research Triangle Institute (RTI), Data Safety Monitoring Board. These organizations need access to your health information to assist the Researchers in the Research Project.
- The UT Southwestern Institutional Review Board (IRB). This is a group of people who are responsible for assuring that the rights of participants in research are respected. Members and staff of the IRB at UT Southwestern may review the records of your participation in this research. A representative of the IRB may contact you for information about your experience with this research. If you do not want to answer their questions, you may refuse to do so.



- **Representatives of domestic and foreign governmental and regulatory agencies may be granted direct access to your health information for oversight, compliance activities, and determination of approval for new medicines, devices, or procedures.**

Medical information collected during this study and the results of any test or procedure done may be included in your medical record and this information may be available to health care providers and authorized persons including your insurance company.

**How will my health information be protected?**

Whenever possible your health information will be kept confidential as required by law. Federal privacy laws may not apply to other institutions, companies or agencies collaborating with UT Southwestern on this research project. There is a risk that the Recipients could share your information with others without your permission. UT Southwestern cannot guarantee the confidentiality of your health information after it has been shared with the Recipients.

**Why is my personal contact being used?**

Your personal contact information is important for the UT Southwestern Medical Center research team to contact you during the study. However, your personal contact information will not be released without your permission.

**What health information will be collected, used and shared (disclosed)?**

The Researchers will collect the following information from the child's medical records and/or caregivers: Name(patient, mother), medical record number, birth history, vital signs, audiology results, ophthalmology results, medications, surgeries, physical and mental history, radiology results, hospitalizations, ER visits, clinic visits, developmental exams, imaging results and nutrition information.

**Will my health information be used in a research report?**

Yes, the research team may fill out a research report. (This is sometimes called "a case report".) The research report will not include your name, address, or telephone or social security number. The research report may include your date of birth, initials, dates you received medical care and a tracking code. The research report will also include information the research team collects for the study.

**Will my health information be used for other purposes?**

Yes, the Researchers and Recipients may use your health information to create research data that does not identify you. Research data that does not identify you may be used and shared by the Researchers and Recipients in a publication about the results of the Research Project or for other research purposes not related to the Research Project.

**Do I have to sign this authorization?**

No, this authorization is voluntary. Your health care providers will continue to provide you with health care services even if you choose not to sign this authorization. However, if you choose not to sign this authorization, you cannot take part in this Research Project.

**How long will my permission last?**

This authorization has no expiration date. You may cancel this authorization at any time. If you decide to cancel this authorization, you will no longer be able to take part in the Research Project. The Researchers may still use and share the health information that they have already collected



before you canceled the authorization. To cancel this authorization, you must make this request in writing to: Roy Heyne, MD, 5323 Harry Hines Blvd. Dallas, TX 75390-9063. Phone 214-648-3753

**Will I receive a copy of this authorization?**

Yes, a copy of this authorization will be provided to you.

**Signatures:**

By signing this document you are permitting UT Southwestern Medical Center to use and disclose health information about you for research purposes as described above.

\_\_\_\_\_  
Signature of Research Participant

\_\_\_\_\_  
Date

**For Legal Representatives of Research Participants (if applicable):**

Printed Name of Legal Representative: \_\_\_\_\_

Relationship to Research Participant: \_\_\_\_\_

*I certify that I have the legal authority under applicable law to make this Authorization on behalf of the Research Participant identified above. The basis for this legal authority is:*

\_\_\_\_\_  
(e.g. parent, legal guardian, person with legal power of attorney, etc.)

\_\_\_\_\_  
Signature of Legal Representative

\_\_\_\_\_  
Date





From: Ahamed Idris  
Institutional Review Board Chairperson  
IRB - 8843

To: Pablo Sanchez , Diana Vasil , Karen Kirby

Date: June 8, 2012

Re: Modification Approval

IRB Number: STU 032011-151

Modification Number: Mod2\_STU 032011-151

Title: Neuroimaging and Neurodevelopmental Outcome: A  
Secondary to Surfactant Positive Airway Pressure and  
Pulse Oximetry Trial (Support-IRB File #012005-019)

Documents: Extended Follow-up Protocol dated 02/2011 and  
Secondary Extended Follow-up Manual of Operations  
dated 3/1/2012 , Consent Form and HIPAA  
Authorization

A modification to the above referenced study (adding extended follow-up sub-studies) has been approved by the UT Southwestern Institutional Review Board (IRB) via an expedited review procedure on May 23, 2012 in accordance with 45 CFR 46.110(a)-(b)(2). The approval period for the modified research study will begin on June 8, 2012 and lasts until March 20, 2013.

If you have any questions related to this approval letter or about IRB policies and procedures, please telephone the IRB Office at 214-648-3060.

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Warning: This is a private message for authorized UT Southwestern employees only. If the reader of this message is not the intended recipient you are hereby notified that any dissemination, distribution or copying of this information is STRICTLY PROHIBITED.



University of Texas Southwestern Medical Center  
Institutional Review Board

5323 Harry Hines Boulevard  
Dallas, Texas 75390-8843  
Room C1.206  
phone: 214-648-3060  
fax: 214-648-2171

**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Enrolled vs Eligible/Nonenrolled FUP  
**Date:** Thursday, June 07, 2012 6:49:15 PM

---

Rose,

Any consensus on email or conference call?

Yvonne

**Yvonne E. Vaucher, M.D., M.P.H.**  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812



**From:** [Wrage, Lisa Ann](#)  
**To:** [Kennedy, Kathleen A](#)  
**Cc:** [Phelps, Dale](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#)  
**Subject:** RE: Updated ROP Secondary Manuscript  
**Date:** Thursday, June 07, 2012 2:09:24 PM  
**Attachments:** [ROP Nat Hist\\_update 7 June 2012.doc](#)  
[ROP Natural History Study Manuscript\\_edlw07June12.doc](#)

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Hi,

I have attached an updated analysis summary document and the latest version of the manuscript with my comments. FYI while I was going through my analysis I found a couple of minor programming errors that I corrected & made the corresponding (minor) corrections in the documents, so you will notice a few places where numbers change slightly from previous.

A couple of other things in response to questions (below):

--The baby who had severe ROP on first exam was 33 weeks PMA at that time.

--There are 3 babies who had severe ROP who had previously had an exam in zone 3.

Let me know if you have any questions.

Thanks.

Lisa

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Wednesday, June 06, 2012 1:47 PM  
**To:** Wrage, Lisa Ann  
**Cc:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD)  
**Subject:** RE: Updated ROP Secondary Manuscript

Fine with me.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

---

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Wednesday, June 06, 2012 12:24 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wrage, Lisa Ann'; Kennedy, Kathleen A  
**Subject:** RE: Updated ROP Secondary Manuscript

Thank you, agree.

Dale

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, June 06, 2012 10:15 AM  
**To:** 'Wrage, Lisa Ann'; Kennedy, Kathleen A; Phelps, Dale  
**Subject:** RE: Updated ROP Secondary Manuscript

Use what was used for the growth secondary study – we need to be consistent across analyses

Thanks

Rose

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

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Wednesday, June 06, 2012 1:09 PM  
**To:** Kennedy, Kathleen A; Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Updated ROP Secondary Manuscript

Hello,

You've asked me to include SGA in Table 1 of the paper. For the SUPPORT growth secondary study we used the Olsen curves (Pediatrics 2010) (recommended by Richard Ehrenkranz). For a long time we used Alexander to define SGA on NRN papers.

Is Olsen ok with you?

Thanks.

Lisa

---

**From:** Wrage, Lisa Ann  
**Sent:** Tuesday, May 29, 2012 12:46 PM  
**To:** 'Kennedy, Kathleen A'; Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Updated ROP Secondary Manuscript

I guess the SUPPORT data for some reason did not include all. Marie made it a point to let me know of these options so that you would know. It is based on inborn infants.

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Tuesday, May 29, 2012 12:35 PM  
**To:** Wrage, Lisa Ann; Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Updated ROP Secondary Manuscript

I don't understand why there were 3404 infants who met the GA criteria in the SUPPORT papers and 4369 when additional info was obtained from GDB. Maybe the SUPPORT screening logs were incomplete and they weren't cross-checked against the GDB in the rush to get the SUPPORT papers out. As long as we're sure that the 4369 were all inborn (no outborn infants in the GDB because of NEST or some other reason), that seems like the right number to me.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

---

**From:** Wrage, Lisa Ann [mailto:wrage@rti.org]  
**Sent:** Tuesday, May 29, 2012 11:26 AM  
**To:** Kennedy, Kathleen A; Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Updated ROP Secondary Manuscript

And some more from me in blue.

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Tuesday, May 29, 2012 11:58 AM  
**To:** Wrage, Lisa Ann; Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Updated ROP Secondary Manuscript

New responses are in gray. (Dale beat me by a hair and used the same color but I don't think we disagree on anything.)

Kathleen A. Kennedy, MD, MPH  
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Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
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713 500-6708

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Friday, May 25, 2012 3:39 PM  
**To:** Wrage, Lisa Ann  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie; Phelps, Dale  
**Subject:** Updated ROP Secondary Manuscript

I hope this will be our last pass at this before we send it out to the SUPPORT Subcommittee. Here's what's left to be done:

For a long time, there's been a comment in the draft about you or Marie still working on the information about eligible non-enrolled subjects. Has that been resolved?

From Lisa: I probably should have changed that comment—I needed to review the options that Marie had pointed out to me which I eventually did and then summarized in that footnote comment, now I really just need to know which number you prefer.

~~Summarized in the footnote comment on actual doc. In email? The only one I see this on~~  
~~From Lisa: I probably should have changed that comment—I needed to review the options that Marie had pointed out to me which I eventually did and then summarized in that footnote comment, now I really just need to know which number you prefer.~~  
Of 3546 infants screened, 3404 inborn infants met inclusion criteria for gestational age (SUPP02 question A.1=Y). This number is under review and will be updated, the update will not affect other numbers.

\*\*From Lisa: It looks like the update came in the 2/24/12 version, here's what it says:

<sup>1</sup> This number is still under review and may be updated, the update will not affect other numbers.

The number 4369 is based on using the GDB + SUPPORT enrollment information and includes 1316 enrolled infants plus an additional 3053 infants of GA 24-27 6/7 weeks born at participating NRN sites during SUPPORT study enrollment who were not enrolled. These numbers are consistent with what is currently being used for the Antenatal consent paper.

\*\*A few comments on possibly using other numbers\*\*:

Based on the SUPPORT data alone: Of 3546 infants screened; 3404 inborn infants met inclusion criteria for gestational age (SUPPO2 question A.1=Y). The number '3546' is the number given in the flowchart for the main trial papers: i.e. "3546 were assessed for eligibility".

Lisa, when we say that no babies had treatable ROP before 31 weeks, I think it's important to note that 1 baby had ROP on the initial exam (based on the foot note in the flow diagram dated 12/16/11). Do you know that baby's PMA at the time of the exam?

Kathleen, I would also want to know what severity it was. -Dale

From Lisa: OK, I will get this info.

We don't have any information in the paper right now about how many babies developed severe ROP after 1 exam with vessels in Zone III. We now have a statement that most of the adjudicated outcomes were for babies who had only 1 exam in Zone III documented. From Lisa: Are you referring to something I sent to you? I summarized reviewer information re: the adjudicated outcomes in the footnotes, but I don't recall getting this information, I am not sure where Dale got it, please clarify.

\*\* From Lisa: OK, like I said, I have not looked at those exams.

Is it true that none of those adjudicated babies were judged to have severe ROP? From Lisa: Yes, in my summary footnote it says that no reviewer gave result 'b' (Probably did meet criteria for ROP intervention...) It might be useful to others who are planning trials to know this. We could also get at the same question by reporting how many babies who followed the study screening criteria developed severe ROP after having 1 exam with vessels in Zone III.

Another way to ask it would be: Among infants who had a first examination in zone III, how many were in zone were NOT in zone III on their next examination? (i.e. went back to zone II). This actually is a valuable clinical and research piece of information. I believe it ran 12% in the CRYO-ROP data (in Reynolds paper). I know we have it somewhere in the STOP-ROP data too - but I would really have to go digging to find it. -Dale

From Lisa: Would you please clarify what you want here; this sounds like two different things (what Kathleen is describing vs. what Dale is describing) thanks.

\*\*From Lisa: OK, what you requested does sound pretty straightforward, what Dale requested would take longer, I will just first do the higher priority one (yours).

There are a few more specific comments/requests in the document.

The figures that we have were sent to me in PowerPoint and inserted into the Word document. That's been working for manuscript drafts and the poster. For the submission to Pediatrics, we will need TIFF, EPS, or PDF files. They won't accept PowerPoint files. It looks like color is ok as long as they are in CMYK mode, but there will be an extra charge (still trying to figure out how much). I think the bar graph could be done in black and white and shades of gray. The cumulative incidence graphs that have only 1 plot per graph would be ok in black and white. The ones that have separate plots for each GA would be hard to do in black and white. Unless someone else has a suggestion on how to do those, we might have to pay for the color graphs for those.

From Lisa: So do you need me to re-do the bar graph and graphs with 1 plot using black/white (& grays for the bar plot), or are you still thinking about it re; cost.

Do you know any more about I do about... usually... at R... All of my experience is with making my own figures using SigmaPlot in using making black and white figures with... font and... has than what... done with data. I haven't seen figures like the... you've done... by the... will find a color bar graph from the... paper... been able... was... for that. I'm... going to... you... figure out...

\*\* From Lisa: My experience is that I typically do the figures and just edit as requested, e.g. change the colors as you are requesting, or make thicker lines, edit for the specific manuscript, or whatever. People sometimes themselves edit what I send to them, and a couple of times someone had done some of their own graphs. I guess it is just a personal preference.

When we started the data analysis process, we had a single document with all the analyses and figures together. Since that time there have been many updates sent in different emails. Do you have a single document of the "final" analyses and figures that I can check against what's in the "final" version of the manuscript?

From Lisa: Yes, I am going through everything and will send an updated final version.

From Lisa: Thanks!

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Director, MS in Clinical Research Degree Program  
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713 500-6708

1

### Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A Kennedy, Lisa A Wrage, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Michelle Walsh, Abbot Laptook, Roger Faix, Brad Yoder, Kurt Schibler, Marie Gantz, Abhik Das, Nancy Newman, Wade Rich, Dale L Phelps

**Comment [KKA1]:** 2257 words excluding title page, abstract, tables, figure legends, and references, needs to be <=3000

#### Abbreviations:

GA – gestational age  
PMA – postmenstrual age  
ROP – retinopathy of prematurity  
SUPPORT – Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

#### Keywords

retinopathy of prematurity, screening, extremely preterm infants

#### Corresponding author:

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713 500-0519 (fax)  
Kathleen.A.Kennedy@uth.tmc.edu

#### Acknowledgments:

**Comment [KKA2]:** Stephanie is working on this. We also need the degrees and correct institutional affiliations for all the authors.

1

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

Comment [KKA3]: Limit each to 40 words

**What This Study Adds**

Our data do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, challenge the accepted notion that the onset of ROP is better correlated with postmenstrual than chronological age.

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Comment [KKA4]:** 259 words, needs to be <=250

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Results:** 1316 infants were enrolled. 997 of the 1121 who survived to first eye exam had an ROP outcome determined by examination or adjudication. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Comment [w5]:** This number does not include any of those infants with adjudicated outcome.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

**Comment [KKA6]:** Last PubMed search of "ROP AND screening" was done on 2/7/12

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27<sup>6</sup>/<sub>7</sub> weeks gestational age who were enrolled in the NICHD Surfactant, Positive



Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

### Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0</sup>/<sub>7</sub> – 27<sup>0</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: Unfavorable (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) vs Favorable (full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

### Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1901 survived to ROP determination (Figure 1). 94 of these outcomes were adjudicated; the most common reason for adjudication was a single examination with vessels or ROP in zone III (no documented second consecutive zone III exam). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. 67% (664/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of patient enrollment

**Comment [w7]:** Just for, we also collected lowest zone of any vessels, retinal detachment info, treatment related variables, location of exam, and some other final status variables on that form.

**Comment [w8]:** Possibly slightly confusing to variably describe the outcome as 'Severe ROP', 'Unfavorable', or simply 'Type I ROP'. I think our flowchart is pretty clear that we used Type I or treated ROP as our outcome (same as main study).

**Comment [KKA9]:** Lisa, this comment has been here for a while. Do you know if anyone is working on it? The number who met GA inclusion criteria is still being reviewed. 4369 is based on SUPPORT and GDB data (need to verify that it's all inborn, not some outborns who had GDB data because they were enrolled in other trials). Main SUPPORT papers say that 3546 were assessed for eligibility and 3404 met GA criteria. We need to clarify this, may need to explain the discrepancy.

**Comment [w10R9]:** Check the flowchart footnote for that top box for explanation; And yes the numbers for inborn infants.

**Comment [w11]:** 1091

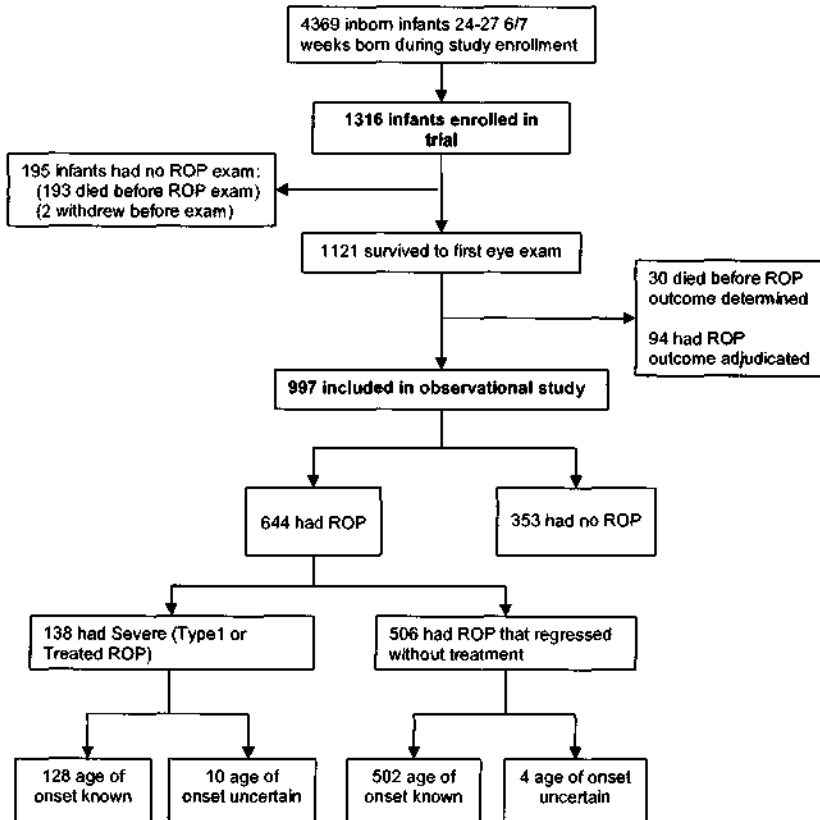
**Comment [KKA12]:** I got this from Dale's email on 4/25. Lisa, could you please verify. Your email from 2/24 has info about the adjudicated outcomes but it doesn't say what the reason for needing adjudication was.

**Comment [w13R12]:** Dale said this was her assumption. I have never looked at this.

**Comment [KKA14]:** Lisa, Dale has asked whether any of the deaths had known age of onset and could therefore be used in the cohort for this paper. If the 30 deaths really were "death before ROP determination" (what I was assuming), the answer would be no. If it is actually death before discharge (the other component of the primary outcome according to the SUPPORT ROP manuscript), then there could be a few. Could you please clarify?

**Comment [w15R14]:** You are right, it is only deaths before final ROP status determined and not all of the deaths.

**Comment [w16]:** It is 644/997 (65%)



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)		
		All ROP Outcomes	By ROP Outcome Category	
			No ROP	Any ROP <sup>1</sup>

Comment [KKA17]: Lisa, could we add SGA to this table?  
 Comment [w18R17]: Done.

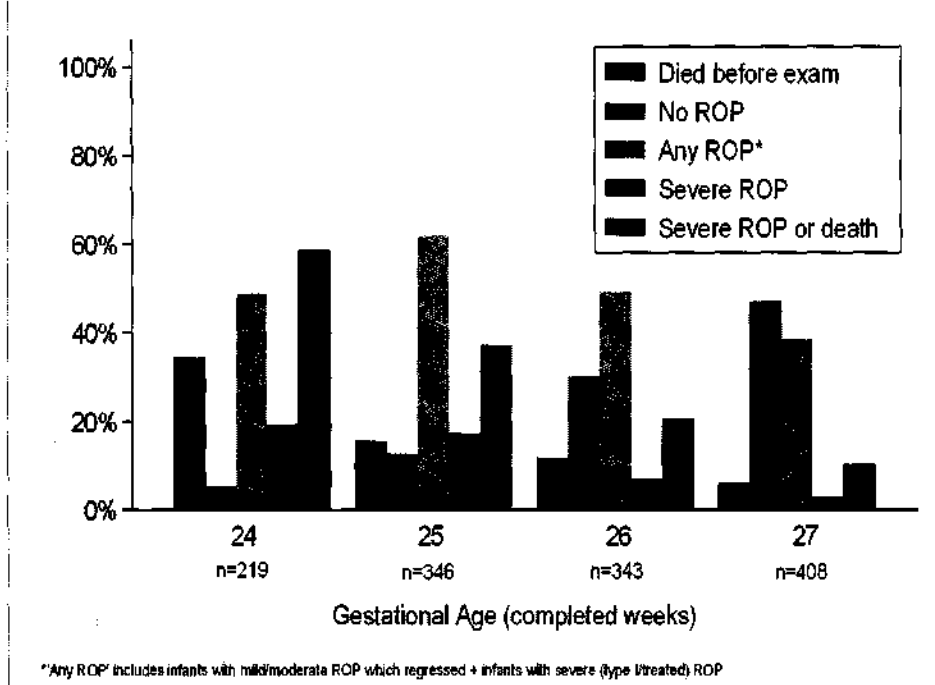
n	1316	997	353	644	138
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.1)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup>	173 (13.2)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



Comment [KKA19]: From 4/4/ email.

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a longer duration of supplemental oxygen than infants without ROP.

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on supplemental oxygen (mean (SD))	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [n (%)]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

<sup>2</sup> missing data

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3.

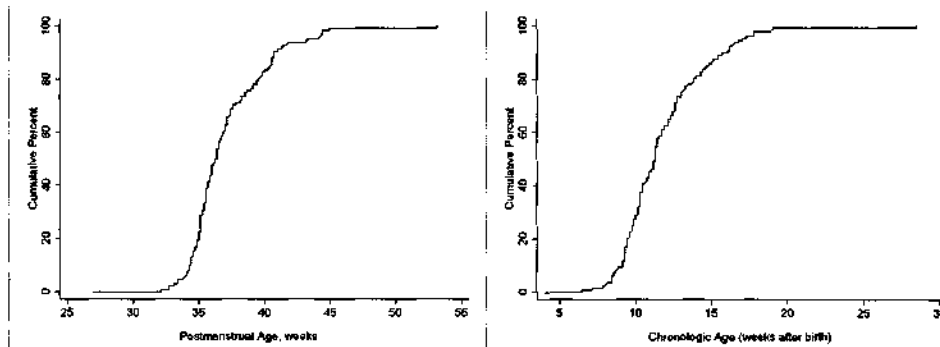
**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

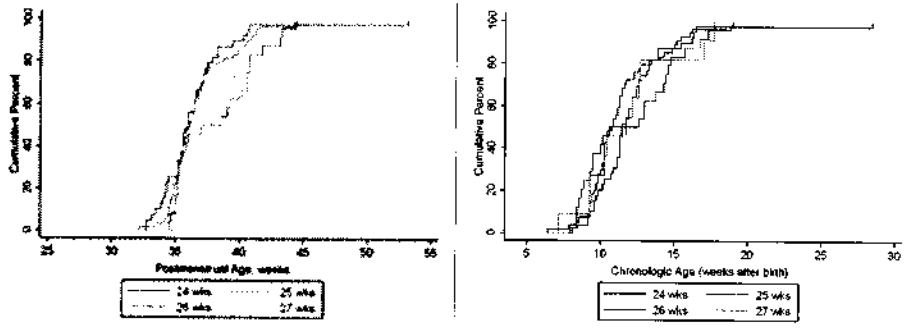
**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



Comment [KKA20]: From 4/27 email

These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**

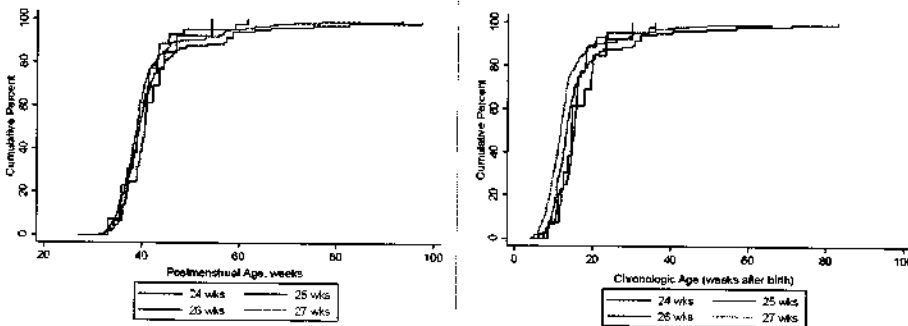


Comment [KKA21]: From 3/29 email

Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth.

Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth

**No ROP**

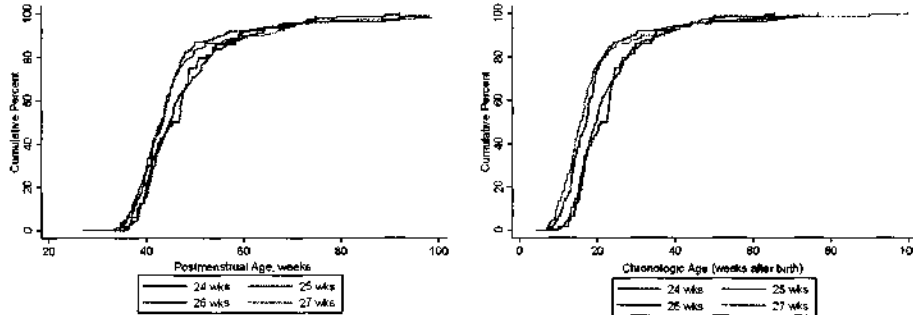


Comment [KKA22]: Lisa, I assume you used the date of the second exam with vessels in zone III for this. Is that correct?

Comment [w23R22]: Yes, if the final ROP outcome was determined by two consecutive exams in zone III, then yes, the second date is the one used.

Comment [KKA24]: From 4/3 email

**Mild/Moderate ROP**



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and	10 (71.4%)	196 (37.2%)

**Comment [law25]:** Just to be clear, this table was based on the exam just prior to discharge.

any stage ROP in any zone		
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50)	148 (28)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

## Discussion

In prior ROP natural history studies,<sup>3</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>2</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum (<750g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological



age and severe ROP did not occur before 6 weeks. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>14</sup>

## Conclusion

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

## References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 1988; 81: 697-706.

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- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 1998; 338: 1572-1576.
  - <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
  - <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233-250.
  - <sup>9</sup> Good WV, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
  - <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tomqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
  - <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.
  - <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
  - <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
  - <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.

**Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

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**Comment [KKA1]:** 2257 words excluding title page, abstract, tables, figure legends, and references, needs to be <=3000

**Abbreviations:**

GA – gestational age  
PMA – postmenstrual age  
ROP – retinopathy of prematurity  
SUPPORT -- Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial

**Keywords**

retinopathy of prematurity, screening, extremely preterm infants

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**Acknowledgments:**

**Comment [KKA2]:** Stephanie is working on this. We also need the degrees and correct institutional affiliations for all the authors.

**What's Known on this Subject**

Timely treatment of retinopathy of prematurity is necessary to optimize outcomes. Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment is now recommended, so updated information regarding the timing of onset of ROP is needed.

**Comment [KKA3]:** Limit each to 40 words

**What This Study Adds**

Our data do not support a change in the 2006 screening guidelines for infants 24-26 6/7 weeks gestation at birth. Our findings, however, challenge the accepted notion that the onset of ROP is better correlated with postmenstrual than chronological age.

## Abstract

**Objective:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Patients and Methods:** Data from the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the trial. Inborn infants of 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included. ROP examinations followed current screening recommendations with follow-up until final eye outcome was determined.

**Results:** 1316 infants were enrolled, 997 of the 1121 who survived to first eye exam had an ROP outcome determined by examination or adjudication. 138 met criteria for severe ROP and 128 (93%) of those had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 1.4% developed severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines, although our results may not be generalizable to infants less than 24 weeks gestational age. Among infants treated for ROP, some do not meet treatment criteria until after discharge home.

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27 6/7 weeks gestational age who were enrolled in the NICHD Surfactant, Positive

**Comment [KKA4]:** 259 words, needs to be <=250

**Comment [w5]:** This number does not include any of those infants with adjudicated outcome.

**Comment [KKA6]:** Last PubMed search of "ROP AND screening" was done on 2/7/12

Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>11</sup> to determine if the current ROP screening guidelines were appropriate to identify Type 1 ROP in a contemporary cohort of infants.

## Patients and Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0</sup>/<sub>7</sub> – 27<sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until one of the study endpoints: Unfavorable (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) vs Favorable (full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams without stage 3 ROP or plus disease). Required ROP follow-up ended at 55 wks postmenstrual age (PMA) but final outcomes were verified at the 18-22 month neurodevelopmental follow-up evaluation.

Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

## Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1901 survived to ROP determination (Figure 1). 94 of these outcomes were adjudicated; the most common reason for adjudication was a single examination with vessels or ROP in zone III (no documented second consecutive zone III exam). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome. 67% (664/997) of these infants developed ROP and 14% (138/997) developed severe ROP. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of patient enrollment

**Comment [w7]:** Just fig. we also collected lowest zone of any vessels, retinal detachment info, treatment related variables, location of exam, and some other final status variables on that form.

**Comment [w8]:** Possibly slightly confusing to variably describe the outcome as "Severe ROP", "Unfavorable", or simply "Type I ROP". I think our flowchart is pretty clear that we used Type I or treated ROP as our outcome (same as main study).

**Comment [KKA9]:** Lisa, this comment has been here for a while. Do you know if anyone is working on it? The number who met GA inclusion criteria is still being reviewed. 4369 is based on SUPPORT and GDB data (need to verify that it's all inborn, not some outboms who had GDB data because they were enrolled in other trials). Main SUPPORT papers say that 3546 were assessed for eligibility and 3404 met GA criteria. We need to clarify this, may need to explain the discrepancy.

**Comment [w10R9]:** Check the flowchart footnote for that top box for explanation. And yes the number is for inborn infants.

**Comment [w11]:** 1091

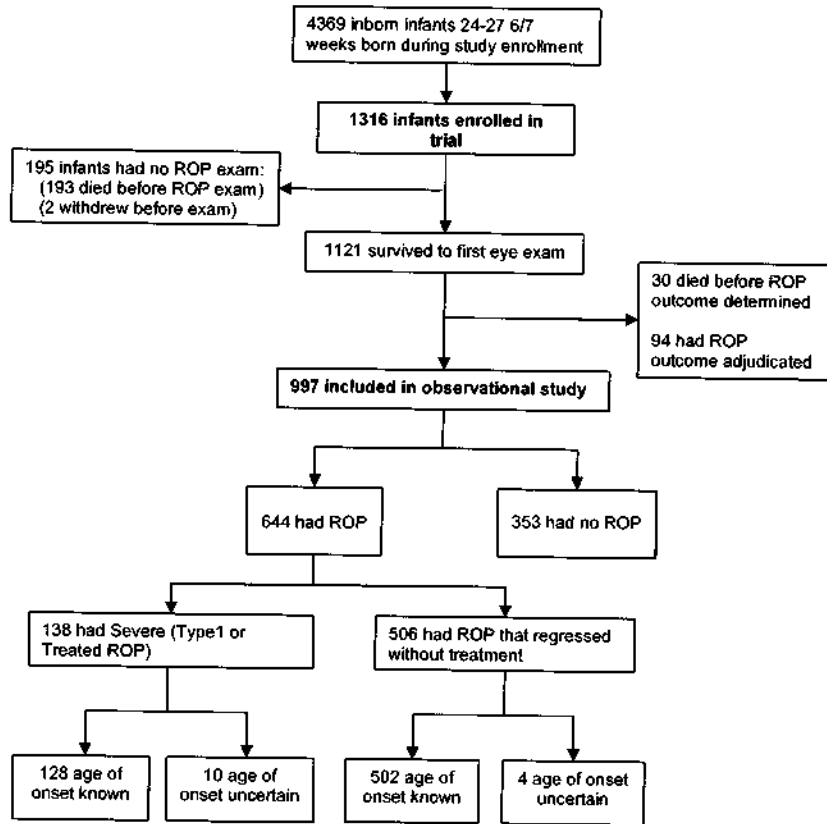
**Comment [KKA12]:** I got this from Dale's email on 4/25. Lisa, could you please verify. Your email from 2/24 has info about the adjudicated outcomes but it doesn't say what the reason for needing adjudication was.

**Comment [w13R12]:** Dale said this was her assumption. I have never looked at this.

**Comment [KKA14]:** Lisa, Dale has asked whether any of the deaths had known age of onset and could therefore be used in the cohort for this paper. If the 30 deaths really were "death before ROP determination" (what I was assuming), the answer would be no. If it is actually death before discharge (the other component of the primary outcome according to the SUPPORT ROP manuscript), then there could be a few. Could you please clarify?

**Comment [w15R14]:** You are right, it is only deaths before final ROP status determined and not all of the deaths.

**Comment [w16]:** It is 644/997 (65%)



The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)		
		All ROP Outcomes	By ROP Outcome Category	
			No ROP	Any ROP <sup>1</sup>

Comment [KKA17]: Lisa, could we add SGA to this table?  
 Comment [w18R17]: Done.

<b>n</b>	<b>1316</b>	<b>997</b>	<b>353</b>	<b>644</b>	<b>138</b>
Gestational age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.1)	25.5 (0.9)
Birth weight [mean (SD)]	830 (193)	849 (190)	942 (173)	798 (180)	708 (148)
SGA <sup>2</sup>	173 (13.2)	117 (11.7)	22 (6.2)	95 (14.8)	30 (21.7)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

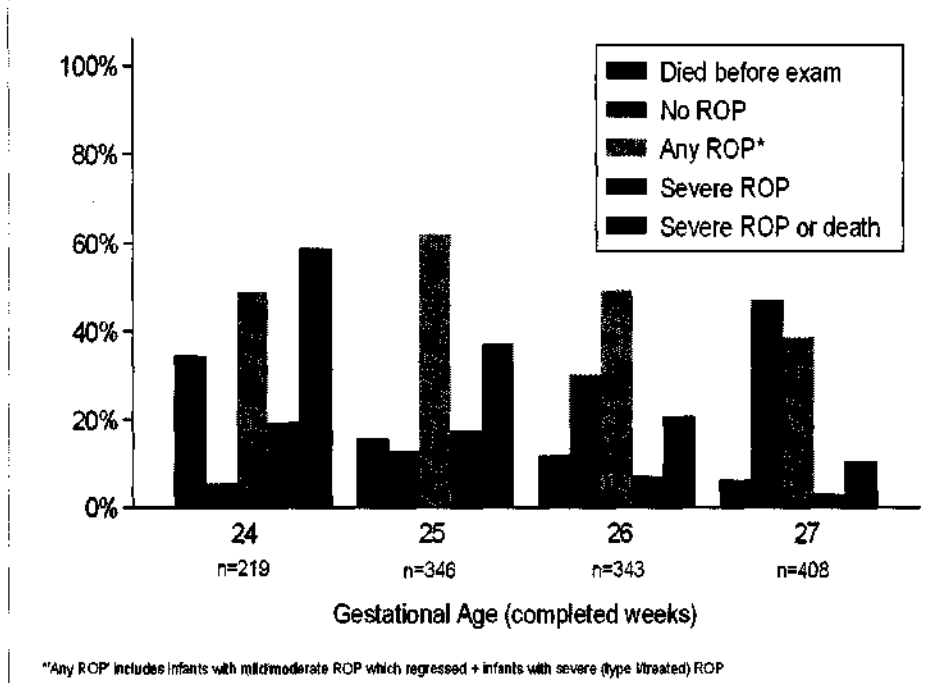
<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

<sup>2</sup> based on Olsen growth curves (Pediatrics, 2010)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.



**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



Comment [KKA19]: From 4/4/ email.

As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for severe ROP are shown in Table 2. Consistent with prior observational studies, as compared to infants without ROP, infants with ROP more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus. In contrast to prior studies, infants with ROP did not have a longer duration of supplemental oxygen than infants without ROP.

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on supplemental oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset sepsis (+ culture) [n (%)]	75 (21.3)	247 (38.4)	76 (55.1)
Fungal sepsis [n (%)]	2 (0.6)	23/643 <sup>2</sup> (3.6)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8.2)	98/643 <sup>2</sup> (15.2)	29 (21.0)
Proven necrotizing enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent ductus arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type 1/treated) ROP (n=138).

<sup>2</sup> missing data

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3.

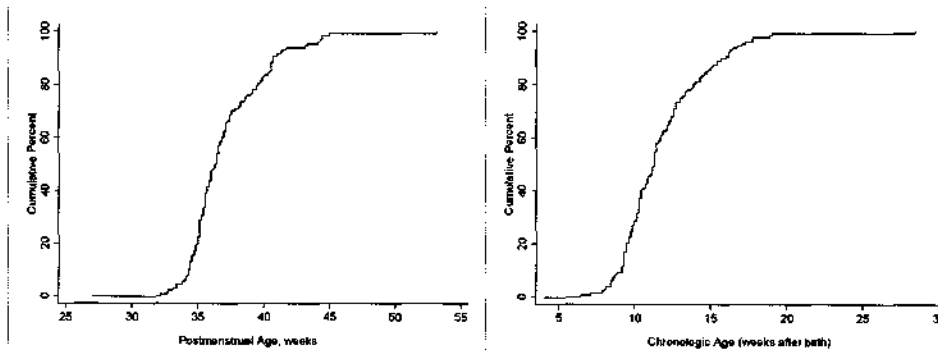
**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	635	29.3	30.4	31.4	32.7	33.9	35.1	38.0	41.0	46.7	4.0	4.6	5.4	6.9	8.0	9.4	11.9	15.3	19.7
Type 2 ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

<sup>2</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

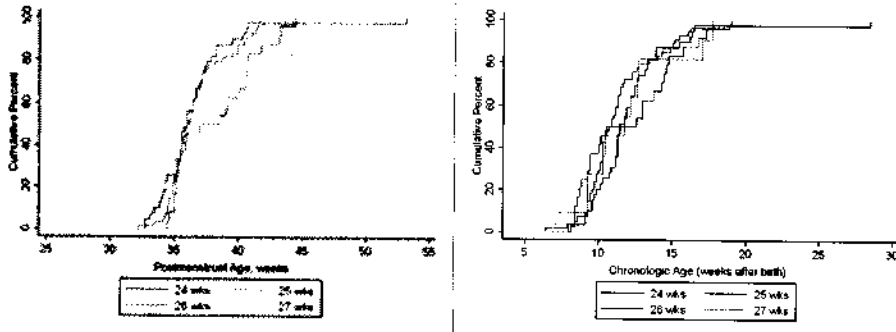
**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



Comment [KKA20]: From 4/27 email

These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**

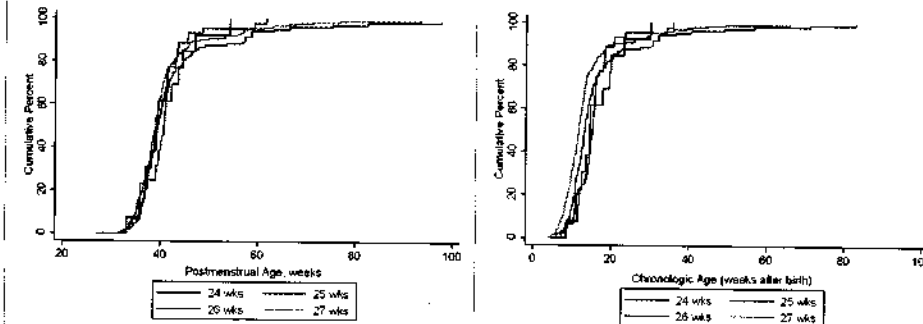


Comment [KKA21]: From 3/29 email

Our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 5 for infants who never had ROP and for infants who had mild or moderate ROP. The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth.

Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth

No ROP

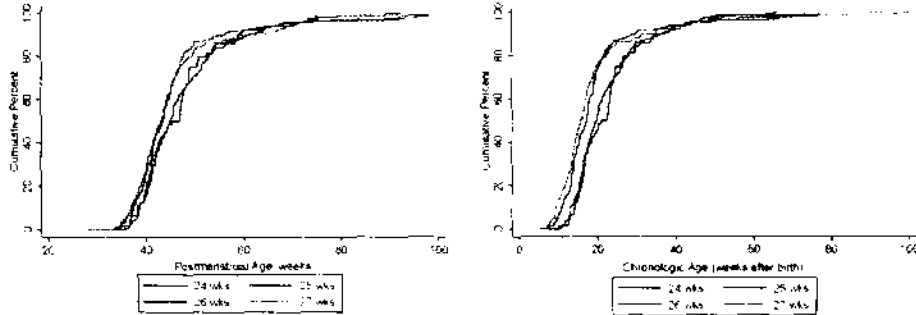


Comment [KKA22]: Lisa, I assume you used the date of the second exam with vessels in zone III for this. Is that correct?

Comment [w23R22]: Yes, if the final ROP outcome was determined by two consecutive exams in zone III, then yes, the second date is the one used.

Comment [KKA24]: From 4/3 email

Mild/Moderate ROP



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

In this referral center cohort of 997 infants, 1 (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and	10 (71.4%)	196 (37.2%)

**Comment [law25]:** Just to be clear, this table was based on the exam just prior to discharge.

any stage ROP in any zone		
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

Table 6. Risk factors for ROP for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, mean (SD)	701 (103)	872 (185)
GA at birth, mean (SD)	25.7 (0.9)	26.4 (1.0)
Days on oxygen, mean (SD)	58.8 (26.9)	46.8 (33.3)
Early onset sepsis, n (%)	0	10 (1.9)
Late onset sepsis, n (%)	7 (50)	148 (28)
Fungal sepsis, n (%)	1 (7.1)	12 (2.2)
Grade 3-4 IVH or PVL, n (%)	0	59 (11.1)
Proven necrotizing enterocolitis	1 (7.1)	36 (6.7)
Patent ductus arteriosus	11 (78.6)	258 (48.2)
Discharge on oxygen, n (%)	2 (14.3)	88 (16.5)

Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop ROP after discharge with reasonable specificity.

## Discussion

In prior ROP natural history studies,<sup>3</sup> lower birth weight infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>12</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>13</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. Because the CRYO-ROP cohort was defined and stratified by birth weight rather than gestational age, it is also possible that the lowest birth weight stratum ( $< 750$ g) was enriched by small-for-gestational age infants and the largest birth weight stratum (1000-1250g) had relatively few small-for-gestational age infants. In our data, age of onset was related to chronological age as well as PMA. Our findings were consistent with prior studies in that we did not observe ROP before 4 weeks chronological

age and severe ROP did not occur before 6 weeks. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have estimated the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>14</sup> The SUPPORT Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>14</sup>

## Conclusion

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

## References

- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006; 117: 572-576. Erratum in: *Pediatrics* 2006; 118: 1324.
- <sup>2</sup> Jefferies A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 2010; 15: 667-674.
- <sup>3</sup> Palmer EA, Flynn JT, Hardy RJ et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98: 1628-1640.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 2002; 120: 1470-1476.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Pediatrics* 1988; 81: 697-706.

- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA, Spencer R, van Heuven WA, Fielder AR. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 1998; 338: 1572-1576.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 2007; 196:147 e1-8.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004; 102: 233-250.
- <sup>9</sup> Good WV, Harky RJ, Dobson V et al for the Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 2005; 116: 15-23.
- <sup>10</sup> Austeng D, Kallen KB, Hellstrom A, Tornqvist K, Holmstrom GE. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 2010; 128: 1289-1294.
- <sup>11</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *New Engl J Med* 2010; 362: 1959-1969.
- <sup>12</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 1991; 87: 7-17.
- <sup>13</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 1999; 135:147-152.
- <sup>14</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012; 129: 480-484.

**From:** Ehrenkranz, Richard  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Romano, Elaine  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; "Gabrio, Jenna"  
**Subject:** RE: FU consent form  
**Date:** Wednesday, June 06, 2012 4:20:11 PM  
**Attachments:** [Cmpd\\_auth valid to 25 Oct12.pdf](#)

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Rose:  
Here it is.  
Richard

Richard A. Ehrenkranz, MD  
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The information contained in this email may be privileged and confidential. If you are the intended recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, June 06, 2012 4:04 PM  
**To:** Ehrenkranz, Richard; Romano, Elaine  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; 'Gabrio, Jenna'  
**Subject:** FU consent form

Hi Richard,  
We are now collecting consent forms (in addition to IRB approvals). Can you forward your most recent FU consent form?  
thanks  
Rose

Rosemary D. Higgins, MD  
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**COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A  
RESEARCH PROJECT  
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL**

**Study Title:** Follow-up of High Risk Infants

**Principal Investigator:** Richard A. Ehrenkranz, MD  
Department of Pediatrics  
Yale University School of Medicine  
333 Cedar Street  
PO Box 208064  
New Haven, CT 06520-8064

**Funding Source:** National Institutes of Health (NIH) /National Institute of Child Health and Human Development (NICHD)

**Invitation to Participate and Description of Project**

You and your child are invited to take part in a research project that has been designed to develop and maintain an ongoing database of newborn developmental follow-up information. You and your child have been asked to take part because your child had a gestational age less than 27 weeks at birth.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and any possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

**Description of Procedures**

All infants with birth weight less than or equal to 1250 grams (about 2 lbs 10 oz) who were cared for in the Newborn Special Care Unit, Yale-New Haven Children's Hospital are invited to participate in a neonatal developmental follow-up program that offers developmental assessments at about 18 months corrected age (corrected age means that the age of the follow-up visit is adjusted by the number of weeks that the child was premature). The developmental assessments are performed at the Yale Child Study Center and include standard, validated tests and questionnaires used to evaluate infant development and family dynamics. The findings of those assessments are discussed with the parents and shared, with permission, with the child's primary care provider.

For this project, the cooperating centers of the NICHD Neonatal Research Network have agreed to submit developmental information obtained during the follow-up visits of former extremely low gestational age neonates (ELGANs, gestational age less than 27 weeks at birth) to a central registry or database. If you agree to participate your child's developmental information obtained during your child's follow-up visits will be included in this registry. This information includes the scores from the assessments, test and questionnaires.

### **Risks and Inconveniences**

There are no risks associated with the developmental tests or questionnaires that are done by the Newborn Follow-up Program at the Yale Child Study Center.

### **Benefits**

You and your child may not receive any direct benefit from participating in the follow-up assessment. However, the findings will be discussed with you, and with your permission, will be shared with your child's primary care provider. This multicenter database has permitted timely evaluations of the relationship between current newborn intensive care practices and long-term neurodevelopmental outcome. Such evaluations have led to improvements in the care provided to newly born ELBW infants.

### **Economic Considerations**

There will be no charge for the Follow-up visit. To show our appreciation to you for your visit, we will provide a \$50.00 gift plus expenses (for example, for parking, childcare) after completion of the follow-up visit.

### **Confidentiality and Privacy**

The medical information obtained during the developmental assessments and questionnaires will include information that identifies you, your child, and some personal health information. This will include information that might directly identify you, such as your name and address. This information will be kept in a locked file at Yale University School of Medicine, maintained by members of our Newborn Follow-Up Program.

Since participation in this project means that information obtained during your child's developmental follow-up visit will be added to a registry, selected information will be abstracted from the information collected during the visit. Any identifying information will be replaced by a code that will be maintained in the locked file, and then the information will be submitted with strict adherence to professional standards of confidentiality. The research files will be maintained for 5 years. The submitted coded information may be reviewed by members of our Neonatal Research Team, representatives of the NICHD, Research Triangle International (the data coordinating center that maintains the information), and the Yale University School of Medicine Human Investigation Committee (the committee that reviews, approves and monitors research on humans).

Reports using information contained in the registry may eventually be published and information may be exchanged between medical investigators. However, your child's name will not be used in any publication which may result from this project.

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies: NICHD Neonatal Research Network, including Research Triangle International

Approved - Valid through 25-OCT-2012

HIC # 9503007879

- Representatives from Yale University and the Human Investigation Committee, who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The Principal Investigator: Richard A. Ehrenkranz, MD
- All members of the Neonatal Research Team, including members of the Newborn Follow-up Program
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study: NICHD Independent Data and Safety Monitoring Committee
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

The research team can only give information about you to others for research with your permission. U.S. or State law may also require that we give information to others. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. As noted above, code numbers linking your's and your child's identity will be kept in a locked file; information directly identifying each participant in this project will not leave Yale.

If you give permission to let us give your identifiable health information to others as listed above, the information may no longer be protected by law. There is a risk that your information will be further released to others without your permission.

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### **Voluntary Participation and Withdrawal**

You are free to choose not to take part in this project, and if you participate, you are free to withdraw from it at any time during its course. If you choose not to participate or if you choose to withdraw, it will not harm your relationship with your own doctors or with Yale-New Haven Hospital. You do not give up any of your legal rights by signing this form.

To withdraw, you can call a member of the Newborn Follow-up Program at any time and tell them that you do no longer want to participate in the project. However, any coded developmental and questionnaire information that has already been submitted to the registry may still be used and given to others to complete the study. This may be done when it is necessary for the research to be reliable. The authorization to use and disclose your health information will never expire unless and until you change your mind and revoke it. To take away, or withdraw, your permission to use and disclose your health information that has been collected during this project, you must also follow up your phone call by sending a written notice to the principal investigator at Department of Pediatrics, PO Box 208064, New Haven, CT 06520-8064.

Approved - Valid through 25-OCT-2012

HIC # 9503007879

### Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

### Authorization and Permission

I have read this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: \_\_\_\_\_

Signature: \_\_\_\_\_

Relationship: \_\_\_\_\_

Date: \_\_\_\_\_

\_\_\_\_\_  
Signature of Principal Investigator

\_\_\_\_\_  
Date

*or*

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Dr. Richard Ehrenkranz at 203-688-2895. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688. If after you have signed this form you have any questions about your rights, please contact the Yale Privacy Officer at 203/436-3650.

**From:** [Susan Hintz](#)  
**To:** [Jean Lowe](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kristi Watterberg](#); [Carla Bann](#); [Janell Fuller](#); [Andrea Duncan](#)  
**Subject:** Re: Manuscript for Support and Object Permanence- Feedback please  
**Date:** Sunday, June 03, 2012 6:46:01 PM  
**Attachments:** [OP\\_EWM\\_SUPPORT\\_52512\\_SRH.docx](#)  
[Carlo\\_SUPPORT\\_NEJM2010.pdf](#)  
[Finer\\_SUPPORT\\_NEJM2010.pdf](#)  
[Stoll\\_NRN\\_GDB\\_short\\_term\\_2010.pdf](#)  
[Hintz\\_Pediatrics\\_Jan\\_2011.pdf](#)

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Hi Jean

These are some more specific comments embedded in the paper. I have attached a few papers that I note in the commented embedded. In terms of specifically spelling out the details of the NEURO secondary, I am concerned that there may be confusion. Because you are referring to IVH and PVL, etc, there may be more questions that are really warranted about other neuroimaging findings, etc. I put a suggestion in the comments about how you might present the SUPPORT study and a generic reference to a secondary study and how the object permanence study fits in. See if it works for you -

Susan

On Jun 3, 2012, at 2:44 PM, Jean Lowe wrote:

<OP\_EWM\_SUPPORT\_52512.docx>

### **Early working memory deficits in extremely preterm children at 18-22 months**

Jean R. Lowe<sup>1</sup>, Kristi L. Watterberg<sup>1</sup>; Carla Bann<sup>2</sup>, Janell Fuller<sup>1</sup>, Susan R. Hintz<sup>3</sup>, Andrea Freeman MD<sup>1</sup>; and for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

### **Disclosures**

The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) provided grant support for the Neonatal Research Network's Generic Database and Follow-up Studies.

The coauthors have no conflicts of interest relevant to this manuscript.

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**Reprint Requests:** Please address reprint requests to Andrea Freeman Duncan MD

**Running title:** Working Memory in Preterm Children

**Key words:** development, prematurity, object permanence, early working memory

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## ABSTRACT

**Objective(s)** The objective of this study was to evaluate the relationship of object permanence (OP) to Bayley Scales of Infant and Toddler Development 3rd edition (BSID-III) scores in extremely preterm children (<28+0 weeks' gestational age) at 18-22 months corrected age.

**Study Design** 540 children born in 3 ethnic groups were included (White, Black, Hispanic-White) were included in this cohort study. Object permanence by medical factors that included:

intraventricular hemorrhage grade ~~II-3~~ and ~~IV-4~~ or periventricular ~~interventricular~~ hemorrhage ~~leukomalacia~~, gestational age retinopathy of prematurity, and SES variables including , race/ethnicity, maternal education, and gender., and using ANOVA (continuous) and chi-square (categorical) analyses. Logistic and linear regression models were used to ~~adjusteontrolling~~ for medical and social factors.

**Results** 517 children were included. Children with OP had higher BSID-III scores than those with lack of OP (PVALUE) after controlling for other factors. There was no difference in OP between race/ethnic and sociodemographic groups.

**Conclusion(s)** OP is associated with higher BSID-III scores in EP children and is unrelated to race/ethnicity or medical and psychosocial factors. OP may be a race/ethnicity neutral measure of early EF and cognition, and assessment of OP at 18-22 mos may improve early detection of EF deficits in these children.

## INTRODUCTION

Executive function (EF) is a critical element of neurodevelopment in humans, and encompasses working memory, inhibition, and cognitive flexibility (Davidson, 2006). Early working memory a component of executive functioning requires the ability to selectively attend to information that is important, while simultaneously inhibiting interfering information which mediates a wide range of activities requiring reasoning and planning (Savage et al 2006). Difficulties with early executive functions has been found in infants born preterm as early as 8 to 18 months independent of maternal education and cognitive skills (Sun 2009). In a study of early working memory in preschool-aged children born preterm, Woodward et al found that 2-year-olds born preterm had more difficulty encoding new information in working memory compared to term infants (Woodward, 2005). Children born extremely preterm continue to exhibit difficulties in cognition, inhibition, and perceptual motor skills in kindergarten compared to peers born full term. (Orchinik et al 2011, J Int'l Neuropsych). Difficulty with executive functioning persists into school age especially in areas of response inhibition, planning, verbal and spatial working memory skills (Aarnoudse-Moens 2011, (Anderson, 2004; Curtis, 2002; Bayless, 2007)).

Comment [J1]: Review references

The Bayley Scales of Infant and Toddler Development (1985, etc..) is used to determine cognitive function in extremely preterm children prior to the age of 3, though these scores have been found to be poor predictors of school-age function (Hack, 2005). Racial/ethnic differences was found on the Bayley Scales of Infant and Toddler Development –II (1998) with a significantly higher mental developmental index found in White children than in Hispanic-White or Black children (Watterberg 2007); these differences were not explained by socioeconomic status or maternal education (Lowe 2009). However a measure of early working memory was similar across all race/ethnic groups and income levels (Lowe, 2009). The finding that early



working memory was not influenced by race and ethnicity or income is an important one when working with diverse populations, as minority populations are at increased risk for preterm birth (Dolan, 2010).

The objective of this study was to evaluate the relationship of early working memory as measured by object permanence items on the BSID-III in a cohort of children born extremely preterm children at 18-22 months corrected age. In addition explored the impact of predefined medical and socio-economic factors on object permanence. Comparison of early working memory skills to both early language and cognitive development occurred as the revised BSID-III has a language measure. We hypothesized that 1) Object permanence would not be affected by the randomization to treatment group 2) Object permanence score would correlate significantly with performance on the BSID-III cognitive and language scores 3) Object permanence would not be affected by maternal education or race/ethnicity in contrast to BSID-III cognitive and language scores.

**Comment [J2]:** Should we say Mat Ed and Ethnicit vs socio-economic?

## **METHODS**

### Study Population

This study was a retrospective cohort study of children born at 24  $\pm$ 0/7 to 27  $\pm$ 6/7 weeks gestational age at the sixteen centers of the NRN who were evaluated at 18 to 22 months adjusted age during the period of February, 2005 to February, 2009. All children in this study were part of the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) multi-center study. Infants were randomly assigned to a lower oxygen saturation target range (85% to 89%) or a more conventional target range (91%-95%) until 36 weeks post-menstrual age or when the child no longer required ventilator support or oxygen (Rich et al, 2012). The study

also compared continuous positive airway pressure and a protocol driven limited ventilator support begun in the delivery room and continued into the Neonatal Intensive Care Unit (NICU).

The infants randomized to the ventilator group received early intratracheal administration of surfactant followed by conventional mechanical ventilation. Of the initial 1,316 infants in the

SUPPORT trial 258 died and 64 were lost to follow-up. Of the remaining -infants- 990 were seen at follow-up and of those 540 had object permanence scores, as this was an ancillary study that began after the SUPPORT follow-up had already begun.

Carla: You will need to put a basic section in Methods about how data were collected, definitions of morbidities you note in Results and will note in your tables, training for psychologists in the NRN. In addition to the NEJM papers, I am attaching the Stoll GDB paper and my <25 week outcomes paper because both have basic verbiage about the NRN methodologies and definitions. Note that the <25 week outcomes paper was from BAYLEY II era – so obviously not that verbiage, but you have that covered in the next section below.

**Comment [SH3]:** Carla: Instead of these sentences, you could just say: "The SUPPORT study was a randomized, multicenter, 2x2 factorial trial of ventilation and oxygenation management strategies beginning in the delivery room among 24-27+6/7 week EGA infants. Infants in the SUPPORT study had a comprehensive neurodevelopmental follow-up visit at 18-22 months of age corrected for prematurity. Object permanence scores were performed and reported only for those children enrolled in a prospective secondary to the SUPPORT study."

**Comment [SH4]:**

**Comment [SH5]:** I would move the description of patient numbers to the results.

#### Test Measures

The Bayley Scales of Infant and Toddler Development – 3<sup>rd</sup> edition (Bayley, 2005) ((BSID-III) was administered to the children between 18 and 22 months, age adjusted for prematurity. The cognitive and language scale was used for this study. Within the cognitive scale 3 items 40, 45 and 50 were used as measures of object permanence. The items sequentially increased in difficulty and were each worth 1 point. First, the child was asked to find a toy hidden under one of two cups (item 40). Second, double visual displacement was used as the toy was hidden under one cup, removed and hidden a second time under the second cup (item 45). Third, the cups were reversed after the toy was hidden (item 50). The number of items correctly completed was

calculated for each child and used as an ordinal measure. Object permanence mastery was defined as a score of 2 or 3.

### Statistical Analyses

Linear regression was used to analyze object permanence scores with BSID-III cognitive and language scores controlling for medical (gender, gestational age, severe intraventricular hemorrhage (IVH) or periventricular leukoamalgia (PVL), retinopathy of prematurity, treatment group) and social covariates (maternal education, race/ethnicity). Logistic regression was used for the object permanence mastery score also controlling for medical and social covariates. Pairwise comparisons between race groups were adjusted for multiple comparisons using the Bonferroni correction.

Comment [SH6]: I assume you mean cystic PVL?

### **RESULTS**

There was no significant difference in object permanence score among the two treatment groups after controlling for social and medical variables. There was also no significant difference among the object permanence score after controlling for both maternal education and race/ethnicity. Those children who obtained object permanence mastery had significantly higher BSID-III cognitive and language scores after controlling for both medical and socio-economic factors. In contrast mothers with high school education or less than high school education had significantly lower BSID-III language scores (F and p values) compared to mothers with greater than high school education (p=0.01). Hispanic children (p=0.002) and males (p=0.001) scored significantly lower on the language scale. In regards to medical factors, children who had a history of retinopathy of prematurity (p=), lower gestational age (p=0.02), grade III-3 or IV-4 intraventricular hemorrhage or periventricular leukoamalgia (p=0.002) had significantly lower

Comment [SH7]: I would put the patient numbers here in the first part of the Results.

BSID-III cognitive scores. Lower BSID-III language scores were also found in males ( $p=0.001$ ) and children born of lower gestational age ( $p=0.008$ ). Object permanence mastery scores were lower for males ( $p=0.001$ ) and children with retinopathy of prematurity diagnosed in the neonatal period ( $p=0.002$ ).

**Comment [38]:** Carla can you add the appropriate p and F values and check what I have and wrote. EDIT anything you want!

## DISCUSSION

In this study we have shown for the first time that children with OPM have higher BSID Cognitive and Language scale scores, and that OPM is a measure of early executive function is not affected by race/ethnicity or socioeconomic status.

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If object permanence mastery is a better predictor of school age EF than BSID cognitive scores, it could significantly improve our ability to identify children who are at risk for later developmental sequelae. Better understanding of EF development in extremely preterm children could lead to earlier diagnosis of and improved interventions for abnormalities of EF. This is relevant to intervention techniques that can be developed to specifically work on tasks that could enhance EF skills. In conjunction with the BSID cognitive score, use of a measure of object permanence may also improve our detection of ongoing problems with EF at 18–22 months, which is highly related to learning difficulties later in life. Early childhood intervention results in significant improvements in cognitive, academic, and social outcomes (Ramey, 2000).

**ROP and IVH/PVL findings add**

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.

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**R**ETINOPATHY 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.<sup>1</sup> In the 1960s, this increase resulted in the practice of restricting the fraction of inspired oxygen (FIO<sub>2</sub>) to no more than 0.50, which was estimated to result in an excess of 16 deaths per case of blindness prevented.<sup>2</sup> 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.<sup>3-5</sup> Oxygen toxicity may also increase the risk of death,<sup>6,7</sup> bronchopulmonary dysplasia,<sup>8-10</sup> periventricular leukomalacia,<sup>11</sup> cerebral palsy,<sup>12</sup> 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<sup>13</sup> and exposure to arterial oxygen levels of 80 mm Hg or more.<sup>14</sup>

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.<sup>1-5</sup> 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%.<sup>3</sup> 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%.<sup>3</sup> 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.<sup>4,15,16</sup> 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*.<sup>17</sup>

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## METHODS

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### 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

#### OXYGEN SATURATION AND OUTCOMES OF PREMATURITY

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,<sup>18</sup> but the algorithm used in the current trial differed, since the oxygen-saturation reading gradually changed and reverted to actual (non-skewed) values when it was less than 84% or higher than 96% in both treatment groups. Limits of 85% and 95% that would trigger an alarm in the delivery system were suggested, but they could be changed for individual patients.

Targeting of levels of oxygen saturation with altered pulse oximetry was initiated within the first 2 hours after birth and was continued until 36 weeks of postmenstrual age or until the in-

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

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

#### 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<sup>19,20</sup>) 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<sup>21</sup> and safety outcomes.

#### STATISTICAL ANALYSIS

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

An absolute between-group difference of 10 percentage points in the rate of the composite primary outcome was considered clinically important. The sample-size calculations were based on the rate of death or threshold retinopathy of 47% in the Neonatal Research Network for the year

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

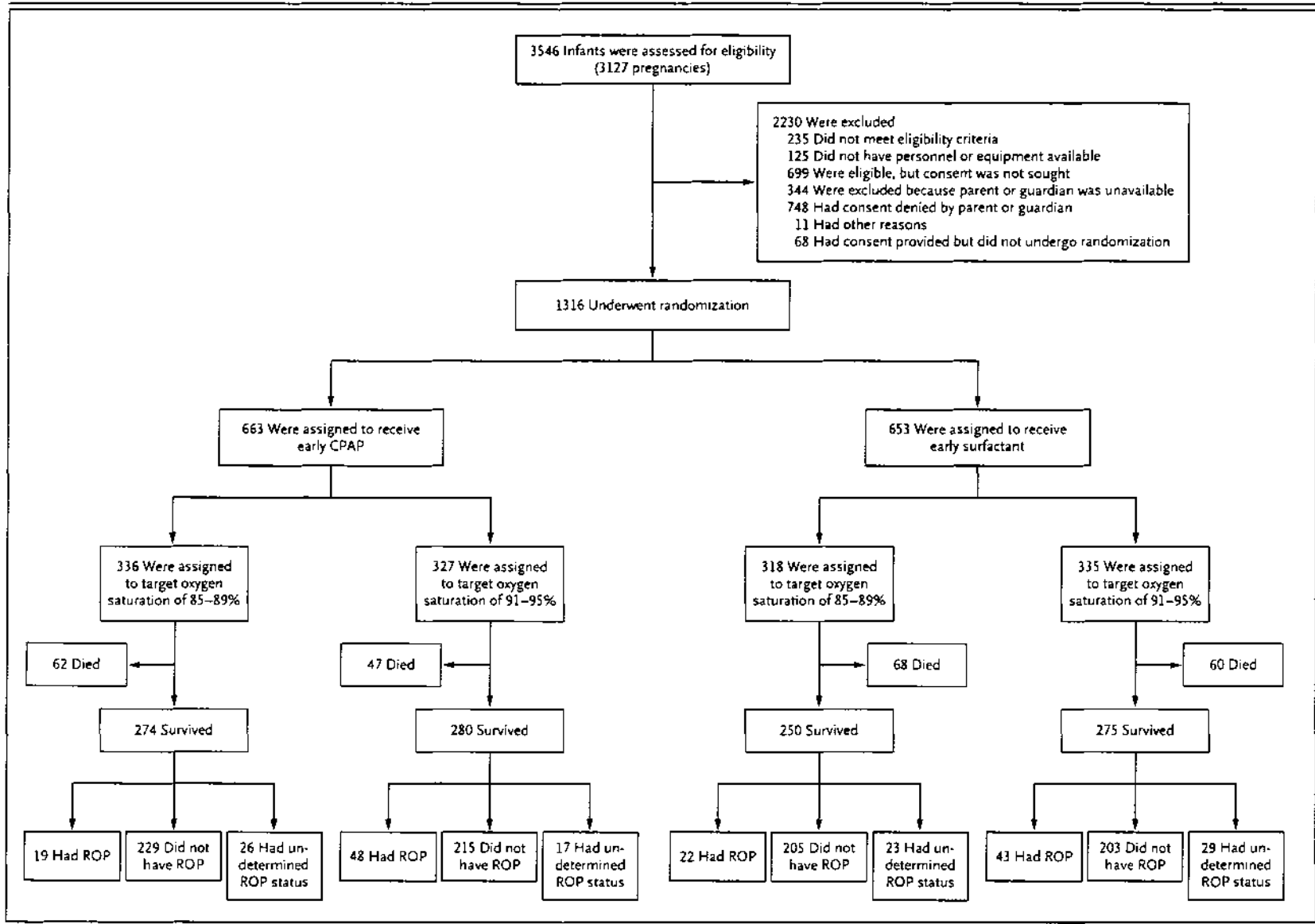
The numbers shown exclude infants of women who were screened during pregnancy but whose babies were not subsequently born at a study center between 24 weeks 0 days and 27 weeks 6 days of gestation. The outcome of severe retinopathy of prematurity (ROP) could not be determined in some infants because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

2000. We increased the sample size by a factor of 1.12 to allow for infants who were part of multiple births to be randomly assigned to the same treatment (since this introduced a clustering effect into the design), and we increased the sample size by an additional 17% to adjust for attrition after hospital discharge. We increased the sample size further to minimize type I error with the use of a conservative 2% level of significance. The result was a target sample of 1310 infants. The study was not powered to detect an interaction effect between the two factorial parts of the study.

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

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





10.1056/NEJM08091781 NEJM.ORG

OXYGEN SATURATION AND OUTCOMES OF PREMATURITY

Table 1. Baseline Characteristics of the Patients.

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

\* Plus-minus values are means ±SD. P>0.05 for all comparisons.

† Race or ethnic group was reported by the mother or guardian of each child.

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

## RESULTS

### CHARACTERISTICS OF THE STUDY SAMPLE

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

tion of enrollment was approved. The baseline characteristics of the two treatment groups were similar (Table 1).

### PRIMARY OUTCOME

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

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**Table 2. Major Outcomes.\***

Outcome	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)	Adjusted Relative Risk (95% CI)
	<i>no./total no. (%)</i>		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76–1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37–0.73)
<b>Death</b>			
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)
<b>Death</b>			
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)
<b>Treatment for patent ductus arteriosus</b>			
Medical	219/634 (34.5)	233/645 (36.1)	0.95 (0.82–1.09)
Surgical	73/641 (11.4)	68/648 (10.5)	1.09 (0.80–1.48)
Any air leaks in first 14 days	51/654 (7.8)	42/662 (6.3)	1.23 (0.83–1.83)

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

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

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

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

full text of this article at NEJM.org). Similar results were observed for both gestational-age strata. Survival analysis with the use of the unadjusted Kaplan–Meier method (Fig. 2) and a Cox proportional-hazards model produced similar results (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07).

The rate of severe retinopathy among survivors who were discharged or transferred to another facility or who reached the age of 1 year was lower in the lower-oxygen-saturation group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; P<0.001; number needed to treat, 11). Although

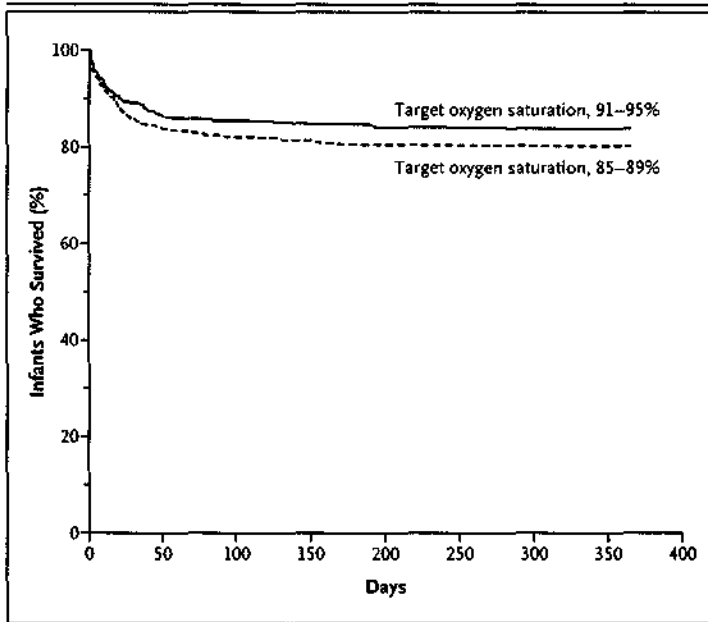


Figure 2. Kaplan-Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life.

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

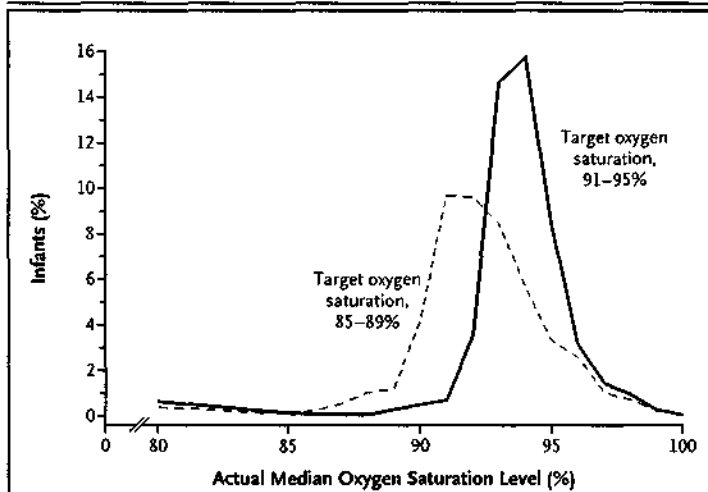


Figure 3. Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups.

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

opathy or surgical intervention for retinopathy. Three ophthalmologists adjudicated results for the patients who did not meet the criteria for retinopathy, and the results were materially unchanged (Table 2 in the Supplementary Appendix).

#### SECONDARY OUTCOMES

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

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

#### DISCUSSION

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

use of bevacizumab was among the criteria for this outcome, only three infants received bevacizumab, and these infants also had threshold retin-

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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,<sup>3-5,15,16</sup> it is becoming common practice to use lower target ranges of oxygen saturation with the goal of reducing the risk of retinopathy of prematurity.<sup>23</sup> 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,<sup>1</sup> 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<sup>18</sup> or after moderately severe retinopathy developed<sup>22</sup> 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.<sup>24</sup> These trials were performed by limiting the  $\text{FiO}_2$  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<sup>24</sup> and most non-randomized studies,<sup>3-5,15,16</sup> 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.<sup>25</sup>

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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#### REFERENCES

1. Duc G, Sinclair JC. Oxygen administration. In: Sinclair JC, Bracken MB, eds. *Effective care of the newborn infant*. New York: Oxford University Press, 1992:178-94.
2. Bolton DP, Cross KW. Further observations on cost of preventing retrolental fibroplasia. *Lancet* 1974;303:445-8.
3. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-F110.
4. Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics* 2003;111:339-45.
5. Anderson CG, Benitz WE, Madan A. Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J Perinatol* 2004;24:164-8.
6. Rabi Y, Rabi D, Yee W. Room air resuscitation of the depressed newborn: a systematic review and meta-analysis. *Resuscitation* 2007;72:353-63.
7. Silvers KM, Gibson AT, Russell JM, Powers HJ. Antioxidant activity, packed cell transfusions, and outcome in premature infants. *Arch Dis Child Fetal Neonatal Ed* 1998;78:F214-F219.
8. Saugstad OD. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? *Acta Paediatr* 1997;86:1277-82.
9. Davis JM. Role of oxidant injury in the pathogenesis of neonatal lung disease. *Acta Paediatr Suppl* 2002;91:23-5.
10. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723-9.
11. Haynes RL, Folkerth RD, Keefe RJ, et

OXYGEN SATURATION AND OUTCOMES OF PREMATURETY

- al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.
12. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
13. Kinsey VE, Arnold HJ, Kalina RE, et al. PaO<sub>2</sub> levels and retrolental fibroplasia: a report of the cooperative study. *Pediatrics* 1977;60:655-68.
14. Flynn JT, Bancalari E, Snyder ES, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med* 1992;326:1050-4.
15. Deulofeut R, Dudell G, Sola A. Treatment-by-gender effect when aiming to avoid hyperoxia in preterm infants in the NICU. *Acta Paediatr* 2007;96:990-4.
16. Wright KW, Thompson SD, Ramanaathan R, Joseph R, Farzavandi S. A physiologic reduced oxygen protocol decreases the incidence of threshold retinopathy of prematurity. *Trans Am Ophthalmol Soc* 2006;104:78-84.
17. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010. DOI: 10.1056/NEJMoa0911783.
18. Askie LM, Henderson-Smart DJ, Irwing L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med* 2003;349:959-67.
19. Hardy RJ, Good WV, Dobson V, et al. Multicenter trial of early treatment for retinopathy of prematurity: study design. *Control Clin Trials* 2004;25:311-25.
20. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003; 121:1684-94.
21. Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics* 2004;114:1305-11.
22. The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized controlled trial. I. Primary outcomes. *Pediatrics* 2000; 105:295-310.
23. Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. *Pediatrics* 2003; 112:1415-9.
24. Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. *Cochrane Database Syst Rev* 2009;1: CD001077.
25. Tin W, Gupta S. Optimum oxygen therapy in preterm babies. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F143-F147.

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ORIGINAL ARTICLE

## Early CPAP versus Surfactant in Extremely Preterm Infants

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

### ABSTRACT

#### BACKGROUND

There are limited data to inform the choice between early treatment with continuous positive airway pressure (CPAP) and early surfactant treatment as the initial support for extremely-low-birth-weight infants.

#### METHODS

We performed a randomized, multicenter trial, with a 2-by-2 factorial design, involving infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation. Infants were randomly assigned to intubation and surfactant treatment (within 1 hour after birth) or to CPAP treatment initiated in the delivery room, with subsequent use of a protocol-driven limited ventilation strategy. Infants were also randomly assigned to one of two target ranges of oxygen saturation. The primary outcome was death or bronchopulmonary dysplasia as defined by the requirement for supplemental oxygen at 36 weeks (with an attempt at withdrawal of supplemental oxygen in neonates who were receiving less than 30% oxygen).

#### RESULTS

A total of 1316 infants were enrolled in the study. The rates of the primary outcome did not differ significantly between the CPAP group and the surfactant group (47.8% and 51.0%, respectively; relative risk with CPAP, 0.95; 95% confidence interval [CI], 0.85 to 1.05) after adjustment for gestational age, center, and familial clustering. The results were similar when bronchopulmonary dysplasia was defined according to the need for any supplemental oxygen at 36 weeks (rates of primary outcome, 48.7% and 54.1%, respectively; relative risk with CPAP, 0.91; 95% CI, 0.83 to 1.01). Infants who received CPAP treatment, as compared with infants who received surfactant treatment, less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia ( $P < 0.001$ ), required fewer days of mechanical ventilation ( $P = 0.03$ ), and were more likely to be alive and free from the need for mechanical ventilation by day 7 ( $P = 0.01$ ). The rates of other adverse neonatal outcomes did not differ significantly between the two groups.

#### CONCLUSIONS

The results of this study support consideration of CPAP as an alternative to intubation and surfactant in preterm infants. (ClinicalTrials.gov number, NCT00233324.)

\*The authors are listed in the Appendix. The affiliations of members of the Writing Committee and other investigators in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network are listed in the Appendix. Address reprint requests to Dr. Neil N. Finer at the University of California at San Diego, 402 Dickinson St., MPF 1-140, San Diego, CA 92103-8774, or at [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu).

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IT HAS BEEN SHOWN THAT SURFACTANT treatment at less than 2 hours of life significantly decreases the rates of death, air leak, and death or bronchopulmonary dysplasia in preterm infants.<sup>1,2</sup> Overall, prophylactic treatment with surfactant has not been shown to significantly reduce the risk of bronchopulmonary dysplasia alone, whereas studies comparing early with later rescue use of surfactant have shown that there is a decreased risk of chronic lung disease with early use.<sup>2</sup> Several studies have shown that the use of surfactant does not have a significant effect on the risk of subsequent neurodevelopmental impairment,<sup>3</sup> although a recent follow-up assessment of infants involved in a randomized trial showed that early surfactant treatment (at a mean of 31 minutes of age) as compared with later surfactant treatment (at a mean of 202 minutes of age) was associated with a significantly higher rate of increased muscle tone in the infants and a delay in the infants' ability to roll from the supine to the prone position.<sup>4</sup> However, in many of the trials of surfactant treatment, the rate of maternal corticosteroid therapy before delivery — an intervention known to improve neonatal survival<sup>5</sup> and decrease the rate of complications — was not high, and none of the infants in the control group received early treatment with continuous positive airway pressure (CPAP). There is a growing body of observational evidence suggesting that in the case of very preterm infants with respiratory distress who are not treated initially with surfactant, the early use of CPAP may decrease the need for mechanical ventilation without an increase in complications.<sup>6-11</sup>

In a previous study reported in the *Journal*, 610 infants, born between 25 weeks 0 days and 28 weeks 6 days of gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress at that time, were randomly assigned to either intubation and ventilation or CPAP at a pressure of 8 cm of water; infants who were randomly assigned to CPAP were intubated if they met certain criteria for the failure of CPAP treatment.<sup>12</sup> There was no significant reduction in the CPAP group, as compared with the intubated group, in the rate of death or the need for supplemental oxygen at 36 weeks (the primary outcome), and there was a significantly higher rate of pneumothorax in the CPAP group than in

the intubated group (9.1% vs. 3.0%); most of the cases of pneumothorax occurred within the first 2 days, which is consistent with the findings of a previous meta-analysis.<sup>13</sup>

We designed the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) to compare early CPAP treatment with early surfactant treatment in extremely preterm infants. Using a factorial design, we also randomly assigned infants to one of two target ranges of oxygen saturation during their exposure to supplemental oxygen.

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## METHODS

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### STUDY DESIGN

In this randomized, multicenter trial, we compared a strategy of treatment with CPAP and protocol-driven limited ventilation begun in the delivery room and continued in the neonatal intensive care unit (NICU) with a strategy of early intratracheal administration of surfactant (within 1 hour after birth) followed by a conventional ventilation strategy. In a 2-by-2 factorial design, infants were also randomly assigned to one of two target ranges of oxygen saturation (85 to 89% or 91 to 95%) until the infant was 36 weeks of age or no longer received ventilatory support or supplemental oxygen. The results of this portion of the study are discussed elsewhere in this issue of the *Journal*.<sup>14</sup> Randomization was stratified according to center and gestational-age group, with the use of specially prepared double-sealed envelopes, and was performed before the actual delivery. Infants who were part of multiple births were randomly assigned to the same group. Written informed consent from a parent or guardian for an infant's participation in the trial was required before delivery.

Infants were eligible for inclusion in the study if they were 24 weeks 0 days to 27 weeks 6 days of gestation at birth according to the best obstetrical estimate, if they were born without known malformations at a participating center, if a decision had been made to provide full resuscitation for them, and if written informed consent had been obtained from a parent or guardian. The infants were randomly assigned within each center and within each gestational-age stratum (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days).

#### EARLY CPAP VS. SURFACTANT AND OUTCOMES OF PREMATURETY

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 human subjects committee at each participating site and at RTI International, which is the data center for the Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for this study.

##### CPAP GROUP

In the delivery room, CPAP was administered by means of a T-piece resuscitator, a neonatal ventilator, or an equivalent device. CPAP or ventilation with positive end-expiratory pressure (PEEP) (at a recommended pressure of 5 cm of water) was used if the infant received positive-pressure ventilation during resuscitation. CPAP was continued until the infant's admission to the NICU. Intubation was not performed for the sole purpose of surfactant administration in infants who were randomly assigned to the CPAP group, but infants who required intubation for resuscitation on the basis of standard indications specified in the Neonatal Resuscitation Program guidelines<sup>15</sup> were given surfactant within 60 minutes after birth.

In the NICU, infants who were randomly assigned to CPAP could be intubated if they met any of the following criteria: a fraction of inspired oxygen ( $\text{FiO}_2$ ) greater than 0.50 required to maintain an indicated saturation of peripheral oxygen ( $\text{SpO}_2$ ) at or above 88% for 1 hour; a partial pressure of arterial carbon dioxide ( $\text{PaCO}_2$ ) greater than 65 mm Hg, documented by a single measurement of blood gases within 1 hour before intubation; or hemodynamic instability, defined as a blood pressure that was low for gestational age, poor perfusion, or both, requiring volume or pressor support for a period of 4 hours or more. Infants who were intubated within the first 48 hours after birth were to receive surfactant. After an infant's admission to the NICU, the unit used its standard method for the delivery of CPAP — that is, a ventilator, a purpose-built flow driver, or a bubble CPAP circuit.

Extubation of an infant in the CPAP group was to be attempted within 24 hours after the infant met all of the following criteria: a  $\text{PaCO}_2$  below 65 mm Hg with a pH higher than 7.20, an  $\text{SpO}_2$  above 88% with an  $\text{FiO}_2$  below 0.50, a mean air-

way pressure of less than 10 cm of water, a ventilator rate of less than 20 breaths per minute, an amplitude of less than twice the mean airway pressure if high-frequency ventilation was being used, hemodynamic stability, and the absence of clinically significant patent ductus arteriosus. Criteria for reintubation were the same as those for initial intubation. After three intubations, infants in the CPAP group received treatment according to the standard practice in the NICU to which they had been admitted.

##### SURFACTANT GROUP

All the infants in the surfactant group were to be intubated in the delivery room and were to receive surfactant within 1 hour after birth with continued ventilation thereafter. The infants were to be extubated within 24 hours after meeting all of the following criteria: a  $\text{PaCO}_2$  of less than 50 mm Hg and a pH higher than 7.30, an  $\text{FiO}_2$  of 0.35 or less with an  $\text{SpO}_2$  of 88% or higher, a mean arterial pressure of 8 cm of water or less, a ventilator rate of 20 breaths per minute or less, an amplitude of less than twice the mean arterial pressure if high-frequency ventilation was being used, and hemodynamic stability without evidence of clinically significant patent ductus arteriosus. Once the infants were extubated, they were treated according to the standard practice in the NICU to which they had been admitted.

The criteria for both groups were in effect for the infants' first 14 days of life, after which the infants were treated according to the standard practice in the NICU to which they had been admitted. In the case of both groups, intubation could be performed at any time if there was an episode of repetitive apnea requiring bag-and-mask ventilation, clinical shock, or sepsis, or if surgery was required.

##### OUTCOMES

The primary outcome was death or bronchopulmonary dysplasia. Bronchopulmonary dysplasia was defined according to the physiological definition, 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.<sup>16,17</sup> Prespecified secondary outcomes included bronchopulmonary dys-

plasia as defined by the receipt of any supplemental oxygen at 36 weeks. Prespecified safety outcomes included death, pneumothorax, intraventricular hemorrhage, and the need for chest compressions or epinephrine during resuscitation.

#### STATISTICAL ANALYSIS

The sample-size calculations were based on data from the Neonatal Research Network from the year 2000, which showed that the rate of death or survival with bronchopulmonary dysplasia at 36 weeks was 67% and the rate of death or survival with neurodevelopmental impairment at 18 to 22 months was 61%. We hypothesized that with early CPAP there would be a reduction of 10% in the incidence of these complications. We increased the sample size by a factor of 1.12 to allow for infants in multiple births to be randomly assigned to the same treatment, because this introduced a clustering effect into the design, and we increased the sample sizes by an additional 17% to adjust for loss to follow-up after 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. We planned to test for an interaction between the two factorial parts of the study, but the study was not powered for that analysis.

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. The primary analyses focused on the percentage of infants in each group who survived to 36 weeks of postmenstrual age without bronchopulmonary dysplasia. 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.

In the analysis of all outcomes, the results were adjusted, as prespecified, for gestational-age strata, center, and familial clustering. Two-sided P values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. An independent data and safety monitoring committee reviewed the interim safety and efficacy results —

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

The numbers in the figure 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. Postmenstrual age is defined as the gestational age plus the postnatal age. BPD denotes bronchopulmonary dysplasia according to the physiological definition (receipt of more than 30% supplemental oxygen at 36 weeks, 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).<sup>16,17</sup>

including those related to adverse outcomes — four times. Lan-DeMets spending functions with Pocock and O'Brien-Fleming boundaries were used to determine stopping rules for interim safety and efficacy monitoring, respectively.

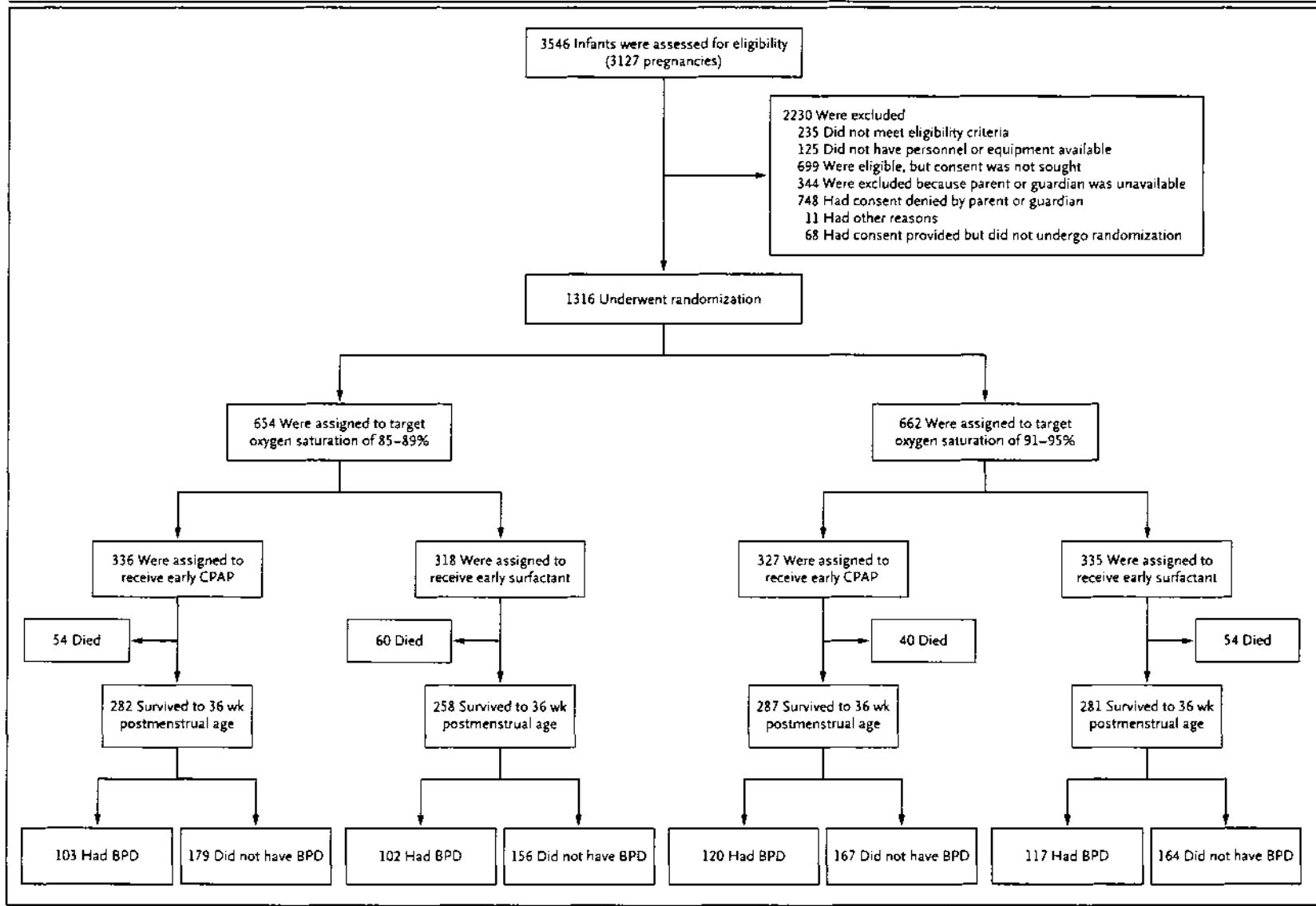
For the 46 planned analyses of secondary outcomes according to treatment, we would expect no more than 3 tests to have P values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for 36 predefined outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than 2 tests per stratum to have P values of less than 0.05 on the basis of chance alone.

## RESULTS

### CHARACTERISTICS OF THE STUDY SAMPLE

From February 2005 through February 2009, a total of 1316 infants were enrolled, of whom 565 were in the lower gestational-age stratum (24 weeks 0 days to 25 weeks 6 days) and 751 were in the higher stratum (26 weeks 0 days to 27 weeks 6 days) (Fig. 1). There were no significant differences between the two treatment groups with respect to sex, birth weight, or race or ethnic group (Table 1).

Delivery room interventions in the two groups are summarized in Table 2. The rates of intubation in the delivery room and of the use of positive-pressure ventilation or epinephrine to treat persistent bradycardia were significantly lower among infants randomly assigned to CPAP than among those assigned to surfactant treatment. Overall, 32.9% of the infants in the CPAP group did not receive surfactant during their hospitalization.



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**Table 1. Demographic and Clinical Characteristics of the Study Participants.\***

Variable	CPAP (N=663)	Surfactant (N=653)
Gestational age — no. (%)		
24 wk 0 days–25 wk 6 days	285 (43.0)	280 (42.9)
26 wk 0 days–27 wk 6 days	378 (57.0)	373 (57.1)
Assignment to low target oxygen-saturation range in 2-by-2 factorial design — no./total no. (%)		
Gestational age of 24–25 wk	142/285 (49.8)	134/280 (47.9)
Gestational age of 26–27 wk	194/378 (51.3)	184/373 (49.3)
Male sex — no. (%)	342 (51.6)	370 (56.7)
Race or ethnic group — no. (%)†		
Non-Hispanic black	254 (38.3)	235 (36.0)
Non-Hispanic white	250 (37.7)	271 (41.5)
Hispanic	138 (20.8)	121 (18.5)
Other or unknown	21 (3.2)	26 (4.0)
Birth weight — g	834.6±188.2	825.5±198.1
Gestational age at birth — wk	26.2±1.1	26.2±1.1
Maternal use of antenatal corticosteroids — no./total no. (%)		
Any	642/663 (96.8)	623/652 (95.6)
Full course	486/660 (73.6)	453/649 (69.8)
Death of infant in the delivery room — no. (%)	1 (0.2)	5 (0.8)

\* Plus-minus values are means ±SD. None of the differences between groups were significant. CPAP denotes continuous positive airway pressure.

† Race or ethnic group was reported by the mother or guardian of each child.

#### PRIMARY OUTCOME

After adjustment for gestational age, center, and familial clustering, the rates of the primary outcome of death or bronchopulmonary dysplasia as assessed according to the physiological definition did not differ significantly between the two groups. The results were similar when bronchopulmonary dysplasia was defined according to the need for any supplemental oxygen at 36 weeks. When components of this composite outcome were analyzed separately, there was no significant between-group difference in the rate of death or the rate of bronchopulmonary dysplasia (Table 3).

There was no significant interaction between the two interventions assessed in the trial with respect to the primary outcome of death or bronchopulmonary dysplasia as assessed either according to the physiological definition ( $P=0.59$ ) or according to the need for any supplemental oxygen at 36 weeks ( $P=0.53$ ). There was no significant

interaction between gestational-age stratum and treatment strategy with respect to the primary outcome ( $P=0.84$  with the physiological definition of bronchopulmonary dysplasia and  $P=0.44$  with bronchopulmonary dysplasia defined according to the need for any supplemental oxygen at 36 weeks), and there was no significant between-group difference in the rate of the primary outcome (with either definition of bronchopulmonary dysplasia) in either gestational-age stratum.

#### SECONDARY OUTCOMES

More infants in the CPAP group than in the surfactant group were alive and free from the need for mechanical ventilation by day 7 ( $P=0.01$ ), and infants in the CPAP group required fewer days of ventilation than did those in the surfactant group ( $P=0.03$ ). There were no significant between-group differences in the rates of air leak in the first 14 days, pneumothorax during the hospital stay, necrotizing enterocolitis requiring medical or surgical treatment, patent ductus arteriosus requiring surgery, severe intraventricular hemorrhage, or severe retinopathy of prematurity, as defined according to the new type 1 threshold in the Early Treatment for Retinopathy of Prematurity study (ETROP; ClinicalTrials.gov number, NCT00027222)<sup>18</sup> or according to the need for surgical intervention among survivors. One infant in the surfactant group died in the delivery room at 21 minutes after birth and was not intubated; 83.1% of the infants in the CPAP group were intubated ( $P<0.001$ ). The rate of use of postnatal corticosteroids to treat bronchopulmonary dysplasia was lower in the CPAP group than in the surfactant group ( $P<0.001$ ) (Table 3). The other secondary outcomes are shown in Table 3.

In post hoc stratified analyses of secondary outcomes, among infants who were born between 24 weeks 0 days and 25 weeks 6 days of gestation, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group (rate of death during hospitalization: 23.9% vs. 32.1%; relative risk with CPAP, 0.74; 95% confidence interval [CI], 0.57 to 0.98;  $P=0.03$ ; rate of death at 36 weeks: 20.0% vs. 29.3%; relative risk, 0.68; 95% CI, 0.5 to 0.92;  $P=0.01$  [see Table A1 in the Supplementary Appendix, available with the full text of this article at NEJM.org]); in contrast, there was no significant between-group difference in the rate of

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**Table 2. Apgar Scores of Newborns and Interventions in the Delivery Room and NICU.\***

Variable	CPAP (N = 663) <i>no./total no. (%)</i>	Surfactant (N = 653) <i>no./total no. (%)</i>	Relative Risk with CPAP (95% CI)	Adjusted P Value
Apgar score <3				
At 1 min	154/661 (23.3)	167/653 (25.6)	0.92 (0.76–1.11)	0.38
At 5 min	26/663 (3.9)	32/653 (4.9)	0.82 (0.5–1.34)	0.43
PPV in the delivery room	435/662 (65.7)	606/652 (92.9)	0.71 (0.67–0.75)	<0.001
CPAP in the delivery room	538/663 (81.1)	146/653 (22.4)	3.66 (3.16–4.25)	<0.001
Intubation in the delivery room				
For any reason	227/660 (34.4)	609/652 (93.4)	0.37 (0.34–0.42)	<0.001
For resuscitation	215/660 (32.6)	176/652 (27.0)	1.21 (1.02–1.43)	0.02
Surfactant treatment				
In the delivery room	93/660 (14.1)	335/652 (51.4)	0.28 (0.23–0.34)	<0.001
In the delivery room or NICU	443/660 (67.1)	646/653 (98.9)	0.67 (0.64–0.71)	<0.001
Chest compressions in the delivery room	36/660 (5.5)	40/653 (6.1)	0.86 (0.57–1.31)	0.48
Epinephrine in the delivery room	13/660 (2.0)	27/653 (4.1)	0.48 (0.25–0.91)	0.02

\* CI denotes confidence interval, CPAP continuous positive airway pressure, NICU neonatal intensive care unit, and PPV positive-pressure ventilation.

death during hospitalization or at 36 weeks among the infants who were born between 26 weeks 0 days and 27 weeks 6 days of gestation (rate of death during hospitalization: 10.8% and 10.2%, respectively; rate of death at 36 weeks: 9.8% and 8.6%, respectively) (see Tables A1 and A3 in the Supplementary Appendix).

**DISCUSSION**

In this multicenter, randomized trial involving extremely preterm infants, there was no significant difference between a strategy of early CPAP and limited ventilation and a strategy of early intubation and surfactant administration within 1 hour after birth with respect to the rate of the composite primary outcome of death or bronchopulmonary dysplasia. We used the physiological definition of bronchopulmonary dysplasia, since it includes as a specification an attempt to withdraw supplemental oxygen from infants receiving less than 30% oxygen at 36 weeks, in order to confirm their need for supplemental oxygen.<sup>16,17</sup> Plausible results, on the basis of the 95% confidence intervals for the relative-risk estimates, included a risk of death or bronchopulmonary dysplasia in the CPAP group that was between 85

and 105% of that in the surfactant group. The results were similar in secondary analyses in which bronchopulmonary dysplasia was defined according to the use of any supplemental oxygen at 36 weeks.

We did not include infants who were born at a gestational age of less than 24 weeks, since the results of a pilot trial showed that 100% of such infants required intubation in the delivery room.<sup>19</sup> A retrospective study showed that some infants in this gestational-age group can be treated successfully with early CPAP, but the majority require intubation.<sup>20</sup>

There was a high rate of intubation and surfactant treatment among infants assigned to CPAP, but this was anticipated, given the design of the study, which was to test an initial strategy of early CPAP as compared with early intubation and surfactant, with crossover planned for ethical reasons in the case of infants in whom CPAP treatment was not successful. Our trial differs from the trial of Morley et al.<sup>12</sup> in that we randomly assigned all eligible preterm infants to a treatment group, irrespective of whether they were breathing spontaneously or whether they had respiratory distress that warranted intervention, and in that we included infants who were born as early

Table 3. Selected Prespecified Outcomes.\*

Outcome	CPAP (N=663)	Surfactant (N=653)	Relative Risk with CPAP (95% CI)	Difference in Means (95% CI)	Adjusted P Value
BPD or death by 36 wk of postmenstrual age — no. (%)					
Physiological definition of BPD†	317 (47.8)	333 (51.0)	0.95 (0.85 to 1.05)		0.30
BPD defined by need for supplemental oxygen	323 (48.7)	353 (54.1)	0.91 (0.83 to 1.01)		0.07
BPD by 36 wk of postmenstrual age — no./total no. (%)					
Physiological definition of BPD†	223/569 (39.2)	219/539 (40.6)	0.99 (0.87 to 1.14)		0.92
BPD defined by need for supplemental oxygen	229/569 (40.2)	239/539 (44.3)	0.94 (0.82 to 1.06)		0.32
Death by 36 wk of postmenstrual age — no. (%)	94 (14.2)	114 (17.5)	0.81 (0.63 to 1.03)		0.09
Need for supplemental oxygen — no. of days‡					0.12
Adjusted mean	62.2±1.6	65.3±1.6		-3.1 (-7.1 to 0.8)	
Unadjusted median	52	56			
Interquartile range	20 to 86	27 to 91			
Need for mechanical ventilation — no. of days‡§					0.03
Adjusted mean	24.8±1.0	27.7±1.1		-3.0 (-5.6 to -0.3)	
Unadjusted median	10	13			
Interquartile range	2 to 32	2 to 36			
Survival without need for high-frequency or conventional ventilation at 7 days — no./total no. (%)	362/655 (55.3)	318/652 (48.8)	1.14 (1.03 to 1.25)		0.01
Any air leak in first 14 days — no. (%)	45 (6.8)	48 (7.4)	0.89 (0.6 to 1.32)		0.56
Necrotizing enterocolitis requiring medical or surgical treatment — no./total no. (%)	83/654 (12.7)	63/636 (9.9)	1.25 (0.92 to 1.71)		0.15
Intraventricular hemorrhage grade 3 or 4 — no./total no. (%)¶	92/642 (14.3)	72/628 (11.5)	1.26 (0.94 to 1.68)		0.12
Postnatal corticosteroid therapy for BPD — no./total no. (%)	47/649 (7.2)	83/631 (13.2)	0.57 (0.41 to 0.78)		<0.001
Severe retinopathy of prematurity among survivors — no./total no. (%)	67/511 (13.1)	65/473 (13.7)	0.94 (0.69 to 1.28)		0.71

\* Plus-minus values are means ±SD. BPD denotes bronchopulmonary dysplasia, CI confidence interval, and CPAP continuous positive airway pressure.

† The physiological definition of BPD includes, as a criterion, the receipt of more than 30% supplemental oxygen at 36 weeks, 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 supplemental oxygen.<sup>16,17</sup>

‡ Data are for 1098 infants who survived to discharge, transfer, or 120 days; the maximum follow-up was 120 days.

§ This variable includes high-frequency ventilation and conventional ventilation.

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

as 24 weeks of gestation. In the study by Morley et al., surfactant was not administered routinely in the intubation group. Our protocol, which called for early CPAP and a determination of the need for intubation, was based on the findings of previous observational studies showing that Neonatal Research Network sites that had the most experience with CPAP also used a higher threshold for intubation and the initiation of mechanical ventilation than did sites with less experience.<sup>4-6</sup> The infants who were randomly assigned to surfactant treatment in our trial were

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treated with a ventilation approach that was used by a majority of the Neonatal Research Network sites before the trial began. We believed that comparing these two methods would provide more clinically relevant results. Data are currently being collected to assess survival without neurodevelopmental impairment at 18 to 22 months.

We found no significant between-group differences in the rates of pneumothorax, intraventricular hemorrhage, or the need for chest compressions or epinephrine in the delivery room, and the rates were similar to those among infants in the Neonatal Research Network population who were born between 2000 and 2004 at similar gestational ages. The rate of air leaks in the first 14 days of life was not increased with the use of early CPAP at a pressure of 5 cm of water, as compared with the use of early surfactant.

In secondary analyses stratified according to gestational age at birth, there was a significant reduction in the risk of death in the CPAP group, as compared with the early-intubation group, among infants born between 24 weeks 0 days and 25 weeks 6 days of gestation but not among infants who were born at a later gestational age. Given the fact that there was no significant interaction between the intervention and gestational age, the post hoc nature of these analyses, and the number of secondary analyses performed, this observation must be interpreted with caution, and

further testing should be performed in this immature population.

In summary, we found no significant difference in the primary outcome of death or bronchopulmonary dysplasia between infants randomly assigned to early CPAP and those assigned to early surfactant treatment. In secondary analyses, the CPAP strategy, as compared with early surfactant treatment, resulted in a lower rate of intubation (both in the delivery room and in the NICU), a reduced rate of postnatal corticosteroid use, and a shorter duration of ventilation without an increased risk of any adverse neonatal outcome. These data support consideration of CPAP as an alternative to routine intubation and surfactant administration in preterm infants.

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

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APPENDIX

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EARLY CPAP VS. SURFACTANT AND OUTCOMES OF PREMATUREITY

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REFERENCES

1. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2000;2:CD000511.
2. Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2000;2:CD001456.
3. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2001;2:CD000510.
4. Hentschel R, Dittrich F, Hilgendorff A, Wauer R, Westmeier M, Gortner L. Neurodevelopmental outcome and pulmonary morbidity two years after early versus late surfactant treatment: does it really differ? *Acta Paediatr* 2009;98:654-9.
5. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006;3:CD004454.
6. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics* 1987;79:26-30.
7. Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? *Pediatrics* 2000;105:1194-201.
8. Vanpee M, WalfridssonSchultz U, Karz-Salamon M, Zupancic JAF, Pursley D, Jonsson B. Resuscitation and ventilation strategies for extremely preterm infants: a comparison study between two neonatal centers in Boston and Stockholm. *Acta Paediatr* 2007;96:10-6.
9. Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birth-weight infants in special-care units and neonatal intensive-care units in Stockholm: early nasal continuous positive airway pressure versus mechanical ventilation: gains and losses. *Acta Paediatr Suppl* 1997;419:4-10.
10. Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. *Eur J Pediatr* 1997;156:384-8.
11. Poets CF, Sens B. Changes in intubation rates and outcome of very low birth weight infants: a population-based study. *Pediatrics* 1996;98:24-7.
12. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med* 2008;358:700-8.
13. Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2002;2:CD002271.
14. 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. DOI: 10.1056/NEJMoa0911781.
15. Kattwinkel J, ed. Neonatal resuscitation textbook. 5th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006.
16. Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics* 2004;114:1305-11.
17. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. *J Perinatol* 2003;23:451-6.
18. Hardy RJ, Good WV, Dobson V, et al. Multicenter trial of early treatment for retinopathy of prematurity: study design. *Control Clin Trials* 2004;25:311-25.
19. Finer NN, Carlo WA, Duara S, et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. *Pediatrics* 2004;114:651-7.
20. Aly H, Massaro AN, Patel K, ElMohandes AAE. Is it safer to intubate premature infants in the delivery room? *Pediatrics* 2005;115:1660-5.

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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, obstetric 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.

FREE



**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  $\leq 12$  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  $\geq 24$  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.<sup>1-6</sup> Increased VLBW infant survival rates have paralleled improvements in prenatal, obstetric, and neonatal care.<sup>7,8</sup> 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.<sup>6</sup> 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 22 $\frac{1}{2}$  to 28 $\frac{1}{2}$  weeks and BWs of 401 to 1500 g were studied, including those with congenital anomalies. These infants were part of the NRN VLBW registry.<sup>1-6</sup>

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 deter-

mined 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.<sup>9</sup> Morbidities were defined in earlier publications,<sup>1-6,10,11</sup> 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  $\geq 6$  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,<sup>12</sup> and BPD determined according to physiologic definition.<sup>13</sup> 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  $\leq 12$  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 ( $\geq$  grade 3), PVL, BPD, necrotizing enterocolitis,  $\geq$  stage 3 ROP, or infection (early-onset sepsis, late-onset sepsis, or meningitis).

Statistical significance for unadjusted comparisons was determined by using  $\chi^2$  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  $\chi^2$  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<sup>14</sup> 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  $\leq 12$  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  $\sim 1\%$  per year during the study period, and rates of cesarean section delivery increased by  $\sim 2\%$  per year (Table 4). Rates of prenatal antibiotic use decreased by  $\sim 3\%$  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  $\geq 24$  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  $\leq 12$  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 <sup>a</sup>								
Mean (range)	27 (22–32)	27 (25–32)	27 (25–31)	27 (25–30)	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) <sup>b</sup>								
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 (6–65)
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) <sup>b</sup>	88 (53–100)	92 (84–100)	93 (85–100)	94 (86–100)	93 (80–100)	95 (85–100)	95 (89–100)	94 (85–100)
Diabetes mellitus, % (range) <sup>c</sup>	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) <sup>b</sup>	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) <sup>b</sup>	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) <sup>b</sup>	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) <sup>b</sup>	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) <sup>b</sup>	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) <sup>b</sup>								
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 = 575	N = 583	N = 732	N = 771	N = 3632
Chorioamnionitis documented in mother's medical record, % (range) <sup>b</sup>	28 (0–100)	28 (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)	85 (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) <sup>b</sup>	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, 8 infants; placental pathologic evaluation, 26 infants; histologic chorioamnionitis, 17 infants. *P* values were determined with the Wald  $\chi^2$  test for differences according to GA, with adjustment for center and BW. ROM indicates rupture of membranes.

<sup>a</sup> *P* ≤ .05.

<sup>b</sup> *P* ≤ .001.

<sup>c</sup> *P* ≤ .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)
<b>BW, g<sup>a</sup></b>								
Mean (range)	511 (473–621)	581 (549–639)	651 (609–677)	744 (709–791)	854 (757–891)	960 (919–1009)	1082 (1022–1207)	856 (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)
<b>Male, % (range)<sup>a</sup></b>	58 (0–93)	55 (43–100)	53 (40–70)	53 (46–81)	53 (45–63)	55 (37–66)	51 (36–58)	53 (47–58)
<b>Race/ethnicity, % (range)</b>								
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)
<b>Intrauterine growth restriction, % (range)<sup>b</sup></b>	0 (0–0)	4 (0–16)	6 (0–30)	8 (0–14)	8 (1–20)	10 (5–15)	9 (0–15)	8 (5–10)
<b>Multiple birth, % (range)<sup>a</sup></b>	28 (0–48)	30 (11–100)	25 (7–32)	21 (6–40)	22 (8–40)	25 (0–40)	28 (16–37)	25 (18–34)
<b>Delivery room resuscitation, % (range)</b>								
Endotracheal intubation <sup>c</sup>	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 <sup>a</sup>	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 <sup>a</sup>	3 (0–40)	10 (0–24)	13 (0–40)	10 (1–37)	7 (0–22)	6 (0–15)	4 (0–14)	8 (2–19)
<b>Apgar score of <math>\leq 3</math>, % (range)<sup>a</sup></b>								
At 1 min <sup>a</sup>	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 <sup>a</sup>	86 (0–100)	49 (0–89)	20 (0–40)	12 (3–25)	8 (0–22)	7 (1–14)	4 (0–9)	16 (3–25)
<b>Admission temperature, °C<sup>a,b</sup></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 (34.6–37.0)
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)
<b>Surfactant therapy, % (range)<sup>a</sup></b>	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.

<sup>a</sup>  $P \leq .001$  from the Wald  $\chi^2$  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.

<sup>b</sup> 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 <sup>a</sup>								
≤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)
≥28 d	1 (0–8)	6 (0–17)	10 (0–30)	8 (0–15)	5 (0–10)	4 (0–8)	2 (0–5)	5 (1–8)
Survived	N = 25	N = 226	N = 748	N = 1078	N = 1319	N = 1616	N = 1847	N = 6859
Survived without morbidity <sup>b</sup>	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 = 2718
Respiratory support withheld/withdrawn before death <sup>c</sup>	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 = 358	N = 375	N = 147	N = 72	N = 46	N = 27	N = 34	N = 1060
Respiratory support withheld/withdrawn before death <sup>d</sup>	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.

<sup>a</sup> Proportions among all infants including survivors.

<sup>b</sup> Proportions among infants who survived. Morbidities included severe IVH, PVL, BPD, necrotizing enterocolitis, infections, and ROP stage ≥3.

<sup>c</sup> Proportions among infants who died. Data on respiratory support withheld/withdrawn were missing for 52 infants.

<sup>d</sup> 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,<sup>3–6,15–18</sup> most reports, including findings for this cohort, failed to demonstrate further progress in reducing neonatal morbidity and mortality rates.<sup>6,16–19</sup> In contrast, a population co-

hort 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.<sup>20</sup> 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 in-

formation 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	85	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
N = 1709		N = 1762	N = 1818	N = 1689	N = 1537		
Never intubated, all infants who survived >12 h <sup>a</sup>	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 (0.85–1.24)	.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		
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 <sup>b</sup>							
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.

<sup>a</sup> Never used conventional or high-frequency ventilator or underwent nasal synchronized intermittent mandatory ventilation.

<sup>b</sup> Morbidities included BPD, severe IVH, PVL, necrotizing enterocolitis, ROP stage  $\geq 3$ , 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)							Total (N = 8515)
	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)	
Respiratory distress syndrome <sup>a</sup>	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 <sup>a</sup>	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 <sup>b</sup>	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 <sup>a</sup>	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 <sup>a,c</sup>	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 <sup>a,d</sup>	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 <sup>b,d</sup>	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 <sup>a,d</sup>	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 <sup>a,d</sup>	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) <sup>a,e</sup>	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 <sup>a,f</sup>								
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 <sup>b,g</sup>	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 <sup>a,h</sup>	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  $\chi^2$  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.

<sup>a</sup> *P* ≤ .001.

<sup>b</sup> *P* ≤ .05.

<sup>c</sup> Never used conventional or high-frequency ventilator or underwent nasal synchronized intermittent mandatory ventilation.

<sup>d</sup> 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.

<sup>e</sup> 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.

<sup>f</sup> 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.

<sup>g</sup> Proportions among infants born in 2006–2007.

<sup>h</sup> 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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>a,c</sup>	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 <sup>a</sup>	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 <sup>d</sup>	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 <sup>d</sup>	35 (0-50)	69 (0-100)	61 (0-100)	48 (0-90)	52 (0-85)	53 (25-77)	42 (0-100)	52 (0-79)
PDA <sup>a</sup>	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 <sup>a,f</sup>	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 <sup>a,g</sup>	50 (0-100)	43 (0-77)	40 (13-62)	33 (13-65)	24 (6-44)	16 (0-35)	12 (0-35)	27 (10-41)
Infants in hospital at 28 d N = 30	N = 30	N = 277	N = 874	N = 1197	N = 1386	N = 1683	N = 1866	N = 7313
ROP examination performed <sup>a,h</sup>	93 (50-100)	91 (71-100)	93 (50-100)	94 (78-100)	96 (67-100)	95 (87-100)	92 (68-99)	94 (82-98)
ROP diagnosed <sup>a,h</sup>	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 $\geq 3$ <sup>a,h</sup>	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 <sup>a,h</sup>	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 = 24	N = 215	N = 736	N = 976	N = 1106	N = 1231	N = 1204	N = 5492
Growth failure at 36 wk <sup>a,i</sup>	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 N = 53	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 <sup>a,k</sup>	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 = 19	N = 174	N = 438	N = 547	N = 566	N = 728	N = 754	N = 3226
PDA <sup>a,l</sup>	53 (0-100)	52 (13-100)	56 (0-100)	55 (20-100)	51 (12-100)	43 (0-80)	34 (0-65)	47 (23-78)
Ibuprofen therapy for PDA <sup>a</sup>	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 = 11	N = 92	N = 320	N = 471	N = 508	N = 678	N = 718	N = 2798
ROP examination performed <sup>a,m</sup>	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 <sup>a,n</sup>								
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, 58 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  $\geq 3$ , 7 infants; intervention/surgical treatment for ROP, 32 infants. *P* values were determined with the Wald  $\chi^2$  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.

<sup>a</sup> *P* < .001.

<sup>b</sup> *P* < .01.

<sup>c</sup> Proportions among infants who survived >3 days after birth.

<sup>d</sup> Proportions among infants with necrotizing enterocolitis.

<sup>e</sup> Proportions among infants with patent ductus arteriosus.

<sup>f</sup> *P*  $\leq$  .05.

<sup>g</sup> Proportions among infants who were still in the hospital at 28 days of life.

<sup>h</sup> Proportions among infants who were still in the hospital at 28 days and underwent a ROP examination.

<sup>i</sup> 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.

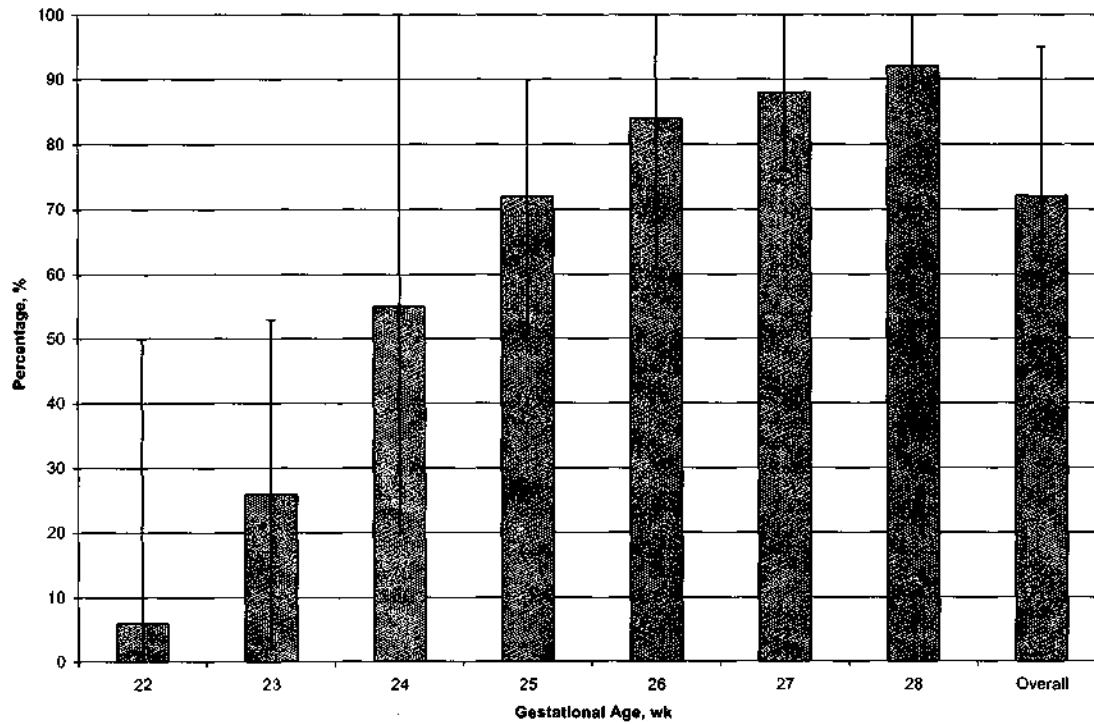
<sup>j</sup> From the sonogram with the most-severe findings. Proportions were determined among those who had sonograms performed within 28 days after birth. Categories shown are mutually exclusive. Some infants with IVH also had PVL, that is, 18 (2%) of 832 infants with grade 1 IVH, 21 (4%) of 506 infants 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.

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

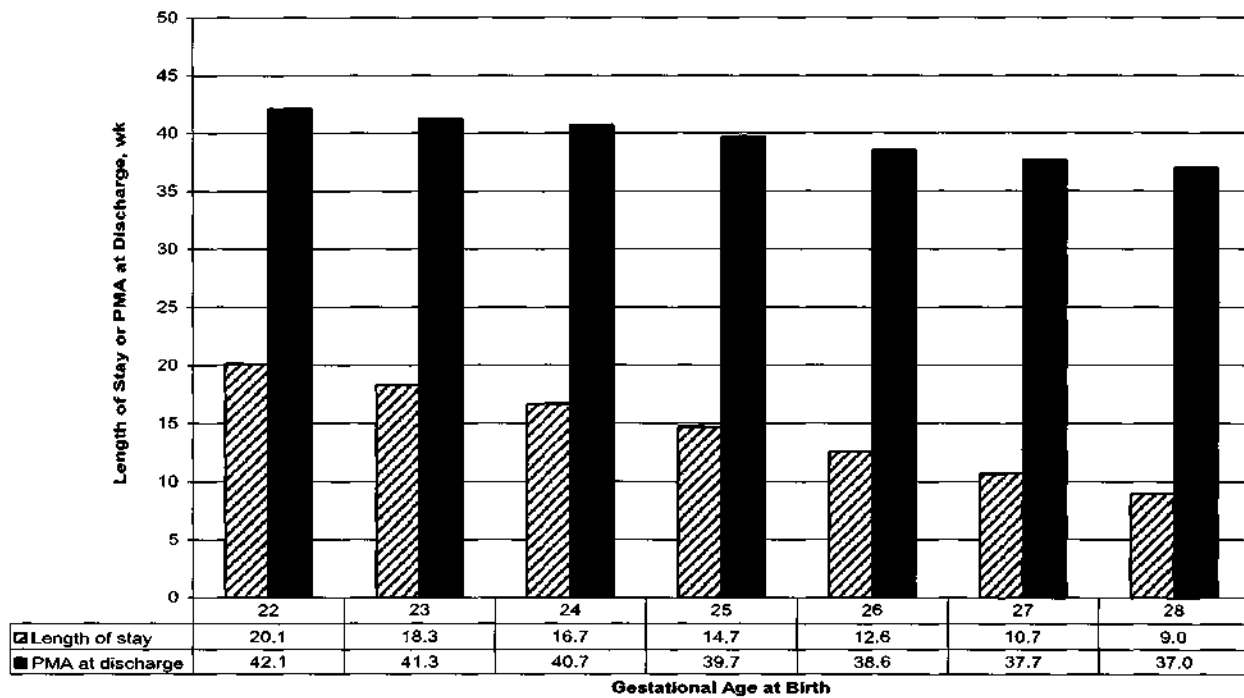
<sup>l</sup> Proportions were determined among infants born in 2006-2007. Ibuprofen treatment proportions are among infants who had patent ductus arteriosus. Information was missing as follows: patent ductus arteriosus, 1 infant; ibuprofen treatment, 1 infant.

<sup>m</sup> 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.

<sup>n</sup> 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.



**FIGURE 2** Median length of hospitalization (in weeks) and median PMA at discharge (in weeks) according to GA at birth among 6359 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.<sup>20</sup> 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 co-

hort, 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 un-

derscores the need for hypothesis-driven clinical trials to assess the efficacy of current neonatal interventions.<sup>21-24</sup> 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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## REFERENCES

1. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics*. 1991;87(5):587-597
2. Hack M, Wright LL, Shankaran S, et al. Very-low-birth-weight outcomes of the National Institute of Child Health and Human Development Neonatal Network, November 1989 to October 1990. *Am J Obstet Gynecol*. 1995;172(2):457-464
3. Fanaroff AA, Wright LL, Stevenson DK, et al. Very-low-birth-weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, May 1991-December 1992. *Am J Obstet Gynecol*. 1995;173(5):1423-1431

4. Stevenson DK, Wright LL, Lemons JA, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. *Am J Obstet Gynecol*. 1998;179(6):1632–1639
5. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. *Pediatrics*. 2001;107(1): Available at <http://www.pediatrics.org/cgi/content/full/107/1/e1>
6. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol*. 2007;196(2):147.e1–147.e8
7. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. *N Engl J Med*. 2010;362(6):529–535
8. Iams JD, Romero R, Culhane JF, Goldenberg RL. Preterm birth, primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet*. 2008;371(9607):164–175
9. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol*. 1996;87(2):163–168
10. Stoll BJ, Hansen N, Fanaroff AA, et al. Late onset sepsis in VLBW neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110(2):285–291
11. Stoll BJ, Hansen NI, Higgins RD, et al. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of Gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002–2003. *Pediatr Infect Dis J*. 2005;24(7):635–639
12. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723–1729
13. Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics*. 2004;114(5):1305–1311
14. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702–706
15. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR, EPICure Study Group. The EPICure Study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics*. 2000;106(4):659–671
16. Horbar JD, Badger GJ, Carpenter JH, et al. Trends in mortality and morbidity for very low birth weight infants, 1991–1999. *Pediatrics*. 2002;110(1):143–151
17. Chan K, Ohlsson A, Synnes A, et al. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. *Am J Obstet Gynecol*. 2001;185(1):220–226
18. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity: moving beyond gestational age. *N Engl J Med*. 2008;358(16):1672–1681
19. Meadow W, Lee G, Lin K, Lantos J. Changes in mortality for extremely low birth weight infants 1990s: implications for treatment decisions and resource use. *Pediatrics*. 2004;113(5):1223–1229
20. EXPRESS Group, Fellman V, Hellström-Westas L, Norman M, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA*. 2009;301(21):2225–2233
21. Vohr BR, Wright LL, Dusick AM, et al. Center differences and outcomes of extremely low birth weight infants. *Pediatrics*. 2004;113(4):781–789
22. Lee SK, Chan K, Ohlsson A, et al. Variations in treatment decisions and outcomes of infants  $\leq 25$  weeks gestation: evidence from Canada. *Pediatr Res*. 1999;45(4):247A
23. Synnes AR, Chien L-Y, Peliowski A, Baboolal R, Lee SK; Canadian NICU Network. Variations in intraventricular hemorrhage incidence rates among Canadian neonatal ICUs. *J Pediatr*. 2001;138(4):525–531
24. Walsh M, Lupton A, Kazzi SN, et al. A cluster-randomized trial of benchmarking and multimodal quality improvement to improve rates of survival free of bronchopulmonary dysplasia for infants with birth weights of less than 1250 grams. *Pediatrics*. 2007;119(5):876–890

(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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## **Early-Childhood Neurodevelopmental Outcomes Are Not Improving for Infants Born at <25 Weeks' Gestational Age**

Susan R. Hintz, Douglas E. Kendrick, Deanne E. Wilson-Costello, Abhik Das, Edward F. Bell, Betty R. Vohr, Rosemary D. Higgins and for the NICHD Neonatal Research Network

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# Early-Childhood Neurodevelopmental Outcomes Are Not Improving for Infants Born at <25 Weeks' Gestational Age



**WHAT'S KNOWN ON THIS SUBJECT:** Early-childhood neurodevelopmental outcomes seem to have improved over the last decade for some groups of preterm infants, but it is not known whether this trend applies to extraordinarily preterm infants who are born at <25 weeks' estimated gestational age.



**WHAT THIS STUDY ADDS:** Despite a dramatic reduction in postnatal steroid exposure, neurosensory and cognitive outcomes at 18 to 22 months' corrected age remain guarded and unchanged for infants who are born at <25 weeks' estimated gestational age in the NICHD Neonatal Research Network between 2 recent birth epochs.

## OBJECTIVE

**OBJECTIVE:** We compared neurodevelopmental outcomes at 18 to 22 months' corrected age of infants born with extremely low birth weight at an estimated gestational age of <25 weeks during 2 periods: 1999–2001 (epoch 1) and 2002–2004 (epoch 2).

**PATIENTS AND METHODS:** We conducted a multicenter, retrospective analysis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Perinatal and neonatal variables and outcomes were compared between epochs. Neurodevelopmental outcomes at 18 to 22 months' corrected age were evaluated with neurologic exams and Bayley Scales of Infant Development II. Logistic regression analyses determined the independent risk of epoch for adverse outcomes.

**RESULTS:** Infant survival was similar between epochs (epoch 1, 35.4%, vs epoch 2, 32.3%;  $P = .09$ ). A total of 411 of 452 surviving infants in epoch 1 and 405 of 438 surviving infants in epoch 2 were evaluated at 18 to 22 months' corrected age. Cesarean delivery ( $P = .03$ ), surgery for patent ductus arteriosus ( $P = .004$ ), and late sepsis ( $P = .01$ ) were more common in epoch 2, but postnatal steroid use was dramatically reduced (63.5% vs 32.8%;  $P < .0001$ ). Adverse outcomes at 18 to 22 months' corrected age were common in both epochs. Moderate-to-severe cerebral palsy was diagnosed in 11.1% of surviving infants in epoch 1 and 14.9% in epoch 2 (adjusted odds ratio [OR]: 1.52 [95% confidence interval (CI): 0.86–2.71];  $P = .15$ ), the Mental Developmental Index was <70 in 44.9% in epoch 1 and 51% in epoch 2 (OR: 1.30 [95% CI: 0.91–1.87];  $P = .15$ ), and neurodevelopmental impairment was diagnosed in 50.1% of surviving infants in epoch 1 and 58.7% in epoch 2 (OR: 1.4 [95% CI: 0.98–2.04];  $P = .07$ ).

**CONCLUSIONS:** Early-childhood outcomes for infants born at <25 weeks' estimated gestational age were unchanged between the 2 periods. *Pediatrics* 2011;127:62–70

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## KEY WORDS

extremely preterm, neurodevelopmental, outcome, cerebral palsy, Bayley Scales of Infant Development II

## ABBREVIATIONS

EGA—estimated gestational age  
NICHD—Eunice Kennedy Shriver National Institute of Child Health and Human Development  
NRN—Neonatal Research Network  
PDA—patent ductus arteriosus  
MDI—Mental Developmental Index  
PDI—Psychomotor Developmental Index  
OR—odds ratio  
CI—confidence interval

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Significant advances in perinatal and neonatal care and changes in the approach to immediate resuscitation have led to improved survival rates among preterm infants.<sup>1,2</sup> This phenomenon has extended to even extremely preterm infants,<sup>3-5</sup> although some analyses<sup>6,7</sup> suggest that major in-hospital morbidity rates for these infants may not have improved. The number of extremely preterm infants who survive to discharge has increased over time; however, these children are at high risk for neurodevelopmental sequelae during childhood.

Studies have suggested that some early-childhood neurosensory and developmental outcomes have improved over the last decade for some groups of preterm infants.<sup>8-10</sup> However, it is not clear whether this trend applies to the most extremely preterm infants, who are less than 25 weeks' estimated gestational age (EGA). A previous study<sup>11</sup> from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) demonstrated that 18- to 22-month outcomes for infants born at less than 25 weeks' EGA did not improve between 2 birth cohorts in the 1990s. Hack et al<sup>12</sup> presented a single-center analysis that showed no improvement in 20-month outcomes for infants born at 23 to 24 weeks' EGA in 2000-2004 compared with those born in 1995-1999. However, there are no large, recent analyses to examine whether neurodevelopmental outcomes improved, worsened, or remained the same for these most vulnerable preterm infants born since 2000.

The primary objective of our study was to compare 18- to 22-month corrected-age neurodevelopmental outcomes of infants born at less than 25 weeks' EGA in the NICHD NRN during 2 recent birth cohorts: epoch 1, which was from 1999 to 2001, and epoch 2, which was from

2002 to 2004. We also compared survival, perinatal characteristics, and neonatal interventions and morbidities between the 2 epochs. We hypothesized that there would be no significant differences in the rates of neurodevelopmental impairment, moderate-to-severe cerebral palsy, or severe developmental delay between epochs 1 and 2.

## METHODS

### Study Design and Patient Population

We conducted a retrospective analysis of prospectively collected data from the NICHD NRN Generic Database and Follow-up Study. Infants were included if they were born at less than 25 weeks' EGA, as determined by best obstetrical estimate; were 401 to 1000 g body weight; and were inborn at an NICHD NRN site between January 1, 1999, and December 31, 2001 (epoch 1), and January 1, 2002, to December 31, 2004 (epoch 2). Only centers that were part of the NRN during the entire 6-year study period were included in this analysis. Each center's institutional review board reviewed and approved the data collection procedures.

Research nurses collected demographic, perinatal, and infant data at each center using common definitions, as described in previous publications.<sup>1</sup> Antenatal antibiotics were defined as any antibiotics given to the mother during admission that resulted in delivery. Antenatal steroid use was defined as administration of any corticosteroid to accelerate fetal lung maturity in the present pregnancy. Intraventricular hemorrhage was reported according to the classification of Papile et al.<sup>13</sup> Cystic periventricular leukomalacia was diagnosed by cranial ultrasound. Early sepsis was defined as culture-proven sepsis in the first 72 hours after birth or treatment with antibiotics for at least 5 days be-

ginning before the age of 72 hours for presumed sepsis regardless of culture result. Late sepsis was defined as culture-proven sepsis at more than 72 hours to discharge or treatment with antibiotics at 72 hours for at least 5 days for presumed sepsis regardless of culture result. Necrotizing enterocolitis was defined as modified Bell's stage IIA or higher<sup>14</sup>; surgery for necrotizing enterocolitis included both laparotomy and drain. High-frequency ventilation was defined as the use of any high-frequency device during hospitalization. Bronchopulmonary dysplasia was defined as the use of supplemental oxygen at 36 weeks' postmenstrual age. Postnatal steroid use was defined as any corticosteroid given for the prevention or treatment of bronchopulmonary dysplasia. Surgery performed while the infant was in the NICU for patent ductus arteriosus (PDA), necrotizing enterocolitis, or retinopathy of prematurity was noted.

### Neurodevelopmental Assessments

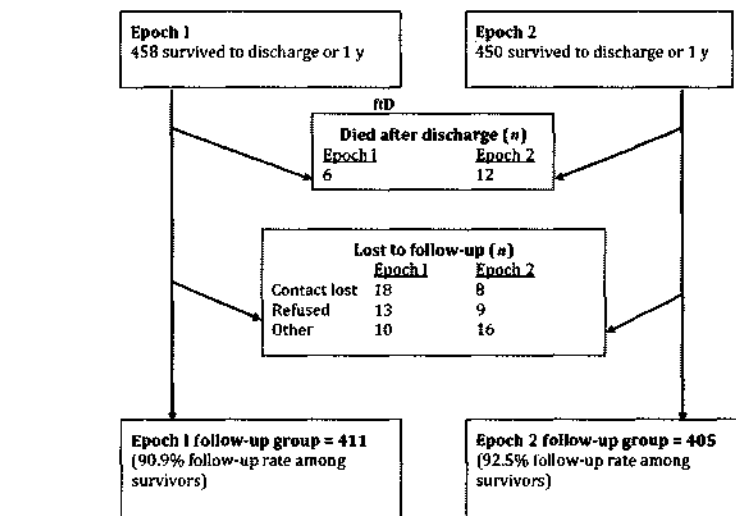
A comprehensive neurodevelopmental assessment was performed on the surviving infants at 18 to 22 months' corrected age. The follow-up visit, as previously described,<sup>3,8</sup> consisted of a battery of developmental, neurologic, and behavioral assessments; medical history; and parent interviews. The neuromotor examinations were based on Amiel-Tison assessments,<sup>15</sup> and gross motor function was based on the work of Palisano et al.<sup>16</sup> Examinations were performed by annually certified examiners who were trained to reliability during a 2-day workshop on neurologic assessment. During the study period, the Bayley Scales of Infant Development II<sup>17</sup> were administered, which included determination of the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI). MDI and PDI scores of  $100 \pm 15$  represent the mean  $\pm 1$  SD. The Bayley Scales of Infant Develop-

ment II was administered by experienced testers, who were annually certified by 1 of 4 gold-standard psychologists.

Cerebral palsy was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture that interfered with or prevented age-appropriate motor activity. Children with moderate-to-severe cerebral palsy were nonambulatory or required an assistive device for ambulation. Bilateral severe hearing loss was defined as permanent hearing loss that required amplification in both ears. Bilateral blindness was defined as the absence of functional vision in either eye. Neurodevelopmental impairment was defined as any of the following: moderate-to-severe cerebral palsy; an MDI or PDI of less than 70; deafness; or bilateral blindness. Profound impairment was defined as an MDI of less than 50 or a Gross Motor Function Classification System level of 4 or 5. Unimpaired or minimally impaired was defined as having none of the following: moderate-to-severe cerebral palsy; bilateral severe hearing loss or blindness; an MDI of less than 85; or a PDI of less than 85.

### Statistical Analyses

Unadjusted Epoch-related comparative analyses were conducted by using the  $\chi^2$  or Fisher's exact test for categorical data and the *t* test for continuous data. Logistic regression models were developed to evaluate the independent risk of epoch 2 versus epoch 1 for neurodevelopmental impairment, an MDI less than 70, and moderate-to-severe cerebral palsy. Model 1 included the following baseline perinatal and case-mix variables: epoch; network center; gender; multiple gestation; cesarean delivery; race; maternal age; body weight; antenatal antibiotic



**FIGURE 1**

Progression of patients in epochs 1 and 2 from survival to neurodevelopmental follow-up. Epoch 1: born January 1, 1999, to December 31, 2001; epoch 2: born January 1, 2002, to December 31, 2004.

use; and antenatal steroid use. Model 2 included all model 1 variables as well as the following subsequent neonatal morbidities and interventions that could be considered a proxy for severity of illness as well as postdischarge factors: surfactant; high-frequency ventilation; sepsis; necrotizing enterocolitis; grade 3 or 4 intraventricular hemorrhage or cystic periventricular leukomalacia; bronchopulmonary dysplasia; surgery for necrotizing enterocolitis; PDA or retinopathy of prematurity; maternal education less than high school; and age at neurodevelopmental assessment. The rationale for this a priori approach was to differentiate epoch-related odds for adverse outcomes adjusted for changes in baseline factors only from epoch-related odds also adjusted for neonatal variables, complications, and postdischarge factors. Because postnatal steroid exposure during epoch 2 may have been influenced by American Academy of Pediatrics recommendations,<sup>18</sup> rather than related to changes in severity of illness between epochs, model 2 was applied both with (model 2 plus postnatal steroid use) and without (model 2) the addition of postnatal steroid use.

### RESULTS

The progression of study patients is shown in Fig 1. During the entire study period, 2428 infants born at less than 25 weeks' EGA were inborn at NICHD NRR sites. Of these, 35.4% of infants in epoch 1 and 32.3% in epoch 2 survived until discharge or 1 year ( $P = .09$ ). In epoch 1, survival according to EGA was as follows: 22 weeks' or less EGA, 12 of 292 (4.1%) infants; 23 weeks' EGA, 101 of 395 (25.6%) infants; and 24 weeks' EGA, 345 of 606 (56.9%) infants. In epoch 2, survival according to EGA was as follows: 22 weeks' or less EGA, 13 of 322 (4.0%) infants; 23 weeks' EGA, 99 of 441 (22.5%) infants; and 24 weeks' EGA 338 of 632 (53.5%) infants. Forty-one infants in epoch 1 and 33 in epoch 2 were lost to follow-up, and a few infants in each epoch died after discharge. This resulted in 411 patients in the epoch 1 and 405 in the epoch 2 follow-up groups. Follow-up rates among survivors were more than 90% in each epoch.

Demographic and perinatal characteristics for the follow-up groups are shown in Table 1. There were no significant differences unadjusted between the groups, with the exception of an

**TABLE 1** Demographic and Perinatal Characteristics

	Epoch 1 (N = 411)	Epoch 2 (N = 405)	P <sup>a</sup>
Body weight, mean $\pm$ SD, g	668.6 $\pm$ 103.0	657.4 $\pm$ 99.7	.114
Body weight 401–500 g, n/N (%)	19/411 (4.6)	18/405 (4.4)	NS
EGA, mean $\pm$ SD, wk	23.7 $\pm$ 0.53	23.7 $\pm$ 0.52	NS
EGA distribution, n/N (%)			
<22 wk	1/411 (0.2)	0 (0.0)	NS
22 wk	11/411 (2.7)	12/405 (3.0)	
23 wk	84/411 (20.4)	93/405 (23.0)	
24 wk	315/411 (76.6)	300/405 (74.1)	
Male, n/N (%)	198/411 (48.2)	212/405 (52.4)	NS
Race, n/N (%)			
Black	209/411 (50.9)	178/405 (44.0)	.104
White	193/411 (47.0)	213/405 (52.6)	
Other	9/411 (2.2)	14/405 (3.5)	
Rupture of membranes $>$ 24 h, n/N (%)	120/404 (29.7)	131/400 (32.8)	NS
Multiple birth, n/N (%)	75/411 (18.3)	91/405 (22.5)	.158
Antenatal antibiotic use, n/N (%)	346/410 (84.4)	323/405 (79.8)	.102
Antenatal steroids use, n/N (%)	328/411 (79.8)	332/404 (82.2)	NS
Cesarean delivery, n/N (%)	168/411 (40.9)	197/404 (48.8)	.028
5-min Apgar score $<$ 5, n (%)	97/408 (23.8)	79/405 (19.5)	.163
Maternal age, mean $\pm$ SD, y	27.2 $\pm$ 6.76	27.4 $\pm$ 6.61	NS
Maternal insurance Medicaid, n/N (%)	283/409 (69.2)	301/403 (74.7)	.096

<sup>a</sup> P  $>$  .2 are reported as not significant.

increase in the proportion of infants born via cesarean delivery from epoch 1 (40.9%) to epoch 2 (48.8%) ( $P = .03$ ).

Common neonatal morbidities and interventions are presented in Table 2. Among the significant epoch-related differences on unadjusted analyses, indomethacin prophylaxis ( $P = .001$ ), surgery for PDA ( $P = .004$ ), and late sepsis ( $P = .01$ ) were more common in epoch 2 than in epoch 1. Surgery during neonatal hospitalization for necrotizing enterocolitis, PDA, or retinopathy of prematurity was slightly more common in epoch 2, with a borderline  $P$  value ( $P = .056$ ). However, the proportion of infants exposed to postnatal steroids in epoch 2 (32.8%) was approximately half that in epoch 1 (63.5%) ( $P < .0001$ ). It should be noted that there were no significant differences between epoch 1 and epoch 2 in PDA, severe intraventricular hemorrhage, or cystic periventricular leukomalacia, or oxygen use at 36 weeks' postmenstrual age.

Major neurosensory outcomes for all epoch 1 and epoch 2 infants, stratified according to EGA ( $\leq 23$  and 24–24%

weeks), are shown in Table 3. There were no significant differences between epochs. Developmental and

composite outcomes are shown in Table 4. Rates of PDI less than 70 and neurodevelopmental impairment were higher in epoch 2 compared with epoch 1 on unadjusted analyses. The proportion of children who were profoundly impaired did not differ significantly between epochs, nor did the proportion of those who were unimpaired or minimally impaired. Of note, approximately one-fifth of children born before 25 weeks' EGA were found to be unimpaired or minimally impaired at 18 to 22 months in both epochs, and this proportion did not change between epochs (21.8% and 21.9% in Epochs 1 and 2, respectively).

Table 5 shows adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for major adverse outcomes at 18 to 22 months of age, corrected for prematurity. Epoch was not independently associated with neurodevelopmental impairment, an MDI of less than 70, or

**TABLE 2** In-Hospital Morbidities and Interventions and Postdischarge Factors

	Epoch 1	Epoch 2	P <sup>a</sup>
Surfactant treatment, n (%)	364/411 (88.6)	367/405 (90.6)	NS
Any intermittent mandatory ventilation, n (%)	409/411 (99.5)	403/405 (99.5)	NS
High-frequency ventilation any time during hospitalization, n (%)	165/411 (40.2)	184/405 (45.4)	.1460
PDA diagnosed, n (%)	259/411 (63.0)	265/405 (65.4)	NS
Indomethacin			
Prophylaxis, n (%)	137/411 (33.3)	181/405 (44.7)	.0011
Treatment, n (%)	231/411 (56.2)	222/405 (54.8)	NS
Surgery for PDA, n (%)	110/411 (26.8)	147/405 (36.3)	.0040
Sepsis, n (%)			
Early	5/411 (1.2)	15/405 (3.7)	.0380
Late	206/411 (50.1)	239/405 (59.0)	.0130
Necrotizing enterocolitis, n (%)	36/411 (8.8)	40/405 (9.9)	.6682
Surgery for necrotizing enterocolitis (lap or drain), n (%)	25/411 (50.1)	27/405 (6.7)	.8430
Grade 3 or 4 intraventricular hemorrhage or cystic periventricular leukomalacia, n (%)	76/409 (18.6)	90/404 (22.3)	NS
Shunt for hydrocephalus, n (%)	11/409 (2.7)	17/403 (4.2)	NS
Oxygen at 36 wk postmenstrual age, n (%)	281/411 (68.4)	289/405 (71.4)	NS
Postnatal steroids, n (%)	261/411 (63.5)	133/405 (32.8)	<.0001
Retinopathy of prematurity stage $\geq 3$ with plus, n (%)	121/409 (29.6)	122/400 (30.5)	NS
Surgery during hospitalization, n (%)	199/410 (48.5)	223/402 (55.5)	.0560
Length of stay, median (interquartile range), d	116 (101–138)	119 (104–147)	.0230
Maternal education less than high school, n (%)	87/386 (22.5)	100/403 (24.8)	NS
Corrected age at the time of follow-up visit, mean $\pm$ SD, mo	20.0 $\pm$ 2.0	20.2 $\pm$ 2.9	NS

<sup>a</sup> P values of  $>$  .2 are reported as not significant (NS).

**TABLE 3** Cerebral Palsy, Deafness, and Blindness at 18 to 22 Months of Age, Corrected for Prematurity

	Epoch 1	Epoch 2	P <sup>a</sup>	Epoch 1		Epoch 2	
				≤23 wk	24 wk	≤23 wk	24 wk
				Cerebral palsy, <i>n</i>	407	403	
Moderate to severe, <i>n</i> (%)	45 (11.1)	60 (14.9)	.129	15 (15.6)	30 (9.7)	19 (18.1)	41 (13.8)
Severe, <i>n</i> (%)	25 (6.1)	25 (6.2)	NS	8 (8.3)	17 (5.5)	9 (8.6)	16 (5.4)
Hearing, <i>n</i>	406	400		93	313	103	297
Severe hearing loss, bilateral <sup>b</sup>	8 (2.0)	17 (4.3)	.096	3 (3.2)	5 (1.6)	5 (4.9)	12 (4.0)
Vision, <i>n</i>	408	405		96	312	105	300
Blind, bilateral, <i>n</i> (%) <sup>c</sup>	8 (2.0)	9 (2.2)	NS	3 (3.1)	5 (1.6)	3 (2.9)	6 (2.0)

<sup>a</sup> P pertains to comparisons of all epoch 1 versus epoch 2. P values of > .2 are reported as not significant (NS).

<sup>b</sup> Severe hearing loss, bilateral indicates bilateral permanent hearing loss that requires amplification in both ears.

<sup>c</sup> Blind, bilateral indicates no functional vision in either eye.

moderate-to-severe cerebral palsy, after adjusting for either differences in baseline and case-mix variables alone (model 1) or after inclusion of neonatal morbidities and postdischarge influences (model 2), with or without postnatal steroid use in the model. Only the unadjusted odds of neurodevelopmental impairment were greater in epoch 2 compared with epoch 1. Variables independently associated with neurodevelopmental impairment in multivariate regression included male gender (OR: 1.8 [95% CI: 1.29–2.60]), sepsis (OR: 1.75 [95% CI: 1.23–2.48]), any high-frequency ventilation during hospitalization (OR: 2.16 [95% CI: 1.44–3.23]), grade 3 or 4 intraventricular hemorrhage or cystic periventricular leukomalacia (OR: 1.67 [95% CI: 1.09–2.56]), surgery (OR: 2.69 [95% CI: 1.85–3.90]), and postnatal steroid use (OR: 1.52 [95% CI: 1.02–2.26]).

Variables inversely associated with neurodevelopmental impairment included antenatal antibiotic exposure (OR: 0.58 [95% CI: 0.35–0.95]) and birth weight (OR: 0.81 [95% CI: 0.68–0.96]) for each 100-g increase in body weight).

### DISCUSSION

This analysis is the largest to date to examine early-childhood outcomes among preterm infants born at less than 25 weeks' EGA during 2 epochs in the recent era. We found that survival rates had not changed from epoch 1 to epoch 2. There were no significant differences between epochs in rates of blindness, severe hearing loss, moderate-to-severe cerebral palsy, or an MDI less than 70. Although the absolute rate of neurodevelopmental impairment was greater in the more recent period, epoch was not independently associated with neurodevelop-

**TABLE 5** Unadjusted and Adjusted ORs for Major Adverse Outcomes at 18 to 22 Months of Age Corrected for Prematurity in Epoch 2 Compared With Epoch 1

Model	Epoch 2 vs 1, OR (95% CI)	P
<b>Neurodevelopmental impairment</b>		
Unadjusted	1.41 (1.06–1.88)	.019
Model 1	1.30 (0.96–1.77)	.096
Model 2	1.22 (0.87–1.72)	.246
Model 2 plus PNS	1.41 (0.98–2.04)	.066
<b>MDI &lt; 70</b>		
Unadjusted	1.28 (0.96–1.70)	.092
Model 1	1.21 (0.89–1.65)	.220
Model 2	1.12 (0.80–1.56)	.513
Model 2 plus PNS	1.30 (0.91–1.87)	.154
<b>Moderate-to-severe cerebral palsy</b>		
Unadjusted	1.41 (0.93–2.13)	.105
Model 1	1.23 (0.79–1.90)	.354
Model 2	1.22 (0.72–2.09)	.463
Model 2 plus PNS	1.52 (0.86–2.71)	.152

PNS indicates postnatal steroid use.

mental impairment based on multivariable analysis. Despite a dramatic reduction in postnatal steroid exposure, neurodevelopmental outcomes in early childhood for this group of extraordinarily preterm infants remain unchanged.

Our results may seem to conflict with previous studies that demonstrated improvements in some neurodevelopmental outcomes for some groups of preterm infants. However, our current analysis focused on the most extremely preterm infants, who may be

**TABLE 4** Bayley Scales of Infant Development 2 Developmental and Composite Outcomes at 18 to 22 Months of Age, Corrected for Prematurity

	Epoch 1, Total	Epoch 2, Total	P <sup>a</sup>	Epoch 1		Epoch 2	
				≤23 wk	24 wk	≤23 wk	24 wk
				MDI, <i>n</i> <sup>b</sup>	374	384	
MDI < 70, <i>n</i> (%)	168 (44.9)	196 (51.0)	.107	52 (58.4)	116 (40.7)	63 (61.8)	133 (47.2)
MDI < 50, <i>n</i> (%)	60 (16.0)	66 (17.2)	NS	21 (23.6)	39 (13.7)	26 (25.5)	40 (14.2)
PDI, <i>n</i> <sup>b</sup>	369	384		88	281	104	280
PDI < 70, <i>n</i> (%)	103 (27.9)	134 (34.9)	.047	31 (35.2)	72 (25.6)	46 (44.2)	88 (31.4)
PDI < 50, <i>n</i> (%)	59 (16.0)	73 (19.0)	NS	23 (26.1)	36 (12.8)	27 (26.0)	46 (16.4)
Neurodevelopmental impairment, <i>n/N</i> (%)	186/371 (50.1)	227/387 (58.7)	.023	57/89 (64.0)	129/282 (45.7)	72/103 (69.9)	155/284 (54.6)
Profound impairment, <i>n/N</i> (%)	63/376 (16.8)	67/383 (17.5)	NS	21/89 (23.6)	42/287 (14.6)	27/102 (26.5)	40/281 (14.2)
Unimpaired/minimally impaired, <i>n/N</i> (%)	82/376 (21.8)	85/389 (21.9)	NS	8/89 (9.0)	74/287 (25.8)	14/104 (13.5)	71/285 (24.9)

<sup>a</sup> P values pertain to comparisons of all epoch 1 versus epoch 2. P values of > .2 are reported as not significant (NS).

<sup>b</sup> Because of acute illness, language, behavioral problems, sensory impairment, and other reasons, there were 37 children without an MDI and 42 children without a PDI in epoch 1 and 21 children without an MDI and 21 children without a PDI in epoch 2.

uniquely vulnerable and developmentally distinct from more advanced preterm infants. Vohr et al<sup>8</sup> reported that rates of severe sequelae at 18 to 22 months of age, including an MDI of less than 70 (41.8%–37.2%) and neurodevelopmental impairment (50.2%–44.6%) had significantly decreased over 3 time periods among infants born at 22 to 26 weeks' EGA in the NICHD NRN, independent of confounding variables. But that analysis included infants born at 25 and 26 weeks' EGA. In a single-center study, Wilson-Costello et al<sup>9</sup> compared 20-month outcomes of infants with extremely low birth weight who were born between 2000 and 2002 to those born during the 2 previous periods. The authors found that the rates of any neurosensory abnormality moved from 18% to 23% to 9% over the 3 time periods ( $P = .001$ ), and cerebral palsy rates moved from 8% to 13% to 5% ( $P = .01$ ). Survival without impairment increased from 1990–1999 to 2000–2002. However, mean body weight among survivors was 90 g greater and mean EGA was ~2 weeks more advanced than in our cohort.

Significant concerns often have been raised regarding mortality and short-term morbidities of infants considered to be at the "border of viability."<sup>19</sup> However, few recent studies have focused on the early-childhood outcomes of infants born at less than 25 weeks' EGA, likely because of small patient numbers. A previous NICHD NRN study, which described 18- to 22-month outcomes of more than 700 infants born at less than 25 weeks' EGA during 2 periods in the 1990s, failed to demonstrate improved neurodevelopmental outcomes over time despite more consistently proactive perinatal and neonatal management.<sup>11</sup> In a single-center study, Hack et al<sup>12</sup> compared 20-month outcomes of infants born at 23 to 24 weeks' EGA in 1995–1999 to those born

during 2000–2004 ( $n = 50$  in each time period). The results, which demonstrated no improvement with regard to an MDI less than 70 (42% vs 54%), an MDI less than 50 (10% vs 12%), or cerebral palsy (6% vs 12%), are consistent with those of our study. The Victorian Infant Collaborative Study Group reported that for infants born at less than 26 weeks' EGA, neurosensory outcomes at 2 years had not improved among those born in 1997 compared with those born between 1991 and 1992.<sup>5</sup> But a recent study<sup>10</sup>, which includes the 2005 Victorian Infant Collaborative Study birth cohort, was more encouraging. Although survival rates and quality-adjusted survival rates had not improved from the 1997 to 2005 cohorts of infants born at less than 28 weeks' EGA overall, the mean utility per survivor was higher (better) at each week of gestation for the 2005 cohort compared with either cohort from the 1990s. There were only 7 survivors from those born at 23 weeks' EGA and 22 survivors from those born at 24 weeks' EGA in the 2005 cohort; therefore, extrapolation to extraordinarily preterm infants should generally be viewed with caution. Unlike the Victorian Infant Collaborative Study Group, we did not include a normal-birth-weight control group, and ours was not a population-based cohort, both of which are limitations of our study. A strength of our analysis is, however, that it included a large number of extraordinarily preterm infants. However, our analysis included a large number of extraordinarily preterm infants, which would not have been possible without the benefit of a multi-center network. This is a strength of our analysis.

It should also be acknowledged that neurodevelopmental follow-up at 18 to 22 months' corrected age is a very early window into childhood out-

comes. Previous research has shown that profound disability in early childhood is a good predictor of moderate or severe disability at early school age.<sup>20</sup> However, for those with mild or moderate disability in early childhood, anticipating later outcomes is much more challenging.<sup>20,21</sup> The Bayley Scales of Infant Development II scores in early childhood have been shown to be poorly predictive of cognitive outcomes at 8 years.<sup>22</sup> However, despite difficulties in predicting outcomes precisely, it is clear that extremely preterm infants continue to have substantial impairments in cognitive, motor, and executive function through childhood.<sup>20,23,24</sup> A recent report<sup>25</sup> of 8-year outcomes among infants born in 1997 at less than 28 weeks' EGA from the Victorian Infant Collaborative Study demonstrated that moderate to severe disability was seen in 19% and mild disability in 40% of the cohort of 142 children. Seminal and truly long-term follow-up to young adulthood has shown that neurodevelopmental impairments persist among very-low-birth-weight infants, although many are able to overcome their initial challenges, and risk-taking behavior is less common than among normal-birth-weight control subjects.<sup>26,27</sup> Evaluation at a later age allows for the identification and delineation of a broader range of concerns and for longitudinal analysis to determine the predictive value of early disability. What is considered to be the "border of viability" has shifted substantially over recent decades; infants born at less than 25 weeks' EGA are now more routinely offered intensive care.<sup>5</sup> It is crucial, therefore, to understand neurologic and cognitive outcomes, both in early and later childhood, to properly counsel families and prepare for supports and services the children may require.



## CONCLUSIONS

Rates of survival and major neurodevelopmental outcomes at 18 to 22 months' corrected age for infants born at less than 25 weeks' EGA born in the NICHD NRN did not improve between 2 recent birth epochs. Our results highlight the importance of ongoing research and evidence-based efforts to achieve the ultimate goal of preventing extremely preterm birth.<sup>28</sup> Nevertheless, opportunities to reduce neonatal morbidities associated with adverse early-childhood neurodevelopmental outcomes, including sepsis, must be pursued. Our results clearly underscore the unique vulnerability of these infants; to substantially improve early-childhood outcomes will likely require steps beyond traditional quality-improvement approaches. Although the majority of studies have focused on the association of perinatal and neonatal factors and events with early-childhood outcomes, it is critically important to evaluate the potential for postdischarge developmental interventions to improve outcomes for these high-risk extremely preterm infants.<sup>29</sup>

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## REFERENCES

- Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol.* 2007;196(2):147.e1-147.e8
- Hakansson S, Farooqui A, Homgren PA, Serenius F, Hogberg U. Proactive management promotes outcome in extremely preterm infants: a population-based comparison of two perinatal management strategies. *Pediatrics.* 2004;114(1):58-64
- Hintz SR, Poole WK, Fanaroff AA, et al. Changes in mortality and morbidity among infants born at less than 25 weeks during the post-surfactant era. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(2):F128-F133
- Serenius F, Ewald U, Farooqui A, Holmgren PA, Hakansson S, Sedin G. Short-term outcome after active perinatal management at 23-25 weeks of gestation: a study from two Swedish tertiary care centres. Part 2: infant survival. *Acta Paediatr.* 2004;93(8):1081-1089
- Doyle LW; Victorian Infant Collaborative Study Group. Neonatal intensive care at borderline viability: is it worth it? *Early Hum Dev.* 2004;80(2):103-113
- Costeloe KL, Hennessy EM, Myles J, Draper ES. EPICure 2: survival and early morbidity of extremely preterm babies in England: changes since. E-PAS2008:5365.1. Available at: <http://www.abstracts2view.com/pasall>. Accessed November 16, 2010
- Fischer N, Steurer MA, Adams M, Berger TM, the Swiss Neonatal Network. Survival rates of extremely preterm infants (gestational age <26 weeks) in Switzerland: impact of the Swiss guidelines for the care of infants born at the limit of viability. *Arch Dis Child Fetal Neonatal Ed.* 2009;94(6):F407-F413
- Vohr BR, Wright LL, Poole SK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. *Pediatrics.* 2005;116(3):635-643
- Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes of extremely low birth weight infants in 2000-2002. *Pediatrics.* 2007;119(1):37-45
- Doyle LW, Roberts G, Anderson PJ; Victorian Infant Collaborative Study Group. Outcomes at age 2 years of infants <28 weeks' gestational age born in Victoria in 2005. *J Pediatr.* 2010;156(1):49.e1-53.e1
- Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins R. Changes in neurodevelopmental outcomes at 18-22 months' corrected age among infants born at less than 25 weeks' gestation 1993-1999. *Pediatrics.* 2005;115(6):1645-1651
- Hack M, Wilson Costello D, Friedman H, Minich N, Siner B. Early childhood outcomes of infants born at the limits of viability have not improved in 2000-2004. E-PAS 2008: 5365.21. Available at: <http://www.abstracts2view.com/pasall>. Accessed November 16, 2010
- Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a case study of infants with birth weights less than 1500 g. *J Pediatr.* 1978;92(4):529-534
- Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin N Am.* 1986;33(1):179-201
- Amiel-Tison C. Neuromotor status. In: Taeusch HW, Yogman MW, eds. *Follow-up Management of the High-Risk Infant.* Boston MA: Little, Brown and Company; 1987:115-126
- Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol.* 1997;39(4):214-223
- Bayley N. *Bayley Scales of Infant Development II.* San Antonio, TX: Psychological Corp; 1993
- Committee on Fetus and Newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics.* 2002;109(2):330-338
- Lucey JF, Rowan CA, Shiono P, et al. Fetal infants: the fate of 4172 infants with birth weights of 401-500 grams: the Vermont Oxford Network Experience (1996-2000). *Pediatrics.* 2004;113(6):1559-1566
- Marlow N, Wolke D, Bracewell MA, Samara M, the EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med.* 2005;352(1):9-19
- Ment LR, Vohr B, Allan W, et al. Change in cognitive function over time in very low-birth-weight infants. *JAMA.* 2003;289(6):705-711
- Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics.* 2005;116(2):333-341
- Woodward LJ, Moor S, Hood KM, et al. Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years. *Arch Dis Child Fetal Neonatal Ed.* 2009;94(5):F339-F344
- Marlow N, Hennessy EM, Bracewell MA, Wolke D, the EPICure Study Group. Motor and executive function at 6 years of age after extremely preterm birth. *Pediatrics.* 2007;120(4):793-804

25. Roberts G, Anderson PJ, De Luca C, Doyle LW, the Victorian Infant Collaborative Study Group. Changes in neurodevelopmental outcome at age eight in geographic cohorts of children born at 22–27 weeks' gestational age during the 1990s. *Arch Dis Child Fetal Neonatal Ed.* 2010;95(2):F90–F94
26. Hack M. Young adult outcomes of very low birth weight children. *Semin Fetal Neonatal Med.* 2006;11(2):127–137
27. Saigal S, Stoskopf B, Streiner D, et al. Transition of extremely low-birth-weight infants from adolescence to young adulthood. Comparison with normal birth-weight controls. *JAMA.* 2006;295(6):667–675
28. Costeloe K; EPICure Study Group. EPICure: facts and figures: why preterm labour should be treated. *BJOG.* 2006;113(suppl 3):10–12
29. Spittle AJ, Ferretti C, Anderson PJ, et al. Improving the outcome of infants born at <30 weeks' gestation- a randomized controlled trial of preventative care at home. *BMC Pediatr.* 2009;9:73–87

**COMMERCIALS FOR SCHOOLS:** For those of us who watch a bit of college football, every weekend we are treated not only to a head-to-head battle between two football teams but their respective universities. As reported on The Wall Street Journal website (November 18, 2010:1–3), as part of the TV contract between the network and the schools and conferences, the schools competing in the televised football game may air a free 30-second commercial. As commercial sponsors may pay \$100,000 for that time, these “institutionals” tend to air at times when viewers attention might have lapsed, e.g. during half time. Most university commercials tend to look similar emphasizing a collection of researchers, musicians, and happy students. To learn which of the commercials were most effective, The Wall Street Journal asked four “experts” to review 112 of the 120 “institutionals” produced by schools in the NCAA’s Football Bowl Subdivision. Experts included an advertising executive, a film instructor, and two students. Grading criteria included strength of message, technical merit, and whether they made the students want to attend the school. Evidently, too many schools cannot decide on a single message and instead try all at the same time to draw teens to apply, build alumni support, and prove to the community their commitment to the local economy. Celebrity appearances or voiceovers seem effective. The highest-rated commercials tended to focus on a single theme without using buzz words or hackneyed images. The BCS (Bowl Championship Series) championship football game will be played in January, but according to the experts, the champion self-promoter is the University of Minnesota. The spot features Massoud Amin, a professor of electrical and computer engineering, speaking about the importance of creating a better power grid. Rarely particularly successful on the football field, the win is a welcome victory for the Golden Gophers.

Noted by WVR, MD

**Early-Childhood Neurodevelopmental Outcomes Are Not Improving for Infants Born at <25 Weeks' Gestational Age**

Susan R. Hintz, Douglas E. Kendrick, Deanne E. Wilson-Costello, Abhik Das, Edward F. Bell, Betty R. Vohr, Rosemary D. Higgins and for the NICHD Neonatal Research Network

*Pediatrics* 2011;127:62-70; originally published online Dec 27, 2010;  
DOI: 10.1542/peds.2010-1150

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**From:** [Jean Lowe](#)  
**To:** [Susan Hintz](#); [Kristi Watterberg](#); [Janell Fuller](#); [Andrea Duncan](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [higgins@mail.nih.gov](mailto:higgins@mail.nih.gov)  
**Subject:** Manuscript for Support and Object Permanence- Feedback please  
**Date:** Sunday, June 03, 2012 5:45:02 PM  
**Attachments:** [OP\\_EWM\\_SUPPORT\\_52512.docx](#)

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Hi

I sent this last week and heard back from Carla and Susan but have not received anything yet from anyone. Can everyone send me some feedback by Wednesday as I feel stuck till I now I am on the right track.

I hope to get this into Archives of Pediatric and Adolescent Medicines sometimes this month of next...

Thanks  
Jean

--

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**Early working memory deficits in extremely preterm children at 18-22 months**

Jean R. Lowe<sup>1</sup>, Kristi L. Watterberg<sup>1</sup>; Carla Bann<sup>2</sup>, Janell Fuller<sup>1</sup>, Susan Hintz<sup>3</sup>, Andrea Freeman MD<sup>1</sup>; and for *the Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

**Disclosures**

The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) provided grant support for the Neonatal Research Network's Generic Database and Follow-up Studies.

The coauthors have no conflicts of interest relevant to this manuscript.

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**Reprint Requests:** Please address reprint requests to Andrea Freeman Duncan MD

**Running title:** Working Memory in Preterm Children

**Key words:** development, prematurity, object permanence, early working memory

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## **ABSTRACT**

**Objective(s)** The objective of this study was to evaluate the relationship of object permanence (OP) to Bayley Scales of Infant and Toddler Development 3rd edition (BSID-III) scores in extremely preterm children (<28+0 weeks' gestational age) at 18-22 months corrected age.

**Study Design** 540 children born in 3 ethnic groups were included (White, Black, Hispanic-White) were included in this cohort study. Object permanence by medical factors that included: intraventricular hemorrhage grade III and IV or periventricular interventricular hemorrhage , gestational age retinopathy of prematurity, and SES variables including , race/ethnicity, maternal education, and gender., and using ANOVA (continuous) and chi-square (categorical) analyses. Logistic and linear regression models were used to controlling for medical and social factors.

**Results** 517 children were included. Children with OP had higher BSID-III scores than those with lack of OP (PVALUE) after controlling for other factors. There was no difference in OP between race/ethnic and sociodemographic groups.

**Conclusion(s)** OP is associated with higher BSID-III scores in EP children and is unrelated to race/ethnicity or medical and psychosocial factors. OP may be a race/ethnicity neutral measure of early EF and cognition, and assessment of OP at 18-22 mos may improve early detection of EF deficits in these children.

## INTRODUCTION

Executive function (EF) is a critical element of neurodevelopment in humans, and encompasses working memory, inhibition, and cognitive flexibility (Davidson, 2006). Early working memory a component of executive functioning requires the ability to selectively attend to information that is important, while simultaneously inhibiting interfering information which mediates a wide range of activities requiring reasoning and planning (Savage et al 2006). Difficulties with early executive functions has been found in infants born preterm as early as 8 to 18 months independent of maternal education and cognitive skills (Sun 2009). In a study of early working memory in preschool-aged children born preterm, Woodward et al found that 2-year-olds born preterm had more difficulty encoding new information in working memory compared to term infants (Woodward, 2005). Children born extremely preterm continue to exhibit difficulties in cognition, inhibition, and perceptual motor skills in kindergarten compared to peers born full term. (Orchinik et al 2011, J Int'l Neuropsych). Difficulty with executive functioning persists into school age especially in areas of response inhibition, planning, verbal and spatial working memory skills (Aarnoudse-Moens 2011, (Anderson, 2004; Curtis, 2002; Bayless, 2007)).

Comment [31]: Review references

The Bayley Scales of Infant and Toddler Development (1985, etc..) is used to determine cognitive function in extremely preterm children prior to the age of 3, though these scores have been found to be poor predictors of school-age function (Hack, 2005). Racial/ethnic differences was found on the Bayley Scales of Infant and Toddler Development –II (1998) with a significantly higher mental developmental index found in White children than in Hispanic-White or Black children (Watterberg 2007); these differences were not explained by socioeconomic status or maternal education (Lowe 2009). However a measure of early working memory was similar across all race/ethnic groups and income levels (Lowe, 2009). The finding that early



working memory was not influenced by race and ethnicity or income is an important one when working with diverse populations, as minority populations are at increased risk for preterm birth (Dolan, 2010).

The objective of this study was to evaluate the relationship of early working memory as measured by object permanence items on the BSID-III in a cohort of children born extremely preterm children at 18-22 months corrected age. In addition explored the impact of predefined medical and socio-economic factors on object permanence. Comparison of early working memory skills to both early language and cognitive development occurred as the revised BSID-III has a language measure. We hypothesized that 1) Object permanence would not be affected by the randomization to treatment group 2) Object permanence score would correlate significantly with performance on the BSID-III cognitive and language scores 3) Object permanence would not be affected by maternal education or race/ethnicity in contrast to BSID-III cognitive and language scores.

Comment [32]: Should we say Mat Ed and Ethnicit vs socio-economic?

## METHODS

### Study Population

This study was a retrospective cohort study of children born at 24 0/7 to 27 5/7 weeks gestational age at the sixteen centers of the NRN who were evaluated at 18 to 22 months adjusted age during the period of February, 2005 to February, 2009. All children in this study were part of the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) multi-center study. Infants were randomly assigned to a lower oxygen saturation target range (85% to 89%) or a more conventional target range (91%-95%) until 36 weeks post menstrual age or when the child no longer required ventilator support or oxygen (Rich et al, 2012). The study

also compared continuous positive airway pressure and a protocol driven limited ventilator support begun in the delivery room and continued into the Neonatal Intensive Care Unit (NICU). The infants randomized to the ventilator group received early intratracheal administration of surfactant followed by conventional mechanical ventilation. Of the initial 1,316 infants in the SUPPORT trial 258 died and 64 were lost to follow-up. Of the remaining infants 990 were seen at follow-up and of those 540 had object permanence scores, as this was an ancillary study that began after the SUPPORT follow-up had already begun.

#### Test Measures

The Bayley Scales of Infant and Toddler Development – 3<sup>rd</sup> edition (Bayley, 2005) ((BSID-III) was administered to the children between 18 and 22 months, age adjusted for prematurity. The cognitive and language scale was used for this study. Within the cognitive scale 3 items 40, 45 and 50 were used as measures of object permanence. The items sequentially increased in difficulty and were each worth 1 point. First, the child was asked to find a toy hidden under one of two cups (item 40). Second, double visual displacement was used as the toy was hidden under one cup, removed and hidden a second time under the second cup (item 45). Third, the cups were reversed after the toy was hidden (item 50). The number of items correctly completed was calculated for each child and used as an ordinal measure. Object permanence mastery was defined as a score of 2 or 3.

#### Statistical Analyses

Linear regression was used to analyze object permanence scores with BSID-III cognitive and languages scores controlling for medical (gender, gestational age, intraventricular hemorrhage or periventricular leukomalacia, retinopathy of prematurity, treatment group) and social covariates

(maternal education, race/ethnicity). Logistic regression was used for the object permanence mastery score also controlling for medical and social covariates. Pairwise comparisons between race groups were adjusted for multiple comparisons using the Bonferroni correction.

## RESULTS

There was no significant difference in object permanence score among the two treatment groups after controlling for social and medical variables. There was also no significant difference among the object permanence score after controlling for both maternal education and race/ethnicity.

Those children who obtained object permanence mastery had significantly higher BSID-III cognitive and language scores after controlling for both medical and socio-economic factors. In contrast mothers with high school education or less than high school education had significantly lower BSID-III language scores (F and p values) compared to mothers with greater than high school education ( $p=0.01$ ). Hispanic children ( $p=0.002$ ) and males ( $p=0.001$ ) scored significantly lower on the language scale. In regards to medical factors children who had a history of retinopathy of prematurity ( $p=$ ), Lower gestational age ( $p=0.02$ ) grade III or IV intraventricular hemorrhage or periventricular leukomalacia ( $p=0.002$ ) had significantly lower BSID-III cognitive scores. Lower BSID-III language scores were also found in males ( $p=0.001$ ) and children born of lower gestational age ( $p=0.008$ ). Object permanence master scores were lower for males ( $p=0.001$ ) and children with retinopathy of prematurity diagnosed in the neonatal period ( $p=0.002$ ).

**Comment [13]:** Caria can you add the appropriate p and F values and check what I have and wrote. EDIT anything you want!

## DISCUSSION

In this study we have shown for the first time that children with OPM have higher BSID Cognitive and Language scale scores, and that OPM is a measure of early executive function is not affected by race/ethnicity or socioeconomic status.

---

If object permanence mastery is a better predictor of school age EF than BSID cognitive scores, it could significantly improve our ability to identify children who are at risk for later developmental sequelae. Better understanding of EF development in extremely preterm children could lead to earlier diagnosis of and improved interventions for abnormalities of EF. This is relevant to intervention techniques that can be developed to specifically work on tasks that could enhance EF skills. In conjunction with the BSID cognitive score, use of a measure of object permanence may also improve our detection of ongoing problems with EF at 18–22 months, which is highly related to learning difficulties later in life. Early childhood intervention results in significant improvements in cognitive, academic, and social outcomes (Ramey, 2000).

**ROP and IVH/PVL findings add**

**From:** [Finer, Neil](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** RE: Neurodevelopmental Outcome:Enrolled vs Eligible/Non-enrolled children  
**Date:** Thursday, May 31, 2012 5:06:00 PM

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I am OK either way  
Neil

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

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Thursday, May 31, 2012 6:00 AM  
To: Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; [mew3@cwru.edu](mailto:mew3@cwru.edu); [ROGER.FAIX@HSC.UTAH.EDU](mailto:ROGER.FAIX@HSC.UTAH.EDU); 'Laptook, Abbot'; [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); Myriam Peralta, M.D.; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
Cc: Rich, Wade; [srhintz@stanford.edu](mailto:srhintz@stanford.edu); 'Gabrio, Jenna'; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Neurodevelopmental Outcome:Enrolled vs Eligible/Non-enrolled children

Would folks like to provide input via email or have me set up a call to discuss?

Thanks  
Rose

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
Sent: Wednesday, May 30, 2012 5:40 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; [mew3@cwru.edu](mailto:mew3@cwru.edu); [ROGER.FAIX@HSC.UTAH.EDU](mailto:ROGER.FAIX@HSC.UTAH.EDU); 'Laptook, Abbot'; [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); Myriam Peralta, M.D.; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
Cc: Rich, Wade; [srhintz@stanford.edu](mailto:srhintz@stanford.edu)  
Subject: Neurodevelopmental Outcome:Enrolled vs Eligible/Non-enrolled children

All,

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I have appended the revised proposal based on the changes suggested on our conference call. The revised proposal includes children born at 24-26 week gestation between 1/2006 and 1/2009 so that all would be evaluated with the same instrument (Bayley Scales 3rd ed). The 27 week group was dropped because in 1/2008 the GDB was restricted to children < 27 weeks gestation. The first step is to determine the potential sample size given these date limitations and the FUP rate in the unenrolled group. The analyses would be the same as those in the combined outcome paper.

Yvonne

**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Neurodevelopmental Outcome:Enrolled vs Eligible/Non-enrolled children  
**Date:** Thursday, May 31, 2012 10:08:08 AM

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Let's do email first.  
Yvonne

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From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Thursday, May 31, 2012 5:59 AM  
To: Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; mew3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
Cc: Rich, Wade; srhintz@stanford.edu; 'Gabrio, Jenna'; Archer, Stephanie (NIH/NICHD) [E]  
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Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Wednesday, May 30, 2012 5:40 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; mew3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
Cc: Rich, Wade; srhintz@stanford.edu  
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**Yvonne**



**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; "Kurt Schibler"; mcw3@cwru.edu; ROGER.FATX@HSC.UTAH.EDU; "Laotook, Abbot"; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; "nancy newman"; Rich, Wade; "Das, Abhik"  
**Cc:** Rich, Wade; rhintz@stanford.edu  
**Subject:** Neurodevelopmental Outcome:Enrolled vs Eligible/Non-enrolled children  
**Date:** Wednesday, May 30, 2012 5:39:55 PM  
**Attachments:** Comparison ND outcome enrolled vs eligible nonenrolled SUPPORT trial children at 18 22moRevYEV053012.docx

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All,

Now that PAS is over and the Combined SUPPORT ND Outcome paper is in the final (hopefully mercifully short) review process for re-submission, I would like to begin the enrolled/unenrolled comparison which we discussed last December. This is a logical extension of Wade's papers and the results will be informative for Susan's 7 year FUP.

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Yvonne

## **Proposal to compare early childhood neurodevelopmental outcome of 24-25 week gestation ELBW children enrolled vs. Those not-enrolled in SUPPORT Trial**

Authors: Yvonne Vaucher, Susan Hintz, Wade Rich

### **RATIONALE**

Neurodevelopmental outcome results from the SUPPORT trial demonstrate that children born at 24-27 week gestation are at high risk for adverse neurodevelopmental outcome including NDI, MDI < 70, cerebral palsy and deafness compared to those born at 26-27 week gestation. These results support the findings of prior studies of ELBW or ELGAN children [1-4].

An important question for any multicenter trial including neurodevelopmental follow-up is whether the sample studied is representative and therefore generalizable to the larger population. Selection bias may arise during study enrollment or through lack of data for those who were lost to follow-up. Concerning the latter, the SUPPORT trial follow-up rate of 94% was outstanding, and as such, the bias resulting from loss to follow-up is likely quite small. However, the need for antenatal consent in the SUPPORT trial resulted in higher rates of adverse demographic, clinical and neonatal outcome factors in the eligible, non-enrolled group ( N=3053) compared with the enrolled group (N=1316). [5, 6] For example the rate of resuscitation at delivery, BPD, severe IVH (Grades 3-4) and death were all significantly higher in the eligible, non-enrolled group.

It is important, therefore, to determine whether enrollment selection bias inherent in the need to obtain antenatal consent which was associated with more adverse demographic characteristics and neonatal outcomes is also associated with more adverse neurodevelopmental outcome in children who were eligible but not enrolled in trial, thereby reducing the generalizability of the study results. Alternatively it is possible that the effect of extremely low gestational age alone might predominate such that the incrementally increased risk associated with the higher rate of adverse demographic and neonatal outcome factors in the non-enrolled group would not be evident.

The SUPPORT trial included a very large group of extremely premature children born in the US at  $\leq 27$  weeks gestation for whom the composite outcome of death or NDI at 18-24 months adjusted age was determined for 93.7% (1234/1316). This group provides a unique opportunity to examine the effect of enrollment selection bias on early childhood neurodevelopmental outcome in children who are at the high neurodevelopmental risk. The initial step of determining the maternal and neonatal outcome biases has already been accomplished. [5, 6] The next logical step is to determine whether there is an associated neurodevelopmental outcome bias evident at 18-22 months corrected age. This short-term outcome information will also inform results from the longer term outcome study planned for SUPPORT children at 7 years.

**We therefore propose to compare the frequency of death and the neurodevelopmental outcome of surviving 24-26 weeks gestation children at 18-22 months corrected age born between February 2005 and February 2009 who were eligible and enrolled in the SUPPORT trial to similar outcomes of**

**surviving 24-26 week gestation children who born during the same time period and who were eligible but were not enrolled in the SUPPORT trial.**

## HYPOTHESES

We hypothesize that:

- 1) the incidence of death and therefore the composite outcome of death or NDI will be higher in the eligible/non-enrolled group compared to the eligible/enrolled group
- 2) among survivors to 18-22 month follow up, the neurodevelopmental outcome of the eligible/enrolled vs. eligible/non-enrolled groups will not be significantly different

## METHODS

This study would be a secondary, post-hoc, subgroup analysis of death and neurodevelopmental outcome for the extremely premature children born at 24-26 weeks gestation and enrolled in the SUPPORT trial. The outcome data for these children would be compared with that of the 24-26 week cohort, who were born during the enrollment period of the SUPPORT trial (2/2005 to 2/2009), were eligible for, but not enrolled in, the SUPPORT trial, and who were included in the NRN GDB.

Comprehensive neurodevelopmental outcome data for both groups were prospectively collected at 18-22 months adjusted age, were sent to RTI and recorded in the GDB which is maintained by RTI. We will not include the outcome for 27 week gestation infants as these infants were excluded from the GDB beginning in 1/2008 when the admission criteria for the GDB was changed from birthweight < 1000 g to gestational age < 27 weeks.

Potential date limiters for developmental outcome results: All children enrolled in the SUPPORT trial (2/2005 to 2/2009) were assessed using the Bayley III exam. However, eligible/non-enrolled children in the GDB born before 1/2006 were evaluated using the Bayley II exam. Due to inherent differences in test design and construction, the rate of developmental impairment is substantially lower using the Bayley III (composite cognitive score < 70) when compared to the Bayley II (MDI or PDI < 70), thereby substantially reducing the rate of NDI which is a composite of developmental /cognitive, neuromotor and neurosensory outcomes. Unfortunately it is not possible to adjust for these differences between the Bayley II and Bayley III developmental scores. Due to this problem we may need to limit the time period for developmental comparison between the two groups to only those children born between 1/2006-2/2009, all of whom would be evaluated using the Bayley III. The rates of cerebral palsy, functional motor score (GMFCS) or blindness (vision <20-200) would not be affected as the assessment and definitions for these outcomes were the same throughout the study period for both groups. Although the definition of hearing impairment was changed from bilateral amplification for permanent deafness to permanent hearing loss  $\pm$  amplification in 2006, the prior definition could be used for both groups.

Sample size: We will determine by week gestation and year of birth how many of the eligible/enrolled vs. eligible/non-enrolled in the GDB born at 24 0/7 to 26 6/7 weeks gestation from 2/2005 to 2/2009 had a developmental assessment using either the Bayley II or Bayley III at 18-22 month corrected age.

From this information we can then determine the available sample size and the magnitude of difference in neurodevelopmental outcomes which could be detected given a power of 80% and a two-sided alpha of  $< 0.05$ .

**Lost-to Follow-Up (LTFU):** The demographics and neonatal outcomes of LTFU vs. those who received follow-up at 18-22 months will be compared within and between eligible/enrolled and eligible/non-enrolled groups. We anticipate that although the LTFU rate for the eligible/non-enrolled group will be greater than for eligible/enrolled children followed in the SUPPORT trial; it will be at  $\geq 85\%$ .

**Outcome variables:** Death, NDI (developmental /cognitive score  $< 70$ , GMFCS  $\geq 2$ , moderate-severe cerebral palsy, blindness (vision  $< 20-200$ ); deafness (permanent hearing impairment with amplification), individual components of NDI, developmental/cognitive score  $< 80$  and  $< 85$ , standardized cognitive score

**Analyses:** Comparative outcomes will include death before 18 to 22 months adjusted age, composite NDI, death or NDI and the individual outcomes included in the composite NDI (cognitive, cerebral palsy, GMFCS  $\geq 2$ , blindness and deafness). We will also compare the standardized Bayley III cognitive scores and the proportions of the cognitive score  $< 80$  and  $< 85$ . Outcomes will be compared for groups as a whole (24-26 weeks gestation) and for week gestation as the most immature infants (24-25 weeks gestation) enrolled in the SUPPORT trial were at significantly higher neurodevelopmental risk compared to the 26-27 weeks gestation infants. Unadjusted comparisons of demographic and treat neonatal characteristics between the groups will be conducted using chi-square test for categorical and t-tests for continuous variables. Analyses of categorical outcomes will be performed using robust Poisson regression in a general-estimating model to obtain adjusted relative risks with 95% confidence intervals. Analyses will be adjusted for center and familial clustering.

Linear and logistic regression models will be developed to examine the independent association of trial enrollment with death, composite NDI and individual neurodevelopmental outcomes. Factors in the regression model will include those demographic (gestational age, birthweight, race/ethnicity, maternal education, insurance status, prenatal care, antenatal steroids) and neonatal factors [Apgar  $< 3$  at 1 and 5 minutes, delivery room resuscitation (chest compressions, epinephrine), oxygen at 36 wk(BPD), Grades 3-4 IVH or PVL] which were previously shown to be significantly different between the eligible/enrolled and eligible/non-enrolled groups [5,6]. When collinearity is present (e.g., birthweight/ gestational age; chest compressions/epinephrine), the most powerful predictor will be used in the final regression model.

Two-sided p values  $< 0.05$  will be considered statistically significant.

## RESULTS

Figure: Consort/Patient flow diagram: Enrolled vs. eligible/non-enrolled for death, follow up, lost-to-follow up, neurodevelopmental assessment determined

Tables: Comparisons of enrolled and eligible/non-enrolled groups

1. Demographic and neonatal factors for LTFU
2. Demographic and neonatal clinical outcomes
3. Death, NDI, death or NDI, individual components of NDI (cognitive < 70, GMFCS  $\geq$  2, moderate-severe CP, bilateral blindness, permanent hearing impairment) for each group as a whole and by week gestation
4. Comparison of additional developmental and neuromotor outcomes (i.e., Bayley III standardized composite cognitive score and proportion <80, >85; abnormal neurologic exam, normal, mild, moderate-severe CP for each group as a whole and by week gestation.
5. Adjusted odds ratios for factors (antenatal, neonatal) independently associated with differences in neurodevelopmental outcome.

n.b. Before January 2008 the criteria for GDB enrollment was birthweight <1000g; since January 2008 it has been a gestational age < 27 weeks.

The transition from administration of the Bayley II to the Bayley III at 18-22 months for GDB children occurred in 2/2007 for all those born in 2006.]

#### REFERENCES

1. Raz, S., et al., *Extreme prematurity and neuropsychological outcome in the preschool years*. J Int Neuropsychol Soc, 2010. **16**(1): p. 169-79.
2. Leversen, K.T., et al., *Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm*. Pediatrics, 2011. **127**(3): p. e630-8.
3. Tyson, J.E., et al., *Intensive care for extreme prematurity--moving beyond gestational age*. N Engl J Med, 2008. **358**(16): p. 1672-81.
4. Wood, N.S., et al., *Neurologic and developmental disability after extremely preterm birth. EPICure Study Group*. N Engl J Med, 2000. **343**(6): p. 378-84.
5. Rich, W.D., et al., *Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment*. Pediatrics, 2010. **126**(1): p. e215-21.
6. Rich, W., *Enrollment of ELBW Infants in a clinical research study may not be representative*. Pediatrics. Pediatrics, 2012. **129**(3): p. 480-484.

**From:** Gabrio, Jenna  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; kurt.schibler@cchmc.org; Michele Walsh; Bradley.Yoder@hsc.utah.edu; ROGER.FAIX@HSC.UTAH.EDU; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy.newman; alaptook@WIHRI.org  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Starlett Williams; fmartinez@ucsd.edu; sharon.gough@hsc.utah.edu; Brenda Vecchio  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET  
**Date:** Wednesday, May 30, 2012 12:22:33 PM  
**Attachments:** SUPPORT Subcommittee Call 05 29 2012.RH.pdf

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Dear all,

Please find the minutes from yesterday's call attached. They will be posted on the website shortly.

Thanks,  
Jenna

**From:** Gabrio, Jenna  
**Sent:** Thursday, May 24, 2012 3:33 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy.newman'; Abbot Laptook (alaptook@WIHRI.org)  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu); 'Brenda Vecchio'  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET

Dear all,

The SUPPORT call to discuss the secondary analysis proposal has been scheduled for:

**Tuesday, 5/29**  
**3:00pm ET**

Dial:  
Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Michele will be unable to join. Roger will also be on service and unable to join.

Thanks,  
Jenna

**From:** Gabrio, Jenna  
**Sent:** Tuesday, May 15, 2012 2:39 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy newman'; Abbot Laptook (alaptook@WIHRI.org)  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu); 'Brenda Vecchio'  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - Availability Request

Dear all,

Unfortunately we were unable to find a time for this call to discuss the SUPPORT secondary analysis proposal (attached) in the first poll, so we need to look at a later date.

Please provide your availability on this NEW Doodle poll (<http://www.doodle.com/28usx4cbpbevxdbi>) for the following dates:

5/29, Tu  
5/30, W  
5/31, Th  
6/1, F

6/4, M  
6/5, Tu  
6/6, W  
6/7, Th  
6/8, F

Thanks,  
Jenna

---

**From:** Gabrio, Jenna  
**Sent:** Wednesday, May 09, 2012 12:50 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy newman'  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu)  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2)

Dear all,

We would like to setup a call to discuss the SUPPORT secondary analysis proposal.

Please provide your availability on this Doodle poll (<http://www.doodle.com/rsy3ndtyd863e5a8>) for the following dates:

5/14, M

5/15, Tu

5/16, W

5/17, Th

5/18, F

5/21, M

5/22, Tu

5/23, W

5/24, Th

5/25, F

Thanks,

Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Wednesday, May 09, 2012 12:41 PM

**To:** 'Finer, Neil'; Wally Carlo, M.D.; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michele Walsh'; Bradley.Yoder@hsc.utah.edu; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman

**Cc:** Gabrio, Jenna; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg

**Subject:** Secondary analyses SUPPORT SNIPPV (2)

Hi

Attached is a proposal for a SUPPORT secondary analysis. Jenna will set up a call to discuss

Thanks

Rose



**SUPPORT Subcommittee Call  
May 29, 2012**

**Participants:** Abbot Luptook, Kurt Schibler, Wally Carlo, Roger Faix, Abhik Das, Neil Finer

**NICHD:** Rose Higgins

**Data Coordinating Center:** Jenna Gabrio, Kris Zaterka-Baxter

---

- Dr. Higgins informed the SUPPORT Subcommittee that the NRN DSMC asked about compliance with criteria for surgical intervention for ROP with respect to the Inositol main trial. Given the detail of the ROP information collected in SUPPORT, Marie Gantz has performed an analysis to look at the most severe ROP exam prior to ROP surgery. There were 23 (of 132) subjects who were surgically treated for ROP that either did not have plus disease or meet ET ROP Type 1 criteria. We need to know what the experience is in the network and we will be referencing the experiences in the SUPPORT trial for the INS trial.
- Dr. Finer summarized the SNIPPV proposal.
  - Dr. Higgins said that this proposal did come to the SUPPORT subcommittee when the trial had first started; however, Dr. Walsh had said it would be better if done on the Benchmarking protocol. This paper on the Benchmarking protocol has already been published, though not referenced in the submitted proposal.
  - Dr. Faix feels this is a poor study design. He doesn't think that NIPPV vs. CPAP or non-NIPPV will make much of a difference since most of the ventilation was when the infants were sick.
  - Dr. Carlo said that there is a RCT of NIPPV so it would not look good if we publish this paper. There would also be confounding with the sites since the number of sites involved in the comparison across sites would be uneven.
  - Dr. Higgins said that the hypotheses don't relate to the primary SUPPORT trial hypotheses. Additionally, we did not collect the nasal IMV rate. We only collected information on whether the infant was on Nasal SIMV or not.
  - How to treat the infants who are extubated to nasal canula or oxyhood is not addressed in the proposal. Practice styles will overlay the whole proposal and this will be center dependent.
  - It was felt that it would be difficult to quantitate the effectiveness of NIPPV.
  - If major message has already been published the subcommittee is not sure the investigators would be saying anything that would make SUPPORT database better than the Benchmarking database.
  - It was noted that a similar study has already been done and the subcommittee is not sure that using retrospective data will improve or add to the care.
  - **Action:** The subcommittee rejected this proposal.
- **Other Business:**
  - **Action:** The subcommittee should send comments on the combined paper to Dr. Vaucher by next Friday (June 8).

**From:** Vaucher, Yvonne  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie; "Kurt Schibler"; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; "Laptook, Abbot"; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; "nancy newman"; Rich, Wade; "Das, Abhik"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Tuesday, May 29, 2012 2:07:31 PM

---

Thanks Wally. We all really appreciate your careful review and thoughtful comments!

Yvonne

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

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, May 29, 2012 7:39 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie; 'Kurt Schibler'; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Great job, Yvonne and Myriam and others.

I have only minor suggestions that I have enclosed.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, May 29, 2012 7:51 AM  
**To:** 'Finer, Neil'; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'Vaucher, Yvonne'; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Combined SUPPORT ND Outcome paper Ver 05.23.2012

Hi,

Here is the combined SUPPORT FU paper to be submitted to NEJM. Please send you comments back to Yvonne Vaucher by June 8.

Thanks  
Rose

**Rosemary D. Higgins, MD**

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For  
overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Wally Carlo, M.D.  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Finer, Neil"; Gantz, Marie; "Kurt Schibler"; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; "Laptook, Abbot"; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; "Vaucher, Yvonne"; "nancy newman"; Rich, Wade; "Das, Abhik"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Tuesday, May 29, 2012 10:43:25 AM  
**Attachments:** CombinedSUPPORT\_NDOutcome\_FU\_PIs\_0525wc.docx

---

Great job, Yvonne and Myriam and others.

I have only minor suggestions that I have enclosed.

Wally

Wally Carlo, M.D.  
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Director, Newborn Nurseries  
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-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, May 29, 2012 7:51 AM  
To: 'Finer, Neil'; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'Vaucher, Yvonne'; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
Cc: Archer, Stephanie (NIH/NICHD) [E]  
Subject: Combined SUPPORT ND Outcome paper Ver 05.23.2012

III,

Here is the combined SUPPORT FU paper to be submitted to NEJM. Please send you comments back to Yvonne Vaucher by June 8.

Thanks  
Rose

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

## **Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

Formatted: Font: Not Bold

Yvonne E. Vaucher, MD MPH<sup>1</sup>; \* Myriam Peralta-Carcelen, MD MPH<sup>2</sup>; \* Neil N. Finer, MD<sup>1</sup>; Waldemar A. Carlo, MD<sup>2</sup>; Michele C. Walsh, MD MS<sup>3</sup>; Marie G. Gantz, PhD<sup>4</sup>; Abbot R. Lupton, MD<sup>5</sup>; Bradley A. Yoder, MD<sup>6</sup>; Roger G. Faix, MD<sup>6</sup>; Abhik Das, PhD<sup>7</sup>; Kurt Schibler, MD<sup>8</sup>; Wade Rich, RRT<sup>2</sup>; Nancy S. Newman, RN<sup>4</sup>; Betty R. Vohr, MD<sup>9</sup>; Kimberly Yolton, PhD<sup>8</sup>; Roy J. Heyne, MD<sup>9</sup>; Deanne E. Wilson-Costello, MD<sup>3,4</sup>; Patricia W. Evans, MD<sup>10</sup>; Ricki F. Goldstein, MD<sup>11</sup>; Michael J. Acarregui, MD<sup>12</sup>; Ira Adams-Chapman, MD<sup>13</sup>; Athina Pappas, MD<sup>14</sup>; Susan R. Hintz, MD MS Epi<sup>15</sup>; Anna M. Dusick, MD FAAP<sup>16</sup>; Elisabeth C. McGowan, MD<sup>17</sup>; Richard A. Ehrenkranz, MD<sup>18</sup>; Anna Bodnar, MD<sup>6</sup>; Charles R. Bauer, MD<sup>19</sup>; Janell Fuller, MD<sup>20</sup>; T.

<sup>1</sup> Department of Pediatrics, University of California at San Diego, San Diego, CA

<sup>2</sup> Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

<sup>3</sup> Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

<sup>4</sup> Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC

<sup>5</sup> Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

<sup>6</sup> Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT

<sup>7</sup> Statistics and Epidemiology Unit, RTI International, Rockville, MD

<sup>8</sup> Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH

<sup>9</sup> Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

<sup>10</sup> Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX

<sup>11</sup> Department of Pediatrics, Duke University, Durham, NC

<sup>12</sup> Department of Pediatrics, University of Iowa, Iowa City, IA (current affiliation Children's Hospital at Providence, Anchorage, AK)

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<sup>15</sup> Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

<sup>16</sup> Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN

<sup>17</sup> Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA

<sup>18</sup> Department of Pediatrics, Yale University School of Medicine, New Haven, CT

<sup>19</sup> University of Miami Miller School of Medicine, Miami, FL

<sup>20</sup> University of New Mexico Health Sciences Center, Albuquerque, NM

Michael O'Shea, MD MPH<sup>21</sup>; Gary J. Myers, MD<sup>22</sup>; Rosemary D. Higgins, MD<sup>23</sup> for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

\*Both authors contributed equally to the manuscript

Corresponding author and reprints:

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University of California, San Diego Fax: 619-543-3812  
Division of Neonatology Email: yvaucher@ucsd.edu  
200 West Arbor Drive  
San Diego, CA, 92013

Text: MeSH terms:

Cerebral palsy  
Infant, Newborn  
Infant, Low Birth Weight  
Infant, Extremely Low Birth Weight  
Infant, Premature  
Infant, Extremely Low Gestational Age  
Infant mortality

---

<sup>21</sup> Wake Forest University School of Medicine, Winston-Salem, NC

<sup>22</sup> Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

<sup>23</sup> *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Intellectual disability  
Intensive care, neonatal  
Neurodevelopmental outcome  
Oximetry  
Randomized controlled trial  
Continuous Positive Airway Pressure  
Intubation, intratracheal  
Pulmonary surfactants/therapeutic use  
Oxygen inhalation therapy/methods  
Oxygen administration & dosage  
Retinopathy of prematurity, epidemiology  
Child development  
Developmental disabilities, epidemiology  
Psychomotor disorders, epidemiology  
Follow-up studies

## ABSTRACT

**BACKGROUND:** The SUPPORT trial showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS:** Infants born at 24 0/7 to 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP with a limited ventilation strategy vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months corrected ageCA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) of all enrolled infants; 93.6% (990/1058) of hospital survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [29.9% (183/613)] groups (RR 0.93, 95% CI 0.78 to 1.1, p=0.38) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)]; oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality at follow up was persistently greater in the lower [22.1% (140/633)] compared to the higher [18.2% (118/648)] oxygen saturation group (RR 1.25, 95% CI 1.004 to 1.55, p=0.046).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

Word Count 250



## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between the lower oxygen saturation target group (85-89%) vs. higher oxygen saturation target group (91-95%). However, the risk of ROP among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

The pre-specified follow-up hypotheses of the SUPPORT were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age.

## METHODS

### Study Design

1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation<sup>18</sup>. Using a 2-by-2 factorial design, participants were also randomly

assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygenation target group) using a specially designed blinded oximeter. Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

#### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected ageCA, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>27</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification; and visual impairment, defined as vision  $< 20/200$ , were based upon examination and parental report.

Certified research staff collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

#### Outcome

The pre-specified primary composite outcome at follow up for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score  $< 70$ , GMFCS  $\geq 2$ , moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality among the entire trial cohort and the individual components of NDI among survivors at follow up. Exploratory secondary outcomes at 18 to 22 months CA included comparisons between treatment arms of death or individual components of NDI, Bayley III cognitive composite scores, and levels of cognitive delay. The primary composite outcome (Death or NDI), and individual components of NDI were also compared for the higher and lower gestational age strata.

### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted.<sup>28</sup> Missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes. Two-sided p values of < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 8 tests to be significant at the 0.05 level on the basis of chance alone.

### **RESULTS**

The pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children lost to follow up, 33 were known to be alive. A neurodevelopmental

assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean corrected age-CA at neurodevelopmental assessment and were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months corrected age-CA mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers received antenatal steroids. At follow up there were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

Primary outcome: The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months corrected age-CA (Table 2 a/b). Results from the sensitivity analysis using multiple imputation were virtually identical to the analysis of the non-missing cases. Neither were there significant differences in the outcome of death or NDI between treatment groups in the higher and lower gestational age strata. (Appendix A) There was no difference in death between the CPAP and Surfactant arms. Mortality remained significantly higher in the lower compared to the higher saturation target group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all  $p$  values  $> 0.7$ ).

Other outcomes: The incidences of cognitive impairment (BSID-III cognitive composite score  $< 70$ , gross motor function level  $\geq 2$ , moderate/severe cerebral palsy, and blindness among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Table 2 a and b) or between the gestational age strata;(Appendix A). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen saturation target group vs. the lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month-CA visit. (Table 3) Neither were there differences between the CPAP and Surfactant arms or between the lower and higher saturation groups in the combined outcome of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix B). Sixty percent (583/977) of children evaluated at 18-22 months-CA had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations.

## DISCUSSION:

This trial tested critical outcome hypotheses related to both ventilatory and oxygenation strategies in a very-high risk, extremely premature population. We found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant or between those randomized to the lower vs. higher oxygen saturation target groups in the SUPPORT trial. Mortality remained significantly higher in the lower compared to the higher saturation target group. There were no significant differences among survivors in any of the treatment arms for NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq 2$ ), hearing impairment, and bilateral blindness. To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which include pre-specified neurodevelopmental outcome at two years of age will not be available until 2014.<sup>29</sup>

Recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>21,30</sup> In SUPPORT death prior to discharge was increased among neonates randomized to the lower-oxygen-saturation target group. As was published previously, causes of death before discharge between the lower and higher oxygen saturation groups were not different.<sup>24</sup> Mortality remained higher in the lower oxygen saturation target group at 18 to 22 months corrected age as well as in the most immature gestational age stratum of the surfactant administration group.

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>31,32</sup> We previously reported that the lower oxygen saturation target was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) among survivors at discharge.<sup>24</sup> Eye surgery was more frequent in higher oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at 18 to 22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher saturation groups.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had comprehensive, standardized neurodevelopmental evaluation at 18-22 months corrected age. As in most trials of interventions starting at birth, the generalizability of this study may be limited by it being center rather than population based and by requiring antenatal consent which is associated with enrollment bias.<sup>33,34</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>35</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome.

**Comment [WC1]:** Very few NICU based studies are population based. Generally they cannot be as babies are selectively referred from level 1 and 2 hospitals.

In summary, there were no significant differences in the composite outcome of death or NDI, or in the individual components of NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation targets. Mortality was lower in the most immature stratum of the Early CPAP group and in the higher oxygen saturation target group.

Word Count 2640

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Figure1: Consort Diagram for SUPPORT

Table 1: Demographic and neonatal characteristics of follow-up cohorts

Table 2: Primary outcome (Death or NDI) and component outcomes: CPAP vs. Surfactant and Lower vs. Higher Oxygen Saturation Target Groups

Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups

Appendix A: Outcomes for treatment groups by gestational age strata

Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Lupton AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.

20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.
23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
27. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
28. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
29. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
30. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
31. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
32. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
33. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
34. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
35. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Date:** Tuesday, May 29, 2012 10:37:42 AM

---

Yeah, I did see this before!

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, May 29, 2012 10:31 AM  
**To:** Das, Abhik  
**Subject:** FW: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

Michele's comments--

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-5575  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Thursday, May 03, 2012 2:39 PM  
**To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wally\_Carlo\_M.D.  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

No I do not recall this- wand would not support since we did this in benchmarking.

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
*216.844.3759*

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Thursday, May 03, 2012 2:28 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]; [mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu)  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

I don't remember this at all, and I did look through my emails and folders, but couldn't find anything!

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 03, 2012 2:23 PM  
**To:** 'wcarlo@peds.uab.edu'; Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]; 'mcw3@po.cwru.edu'  
**Cc:** Das, Abhik  
**Subject:** Fw: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Do any of you recall this? Talking to Neil would not meet the network's approval process for a secondary analysis approval. I am not sure the SUPPORT subcommittee granted approval. I thought we directed this to Benchmarking.

Let me know if I have dropped the ball on this one. I have included Michele as she was quite involved during the time when (b)(6)

Thanks for your help

Rose

---

**From:** Bhandari, Vineet [mailto:vineet.bhandari@yale.edu]  
**Sent:** Thursday, May 03, 2012 12:37 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Ehrenkranz, Richard <richard.ehrenkranz@yale.edu>; Das, Abhik (adas@rti.org) <adas@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

Hello Rose,

I apologize for the confusion that I have created inadvertently. Ignore the "Response to Reviewers Comments" document as it was in relation to the Benchmarking dataset and as you mentioned, resulted in the PAS abstract and the paper that has already been published in Pediatrics. (I had saved the document in the wrong folder in error).

1. Now, regarding the secondary analysis of the SUPPORT Trial stuff, I am a little surprised that there is no record of it, as I had talked about it with Neil initially at one of the SUPPORT meetings and later told by him, that it was "approved". I would try and touch base with him at least once a year about it, and he had told me to wait till the follow up was completed and that manuscript was written up.

I spent the last few hours scouring my old files and emails. Unfortunately, I tend to clean up emails >5 years old, and also moved onto to a new email server recently (which did not help matters). I am going to give a listing of dates and copies of emails regarding the same, that I could "find/recover". (I can forward the actual emails, if you wish, but I did not want to clog everybody's inboxes). Perhaps, it will help Neil and/or Abhik to locate some documents. I spoke with Rich, and he has at least found the Secondary Analysis proposal in his file collection.

(i) Date: 11/12/2004, 11:10 AM. "Hello Rich. I wrote up a (hopefully) succinct request for doing a "Secondary analyses SUPPORT SNIPPV" (do you like that title?). Please review. Your suggestions/comments will be helpful, as always. Then, I will send it over to Neil and hopefully, it will be a go ..."

(ii) Date: 11/12/2004, 3:45PM. "Hello, Neil, Please find attached a draft of my proposal for secondary analyses of babies receiving SNIPPV as part of the SUPPORT study." [cc'ed to Rich]

Date: 11/15/2004, 12:25 PM. "Hello Vineet, Could you please specify the actual analyses for this secondary? This requires a bit more detail, and should include what you will actually

(iii) evaluate by which statistic. What is the Primary hypothesis of this Secondary? I realize that you want to use already collected data, but if you don't present in a clear fashion, this will not be considered. Thanks Neil Finer"

(iv) Date: 11/15/2004, 2:11 PM. "Hello, Neil. Please see attached. Specifically, please see page 2 for the primary and secondary hypotheses of the "secondary analyses" and page 5 for the "statistical analyses". I hope the above is sufficiently detailed. Please let me know if it still does not meet the requirements. Thanks for your help. Vineet."

(v) Date: 5/4/2011, 4:52 PM. "Hello Neil, It was nice to catch up with you at PAS in Denver.....As the time is coming up for the "follow -up" to be completed, I just wanted to be in the queue.....As with our earlier collaboration, thank you for your support (no pun intended :-)). Regards. Vineet."

Sorry for the long email, but, I am hoping Neil can help me out here....

Thanks.

Vineet.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, May 02, 2012 4:38 PM  
**To:** Bhandari, Vineet  
**Cc:** Ehrenkranz, Richard; Das, Abhik ([adas@rti.org](mailto:adas@rti.org))  
**Subject:** FW: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Vineet

I have gone back through our files and found an evaluation for a PAS abstract from the Benchmarking dataset for which a manuscript has been published. I have asked RTI and looked through our records and we cannot find a record of approval for this SUPPORT secondary – can you forward us the approval.

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](mailto:higginsr@mail.nih.gov)

---

**From:** Bhandari, Vineet [<mailto:vineet.bhandari@yale.edu>]  
**Sent:** Wednesday, May 02, 2012 11:31 AM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Hello Neil (and Rose),

It was nice to catch up with you at PAS in Boston. As I had mentioned to you, I am sending you a copy of my "secondary analysis" proposal of SNIPPV/NIPPV (initially submitted on 11-15-2004) in the SUPPORT study as well as my "response" to comments by the reviewers of the proposal (initially submitted on 6-21-2006). Following this, I was told that it had been "approved". (The only clarification that I would make is that I would combine SNIPPV/NIPPV as the "nasal ventilation group" since we lost our Infant Star ventilators in Dec 2006).

As I believe the "follow -up" is completed, I just wanted to know who should I contact to initiate the analysis.

As with our earlier collaboration, thank you for your support (no pun intended ☺).

Regards.  
Vineet.

Vineet Bhandari, MD, DM  
Associate Professor of Pediatrics, Obstetrics, Gynecology  
and Reproductive Sciences  
Director, Program in Perinatal Research  
Yale University School of Medicine  
Yale Child Health Research Center  
Room Number: 219  
P.O. Box 208081  
464 Congress Avenue  
New Haven, CT 06520-8081  
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Fax: 203-737-2805



**From:** [Gabrio, Jenna](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [Wally Carlo, M.D.](#); [kurt.schibler@cchmc.org](#); [Michele Walsh](#); [Bradley.Yoder@hsc.utah.edu](#); [ROGER.FAIX@HSC.UTAH.EDU](#); [Das, Abhik](#); [Gantz, Marie](#); [Wright, Linda \(NIH/NICHD\) \[E\]](#); [nancy.newman](#); [alaptook@WIHRI.org](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Zaterka-Baxter, Kristin](#); [Cunningham, Meg](#); [Starlett Williams](#); [fmartinez@ucsd.edu](#); [sharon.gough@hsc.utah.edu](#); [Brenda Vecchio](#)  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET  
**Date:** Tuesday, May 29, 2012 10:33:15 AM

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A friendly reminder for today's call.

**From:** [Gabrio, Jenna](#)  
**Sent:** Thursday, May 24, 2012 3:33 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy.newman'; Abbot Laptook (alaptook@WIHRI.org)  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu); 'Brenda Vecchio'  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET

Dear all,

The SUPPORT call to discuss the secondary analysis proposal has been scheduled for:

**Tuesday, 5/29**  
**3:00pm ET**

Dial:  
Within the USA

or

Outside the USA

Then, enter Participant Passcode:

Unfortunately we couldn't find a time that worked for everyone so Michele will be unable to join. Roger will also be on service and unable to join.

Thanks,  
Jenna

---

**From:** [Gabrio, Jenna](#)  
**Sent:** Tuesday, May 15, 2012 2:39 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy.newman'; Abbot Laptook (alaptook@WIHRI.org)  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu); 'Brenda Vecchio'

**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - Availability Request

Dear all,

Unfortunately we were unable to find a time for this call to discuss the SUPPORT secondary analysis proposal (attached) in the first poll, so we need to look at a later date.

Please provide your availability on this NEW Doodle poll (<http://www.doodle.com/28usx4cbpbvxdbi>) for the following dates:

5/29, Tu  
5/30, W  
5/31, Th  
6/1, F

6/4, M  
6/5, Tu  
6/6, W  
6/7, Th  
6/8, F

Thanks,  
Jenna

---

**From:** Gabrio, Jenna

**Sent:** Wednesday, May 09, 2012 12:50 PM

**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy newman'

**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu)

**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2)

Dear all,

We would like to setup a call to discuss the SUPPORT secondary analysis proposal.

Please provide your availability on this Doodle poll (<http://www.doodle.com/rsy3ndtyd863e5a8>) for the following dates:

5/14, M  
5/15, Tu  
5/16, W  
5/17, Th  
5/18, F

5/21, M  
5/22, Tu  
5/23, W  
5/24, Th  
5/25, F

Thanks,  
Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 09, 2012 12:41 PM  
**To:** 'Finer, Neil'; Wally Carlo, M.D.; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michele Walsh'; Bradley.Yoder@hsc.utah.edu; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman  
**Cc:** Gabrio, Jenna; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** Secondary analyses SUPPORT SNIPPV (2)

Hi

Attached is a proposal for a SUPPORT secondary analysis. Jenna will set up a call to discuss

Thanks

Rose

**From:** Rich, Wade  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Tuesday, May 29, 2012 10:32:26 AM

---

Tx.

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, May 29, 2012 7:29 AM  
**To:** Rich, Wade  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Approved with a request for revisions to Yvonne- minutes are at:

<https://neonatal.rti.org/private/pdf/Administration/Minutes/Subcommittee/SUPPORT/SUPPORT20120117.pdf>

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

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

**From:** Rich, Wade [mailto:wrich@ucsd.edu]  
**Sent:** Tuesday, May 29, 2012 10:24 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Did we ever get approval from the network to do the follow-up analysis of enrolled vs. non-enrolled?  
wade

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, May 29, 2012 5:51 AM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu';  
'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; 'Myriam Peralta, M.D.';  
Vaucher, Yvonne; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Combined SUPPORT ND Outcome paper Ver 05.23.2012

HI,

Here is the combined SUPPORT FU paper to be submitted to NEJM. Please send you comments back to Yvonne Vaucher by June 8.

Thanks  
Rose

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

**From:** Wally Carlo, M.D.  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Finer, Neil"; Gantz, Marie; "Kurt Schibler"; mcw3@cwru.edu; ROGER.FAIX@HSC.UTAH.EDU; "Laptook, Abbot"; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; "Vaucher, Yvonne"; "nancy newman"; Rich, Wade; "Das, Abhik"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Tuesday, May 29, 2012 10:22:44 AM

---

Sorry, saw Rose's name below!!

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, May 29, 2012 7:51 AM  
**To:** 'Finer, Neil'; Wally Carlo, M.D.; Gantz, Marie; 'Kurt Schibler'; 'mcw3@cwru.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; 'Laptook, Abbot'; Bradley.Yoder@hsc.utah.edu; Myriam Peralta, M.D.; 'Vaucher, Yvonne'; 'nancy newman'; Rich, Wade; 'Das, Abhik'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Combined SUPPORT ND Outcome paper Ver 05.23.2012

HI,  
Here is the combined SUPPORT FU paper to be submitted to NEJM. Please send you comments back to Yvonne Vaucher by June 8.

Thanks  
Rose

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

**From:** Das, Abhik  
**To:** [alaprook@WIHRI.org](mailto:alaprook@WIHRI.org); [Bradley Yoder](mailto:Bradley.Yoder); [adas@rti.org](mailto:adas@rti.org); [mgantz@rti.org](mailto:mgantz@rti.org); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [MPeralta@PEDS.UAB.EDU](mailto:MPeralta@PEDS.UAB.EDU); [nancy.newman](mailto:nancy.newman); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [Roger.Fajx@hsc.utah.edu](mailto:Roger.Fajx@hsc.utah.edu); [Wallace, Dennis](mailto:Wallace.Dennis); [Wally Carlo, M.D.](mailto:Wally.Carlo.M.D.); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [Yvonne Vaucher](mailto:Yvonne.Vaucher)  
**Subject:** FW: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET  
**Date:** Tuesday, May 29, 2012 10:18:22 AM

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FYI, Marie is unable to join the call today to review the secondary analysis proposal from Dr. Bhandari. She has thus sent in the following written comments for our consideration.

Thanks

Abhik

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**From:** Gantz, Marie  
**Sent:** Thursday, May 24, 2012 4:33 PM  
**To:** Das, Abhik  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET

Here are my comments. Let me know if you want me to circulate them more widely.

It is not entirely clear to me how Vineet intends to classify infants as being in the SNIPPV group vs. the NCPAP group based on the data, but I am fairly confident that doing so will not be a simple task. Specific comments, questions, and considerations are listed below.

- Is SNIPPV the same as Nasal SIMV, which is recorded on the SUPPORT forms? If not, I'm not sure how we would identify its use.
- By my read, Vineet wants to identify the mode of support the infant was placed on after being extubated. This would require matching extubation dates and times with the next recorded mode of support which likely will not be straightforward. Considerations:
  - Would the classification be based only on the first recorded extubation? If not, how will multiple extubations be handled? Would this be planned extubations only?
  - In the first 14 days, we have support data every 2 hours at best (and every 8 hours at the start of the study). After the first 14 days, we have support data every 6 hours at best.
  - In my prior experience looking at the intubation and extubation data, there seemed to be a lot of cases where there were either two intubations or two extubations in a row, which made me wonder about the quality of those data. This will also make it difficult to assess the total length of time intubated.
- If preference for SNIPPV vs. NCPAP differs by center as Vineet suggests, then that preference will be confounded with other center differences, making it more difficult to pinpoint as the source of differences in outcome rates.

The bottom line is that this analysis will likely be time-consuming and the data will likely not be very clean, so those factors should be considered in deciding whether to pursue the analysis.

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-251-6275

---

**From:** Gabrio, Jenna  
**Sent:** Thursday, May 24, 2012 3:33 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; Wally Carlo, M.D.; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michele Walsh'; Bradley.Yoder@hsc.utah.edu; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman; Abbot Laptok (alaptok@WIHL.org)  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Starlett Williams; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu); 'Brenda Vecchio'  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET

Dear all,

The SUPPORT call to discuss the secondary analysis proposal has been scheduled for:

**Tuesday, 5/29**  
**3:00pm ET**

Dial:

**Within the USA**

(b)(6)

or

**Outside the USA**

(b)(6)

**Then, enter Participant Passcode:**

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Michele will be unable to join. Roger will also be on service and unable to join.

Thanks,  
Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 09, 2012 12:41 PM  
**To:** 'Finer, Neil'; Wally Carlo, M.D.; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michele Walsh'; Bradley.Yoder@hsc.utah.edu; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman  
**Cc:** Gabrio, Jenna; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** Secondary analyses SUPPORT SNIPPV (2)

Hi

Attached is a proposal for a SUPPORT secondary analysis. Jenna will set up a call to discuss

Thanks

Rose



**From:** Wally Carlo, M.D.  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Finer, Neil; Gantz, Marie; Myriam Peralta, M.D.; Vaucher, Yvonne  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 6:15:37 PM

---

Great. Thx

Wally

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

**From:** "Vaucher, Yvonne" <yvaucher@ucsd.edu>  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Cc:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Finer, Neil" <nfiner@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu>, "Vaucher, Yvonne" <yvaucher@ucsd.edu>  
**Sent:** Fri, May 25, 2012 18:34:25 GMT+00:00  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

All,

Use these attachments. Paper orientation on preceding had been changed by my errant fingers to "landscape"-now correctly on portrait. Also corrected title of Table 2 from "Death and NDI" to "Death or NDI".

Yvonne

All,

SUPPORT paper for the FUP PI reviews is attached.

Re Wally's suggestions:

1. Marie checked the numbers which are clear in the consort diagram. I rephrased the LTFU sentence in the 1st paragraph of results to indicate that survival was known for 33 of the 68 LTFU.
2. Mortality precedes NDI outcomes in 1st paragraph of Discussion
3. Added Stenson's ref to 2nd paragraph of discussion
4. Order of last paragraph changed to put primary outcome first. I discussed deleting the CPAP lower GA stratum mortality with Neil. He would like to leave it in for now as it is an 8% difference for the highest risk group and let the NEJM editors decide whether to delete it or not.
5. Deleted "Although" in first paragraph of results
6. I think the significances are OK. The only one in question (as almost all are  $> 0.01$ ) is the lower vs. higher sat mortality which is 0.046 and if we didn't round up but left to 3 decimal places although it is  $>0.01$ .

The word counts for abstract and body are within the NEJM limits.

I am sure our FUP PIs will have some thoughts so if I have missed anyones changes we can catch them later.

Thanks for all you help!!!!!!

Yvonne

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Friday, May 25, 2012 6:39 AM  
To: Vaucher, Yvonne  
Cc: Gantz, Marie; 'Wally Carlo, M.D.'  
Subject: RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

I

I'd like to send today - would this be possible??

Thanks

Rose

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

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Thursday, May 24, 2012 9:03 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Rose,

Here is the latest. After Maries final check and Wally's comments I think we can send it on to the PIs.

Yvonne

---

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 10:00 PM  
To: Vaucher, Yvonne  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 9:57 PM  
To: 'Gantz, Marie'  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Marie,

Here is the latest and I hope the now correct version of the Combined Outcome SUPPORT paper. I used the corrected copy that you sent me on 4/16 so it should include all your corrections plus the few

additional comments and tables you sent later on 5/1. The references are updated. I added age at FUP and FUP rates to Table 1. Please review the first para of the results. I did move things around and say things a bit differently.

I tried to address Wally's issues. Should we look at the FUP rate differently? Wally and Abhik had some issues about how we calculated it. Do we need to say anything more specific about the differences in the FUP cohorts in SGA, NEC, PNS status?

If we want to compare the demographics for all 1234 children with the primary composite outcome of Death or NDI (Table 1) we will need to run the demographics for this entire group. Table 1 includes only the 990 who were seen in FUP.

The abstract word count is 250 (NEJM limit 250) and paper body word count is 2626 (NEJM limit 2700).

Thanks so much for your careful review. It is really appreciated!

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 9:48 PM  
To: 'Wally Carlo, M.D.'  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Wally,

Here is the latest version I think with everyone's corrections. I hope this version addresses your concerns. I changed the order of the first para in the Results and began the para with a sentence about the importance of the study. I think it is fine to give the FUP rate as 94%. It does assume that all children LTFU with unknown survival lived which would yield the most conservative estimate of the FUP rate. The FUIP rate is really very high and I don't think anyone will criticize it. I eliminated all reference to BOOST and the oximeter algorithm, "specific visual outcomes", ANS. The p values are all presented to two decimal places since none are  $<0.001$  per the NEJM guidelines.

I think it is ready to go out to the other PIs. We can address any other issues in the meantime.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**From:** Gantz, Marie  
**To:** Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Friday, May 25, 2012 3:25:39 PM  
**Attachments:** SUPP10\_data\_for\_infants\_meeting\_ROP\_surgery\_criteria\_25MAY12.rtf

---

Dale also wanted to see data for infants who met criteria for surgery but who did not have surgery recorded. SUPP10 data on 10 infants is attached. Note that 126+10 is greater than the 132 with severe ROP reported in Wally's paper because there were several infants who had severe ROP and also died, and the paper reported severe ROP among survivors. The 10 infants in the attached document survived to discharge. Note that the center and infant IDs in this document do not correspond to the codes used in the last document (I used the same letters and numbers but they do not correspond to the same centers and/or infants).

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-354-6225

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Thursday, May 24, 2012 5:15 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi Marie,

There are quite a few more cases of treatment before documented criteria for treatment than I had expected.

As we go back to the DSMC with this, I think it would be important to be able to better explain it.

Also, just to confirm with you. Infants who might have had ROP disease worse than Type 1 would also be considered treated appropriately. Did you exclude any infants because they had stage 4a or 4b or stage 5?

If it is going to take a lot of time, please discuss it with Dr. Das first. He and Dr. Higgins and I can discuss whether to go forward.

I do think it will be important to understand and be able to account for at least some of them -- and the fuller clinical ROP picture is likely to do that.

Therefore, I would like to request that you provide the more detailed data.

I also volunteer to individually review the ROP printouts from the subgroups listed below: (there is a nice de-identified format that was used for INS-2 that you could use that gives me basically two

pages per infant – one for each eye)

5 who met criteria for surgery, but were not recorded as having had surgery (123-127=5)

23 who did receive surgery, but did not meet criteria for surgery

Thanks!

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 1:39 PM  
**To:** Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Dale, do you still need the more detailed data you requested?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-354-6255

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Thursday, May 24, 2012 4:18 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Thank you Marie,

The answers provide very interesting data for discussion.

We will have some work to do with the Ophthalmologists in the inositol Study.

Particularly: treating in zone II without evidence of plus disease.

One the cases below not meeting criteria is unlikely enough that it is probably a keying error, but I would not want to go back at this point in time to do a query.

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi all, I included answers to Rose's questions below, based on my preliminary look at the SUPPORT data. I will send more complete answers to Dale's questions when I have them.

Marie

Marie Gantz, Ph.D.

Senior Research Statistician  
RTI International  
mgantz@rti.org  
828 254 4255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery 127 (based on Wally's paper, this looks like 132) MG: 132 includes infants with severe ROP as defined in the paper who did not have surgery recorded.

Can you tell us how many had each of these categories:

**1. type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);**

MG: 22 met these criteria in at least one eye

**2. zone I, stage 3 ROP without plus disease;**

MG: An additional 6 met these criteria in at least one eye (there were a total of 11 but 5 also met criteria for type I ROP in #1)

**3. zone II, stage 2 or 3 ROP with plus disease.**

MG: An additional 76 met these criteria in at least one eye (there were a total of 80 but 4 also met criteria in #1 or #2)

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

MG: There were 23 who did not meet criteria in #1-3 but who did have surgery:

1 had zone II stage 2 with plus disease missing

2 had zone II stage 2 no plus disease

18 had zone II stage 3 no plus disease

1 had zone III stage 3 no plus disease

1 had missing zone and stage but plus disease

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch

**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** "Wally Carlo, M.D."; Finer, Neil; Gantz, Marie; Myriam Peralta, M.D.; Vaucher, Yvonne  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 2:34:44 PM  
**Attachments:** [Table 3 Vision Outcome\\_MG04262012YV0522\\_MG0525YV0525.docx](#)  
[Appendix A\\_B\\_042512\\_MGYV0522\\_MG0525YV0525.docx](#)  
[Consort Figure Correct MP\\_0523MG0525YV0525.doc](#)  
[Table 1\\_04112012\\_MG0426YV0523MG0525YV0525.docx](#)  
[Table 2CPAP\\_MG04262012YV0522MG0525YV0525.docx](#)  
[CombinedSUPPORT\\_NDOutcome\\_FU\\_PIs\\_0525.docx](#)

---

All,

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**Sent:** Friday, May 25, 2012 6:39 AM  
**To:** Vaucher, Yvonne  
**Cc:** Gantz, Marie; 'Wally Carlo, M.D.'  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Thursday, May 24, 2012 9:03 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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Sent: Wednesday, May 23, 2012 10:00 PM  
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Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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To: 'Wally Carlo, M.D.'  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower	Higher	ARR*	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness and other abnormal eye findings were not adjusted for study center due to small N)

## Appendix A: Outcomes for treatment groups by gestational age strata

### CPAP vs. SURFACTANT

<u>24 0/7-25 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral –no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

<u>26 0/7-27 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

**LOWER VS. HIGHER OXYGEN SATURATION TARGETS**

<u>24 0/7-25 6/7 weeks Gestational Age</u>	Lower	Higher	ARR*	p
Death or NDI-no./total no.(%)	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA-no./total no.(%)	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined-no./total no.(%)	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI-no./total no.(%)	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70-no./total no.(%)	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2-no./total no.(%)	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy-no./total no.(%)	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral -no./total no.(%)	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Hearing impairment-no./total no.(%)	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22

<u>26 0/7-27 6/7 weeks Gestational Age</u>	Lower	Higher	ARR*	P
Death or NDI-no./total no.(%)	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA-no./total no.(%)	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined-no./total no.(%)	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI-no./total no.(%)	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70-no./total no.(%)	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level ≥ 2-no./total no.(%)	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral palsy-no./total no.(%)	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral –no./total no.(%)	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Hearing impairment-no./total no.(%)	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

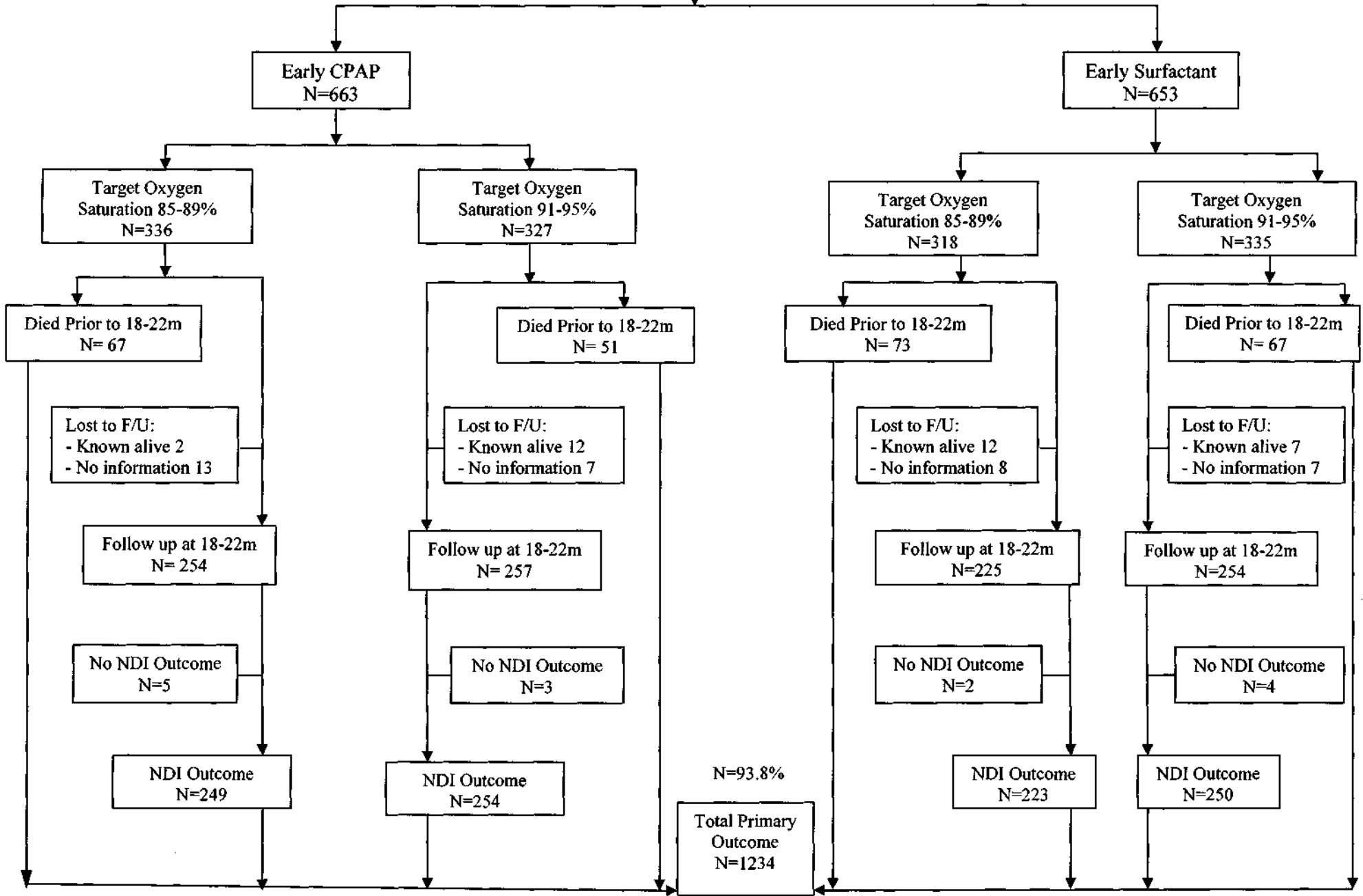
\*Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

## Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms

<u>CPAP vs. Surfactant</u>	CPAP	SURF	ARR*	p
BSID-III cognitive composite score (adjusted mean)	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score < 85-no./total no.(%)	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 80-no./total no.(%)	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05
<u>Lower vs. Higher Oxygen Saturation Targets</u>	<u>LOWER</u>	<u>HIGHER</u>	ARR*	p
BSID-III cognitive composite score (adjusted mean)	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85-no./total no.(%)	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80-no./total no.(%)	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

\*Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

SUPPORT TRIAL  
N=1316



Primary Outcome

Primary Outcome



**Table 1: Demographics and Characteristics of Follow-up (FUP) Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)

Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < 12 <sup>th</sup> grade-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%) †	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language -no./total no.(%) ‡	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%)†	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	117/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months, Mean ± SD)	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7
Follow up-no./total no.(%)	511/545(93.8)	479/513(93.4)	479/514(93.2)	551/544(93.9)

\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

¶ Among survivors to 36 weeks postmenstrual age

‡ Only available at 18-22 months corrected age† Among survivors to discharge or transfer

Comparisons of neonatal outcomes are adjusted for stratification by center and gestational age and for familial clustering

**Table 2: Death or NDI: CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups\***

<u>a. CPAP vs. Surfactant</u>	<u>CPAP</u>	<u>Surfactant</u>	<u>ARR*</u>	<u>p</u>
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

<b><u>b. Lower vs. Higher Oxygen Saturation</u></b>	<b><u>Lower</u></b>	<b><u>Higher</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA-no./total no.(%)	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined-no./total no.(%)	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI-no./total no.(%)	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70-no./total no.(%)	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2-no./total no.(%)	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy-no./total no.(%)	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral-no./total no.(%)	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment-no./total no.(%)	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

## **Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

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**Text: MeSH terms:**

**Cerebral palsy**

**Infant, Newborn**

**Infant, Low Birth Weight**

**Infant, Extremely Low Birth Weight**

**Infant, Premature**

**Infant, Extremely Low Gestational Age**

**Infant mortality**

**Intellectual disability**

**Intensive care, neonatal**

**Neurodevelopmental outcome**

**Oximetry**

**Randomized controlled trial**

**Continuous Positive Airway Pressure**

**Intubation, intratracheal**

**Pulmonary surfactants/therapeutic use**

**Oxygen inhalation therapy/methods**

**Oxygen administration & dosage**

**Retinopathy of prematurity, epidemiology**

**Child development**

**Developmental disabilities, epidemiology**

**Psychomotor disorders, epidemiology**

**Follow-up studies**

## **ABSTRACT**

**BACKGROUND:** SUPPORT showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS:** Infants born at 24 0/7 to 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months CA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) of all enrolled infants; 93.6% (990/1058) of hospital survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [29.9% (183/613)] groups (RR 0.93, 95% CI 0.78 to 1.1,  $p=0.38$ ) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)]; oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32,  $p=0.21$ ). Mortality at follow up was persistently greater in the lower [22.1% (140/633)] compared to the higher [18.2% (118/648)] oxygen saturation group (RR 1.25, 95% CI 1.004 to 1.55,  $p=0.046$ ).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

Word Count 250

## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between the lower oxygen saturation target group (85-89%) vs. higher oxygen saturation target group (91-95%). However, the risk of ROP among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

The pre-specified follow-up hypotheses of the SUPPORT were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age.

## METHODS

### Study Design

1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation<sup>18</sup>. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygenation target group) using a specially designed blinded oximeter. Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent



data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months CA, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>27</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification; and visual impairment, defined as vision  $< 20/200$ , were based upon examination and parental report.

Certified research staff collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

### Outcome

The pre-specified primary composite outcome at follow up for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score  $< 70$ , GMFCS  $\geq 2$ , moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality among the entire trial cohort and the individual components of NDI among survivors at follow up. Exploratory secondary outcomes at 18 to 22 months CA included comparisons between treatment arms of death or individual components of NDI, Bayley III cognitive composite scores, and levels of cognitive delay. The primary composite outcome (Death or NDI), and individual components of NDI were also compared for the higher and lower gestational age strata.

### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a

10% absolute reduction in composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted.<sup>28</sup> Missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes. Two-sided p values of < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 8 tests to be significant at the 0.05 level on the basis of chance alone.

## RESULTS

The pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Of the 68 children lost to follow up, 33 were known to be alive. A neurodevelopmental assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean CA at neurodevelopmental assessment and were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months CA mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers received antenatal steroids. At follow up there were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group.

Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

**Primary outcome:** The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months CA (Table 2 a/b). Results from the sensitivity analysis using multiple imputation were virtually identical to the analysis of the non-missing cases. Neither were there significant differences in the outcome of death or NDI between treatment groups in the higher and lower gestational age strata. (Appendix A) There was no difference in death between the CPAP and Surfactant arms. Mortality remained significantly higher in the lower compared to the higher saturation target group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI among survivors) (all p values > 0.7).

**Other outcomes:** The incidences of cognitive impairment (BSID-III cognitive composite score < 70, gross motor function level  $\geq 2$ , moderate/severe cerebral palsy, and blindness among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Table 2 a and b) or between the gestational age strata;(Appendix A). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen saturation target group vs. the lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month CA visit. (Table 3) Neither were there differences between the CPAP and Surfactant arms or between the lower and higher saturation groups in the combined outcome of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix B) Sixty percent (583/977) of children evaluated at 18-22 months CA had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations.

## **DISCUSSION:**

This trial tested critical outcome hypotheses related to both ventilatory and oxygenation strategies in a very high risk, extremely premature population. We found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant or between those randomized to the lower vs. higher oxygen saturation target groups in the SUPPORT trial. Mortality remained significantly higher in the lower compared to the higher saturation target group. There were no significant differences among survivors in any of the treatment arms for NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq 2$ ), hearing impairment, and bilateral blindness. To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which include pre-specified neurodevelopmental outcome at two years of age will not be available until 2014.<sup>29</sup>

Recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>21,30</sup> In SUPPORT death prior to discharge was increased among neonates randomized to the lower-oxygen-saturation target group. As was published previously, causes of death before discharge between the lower and higher oxygen saturation groups were not

different.<sup>24</sup> Mortality remained higher in the lower oxygen saturation target group at 18 to 22 months corrected age as well as in the most immature gestational age stratum of the surfactant administration group..

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>31,32</sup> We previously reported that the lower oxygen saturation target was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) among survivors at discharge.<sup>24</sup> Eye surgery was more frequent in higher oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at 18 to 22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher saturation groups.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had comprehensive, standardized neurodevelopmental evaluation at 18-24 months CA. The generalizability of this study may be limited by it being center rather than population based and by requiring antenatal consent which is associated with enrollment bias.<sup>33,34</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>35</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome.

In summary, there were no significant differences in the composite outcome of death or NDI, or in the individual components of NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation targets. Mortality was lower in the most immature stratum of the Early CPAP group and in the higher oxygen saturation target group.

Word Count 2640

## Acknowledgements

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

Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We 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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Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

**Figure1: Consort Diagram for SUPPORT**

**Table 1: Demographic and neonatal characteristics of follow-up cohorts**

**Table 2: Primary outcome (Death or NDI) and component outcomes : CPAP vs. Surfactant and Lower vs. Higher Oxygen Saturation Target Groups**

**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

**Appendix A: Outcomes for treatment groups by gestational age strata**

**Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms**



## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Lupton AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.

23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
27. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
28. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
29. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
30. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *N Engl J Med* 2011;364:1680-2.
31. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
32. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
33. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
34. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
35. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.

**From:** [Vaucher, Yvonne](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Vaucher, Yvonne](#)  
**Subject:** Recall: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 2:26:38 PM

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Vaucher, Yvonne would like to recall the message, "Combined SUPPORT ND Outcome paper Ver 05.23.2012".

**From:** [Vaucher, Yvonne](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Vaucher, Yvonne](#)  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 2:24:41 PM  
**Attachments:** [Table 3 Vision Outcome\\_MG04262012YV0522\\_MG0525YV0525.docx](#)  
[Appendix A\\_B 042512\\_MGYV0522\\_MG0525YV0525.docx](#)  
[CombinedSUPPORT\\_NDOOutcome\\_FU\\_PIs\\_0525.docx](#)  
[Consort Figure Correct MP\\_0523MG0525YV0525.doc](#)  
[Table 1\\_04112012\\_MG0426YV0523MG0525YV0525.docx](#)  
[Table 2CPAP\\_MG04262012YV0522MG0525YV0525.docx](#)

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Rose-Please send this group instead of the group in the preceding email. I made a small correction in the title of Table 2.

All,

SUPPORT paper for the FUP PI reviews is attached.

Re Wally's suggestions:

1. Marie checked the numbers which are clear in the consort diagram. I rephrased the LTFU sentence in the 1st paragraph of results to indicate that survival was known for 33 of the 68 LTFU.
2. Mortality precedes NDI outcomes in 1st paragraph of Discussion
3. Added Stenson's ref to 2nd paragraph of discussion
4. Order of last paragraph changed to put primary outcome first. I discussed deleting the CPAP lower GA stratum mortality with Neil. He would like to leave it in for now as it is an 8% difference for the highest risk group and let the NEJM editors decide whether to delete it or not.
5. Deleted "Although" in first paragraph of results
6. I think the significances are OK. The only one in question (as almost all are  $> 0.01$ ) is the lower vs. higher sat mortality which is 0.046 and if we didn't round up but left to 3 decimal places although it is  $>0.01$ .

The word counts for abstract and body are within the NEJM limits.

I am sure our FUP PIs will have some thoughts so if I have missed anyones changes we can catch them later.

Thanks for all you help!!!!!!

Yvonne

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, May 25, 2012 6:39 AM  
**To:** Vaucher, Yvonne  
**Cc:** Gantz, Marie; 'Wally Carlo, M.D.'  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

I  
I'd like to send today - would this be possible??  
Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
and Perinatology Branch CDBPM, NIH

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Thursday, May 24, 2012 9:03 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Rose,

Here is the latest. After Maries final check and Wally's comments I think we can send it on to the PIs.

Yvonne

---

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 10:00 PM  
To: Vaucher, Yvonne  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 9:57 PM  
To: 'Gantz, Marie'  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Marie,

Here is the latest and I hope the now correct version of the Combined Outcome SUPPORT paper. I used the corrected copy that you sent me on 4/16 so it should include all your corrections plus the few additional comments and tables you sent later on 5/1. The references are updated. I added age at FUP and FUP rates to Table 1. Please review the first para of the results. I did move things around an say things a bit differently.

I tried to address Wally's issues. Should we look at the FUP rate differently? Wally and Abhik had some issues about how we calculated it. Do we need to say anything more specific about the differences in the FUP cohorts in SGA, NEC, PNS status?

If we want to compare the demographics for all 1234 children with the primary composite outcome of Death or NDI(Table 1) we will need to run the demographics for this entire group. Table 1 includes only the 990 who were seen in FUP.

The abstract word count is 250 (NEJM limit 250) and paper body word count is 2626 (NEJM limit 2700).

Thanks so much for your careful review. It is really appreciated!

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 9:48 PM

To: 'Wally Carlo, M.D.'

Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Wally,

Here is the latest version I think with everyone's corrections. I hope this version addresses your concerns. I changed the order of the first para in the Results and began the para with a sentence about the importance of the study. I think it is fine to give the FUP rate as 94%. It does assume that all children LTFU with unknown survival lived which would yield the most conservative estimate of the FUP rate. The FUIP rate is really very high and I don't think anyone will criticize it. I eliminated all reference to BOOST and the oximeter algorithm, "specific visual outcomes", ANS. The p values are all presented to two decimal places since none are  $<0.001$  per the NEJM guidelines.

I think it is ready to go out to the other PIs. We can address any other issues in the meantime.

Yvonne

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UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**From:** [Gantz, Marie](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Phelps, Dale](#)  
**Cc:** [Das, Abhik](#)  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Friday, May 25, 2012 2:15:33 PM  
**Attachments:** [SUPP10\\_data\\_for\\_infants\\_not\\_meeting\\_ROP\\_surgery\\_criteria\\_25MAY12.rtf](#)

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Rose and Dale,

SUPP10 data for the 23 infants who did not meet criteria for surgery are attached. I've coded the center and infant IDs, but you can see that the 23 infants were spread across 11 centers. Note that there were a couple of cases where "Threshold (New Type 1)" was coded as "Y" on the SUPP10, but the other individual variables (zone, stage and plus disease) did not back that up. I know that when we were doing the original analysis, we queried cases where there were similar disagreements in the data, but I think we must have only queried cases where the ROP final outcome was based on threshold ROP rather than on surgery (these 23 cases were all classified based on surgery). Let me know if you have any questions.

Marie

**Marie Gantz, Ph.D.**  
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RTI International  
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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, May 25, 2012 9:53 AM  
**To:** Das, Abhik  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Yes – maybe some of them had other issues and we need to know. We also need to know if this is only a few sites or spread across the network.

Rose

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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Friday, May 25, 2012 9:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Rose:

I was surprised to see that as well. We can pull all the data from the SUPP10 forms for each of these babies for you to review. Is that what you had in mind?

Thanks

Abhik

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, May 25, 2012 9:49 AM  
**To:** Das, Abhik  
**Subject:** FW: ROP data from SUPPORT TRIAL FOR DSMC

Abhik

I am a little concerned that we had 23 infants who got ROP surgery, but didn't meet the criteria- we should look at these cases in a little more detail (as well as see if this is site dependent)>

Is it possible to get the SUPP 10 forms on each of these infants – this will help to try to figure out why they had surgery and didn't reach the usual "Threshold" definition??

We need this to be able to explain this to the DSMC.

Thanks

Rose

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301-496-3790 (FAX)  
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**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Thursday, May 24, 2012 5:15 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC



Hi Marie,

There are quite a few more cases of treatment before documented criteria for treatment than I had expected.

As we go back to the DSMC with this, I think it would be important to be able to better explain it.

Also, just to confirm with you. Infants who might have had ROP disease worse than Type 1 would also be considered treated appropriately. Did you exclude any infants because they had stage 4a or 4b or stage 5?

If it is going to take a lot of time, please discuss it with Dr. Das first. He and Dr. Higgins and I can discuss whether to go forward.

I do think it will be important to understand and be able to account for at least some of them -- and the fuller clinical ROP picture is likely to do that.

Therefore, I would like to request that you provide the more detailed data.

I also volunteer to individually review the ROP printouts from the subgroups listed below: (there is a nice de-identified format that was used for INS-2 that you could use that gives me basically two pages per infant -- one for each eye)

- 5 who met criteria for surgery, but were not recorded as having had surgery (123-127=5)
- 23 who did receive surgery, but did not meet criteria for surgery

Thanks!

Dale

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**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Thursday, May 24, 2012 1:39 PM  
**To:** Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Dale, do you still need the more detailed data you requested?

Marie

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828-351-4255

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**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Thursday, May 24, 2012 4:18 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Thank you Marie,

The answers provide very interesting data for discussion.

We will have some work to do with the Ophthalmologists in the inositol Study.

Particularly: treating in zone II without evidence of plus disease.

One the cases below not meeting criteria is unlikely enough that it is probably a keying error, but I would not want to go back at this point in time to do a query.

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi all, I included answers to Rose's questions below, based on my preliminary look at the SUPPORT data. I will send more complete answers to Dale's questions when I have them.

Marie

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery 127 (based on Wally's paper, this looks like 132) MG: 132 includes infants with severe ROP as defined in the paper who did not have surgery recorded.

Can you tell us how many had each of these categories:

1. **type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);**

MG: 22 met these criteria in at least one eye

2. **zone I, stage 3 ROP without plus disease;**

MG: An additional 6 met these criteria in at least one eye (there were a total of 11 but 5 also met criteria for type I ROP in #1)

**3. zone II, stage 2 or 3 ROP with plus disease.**

MG: An additional 76 met these criteria in at least one eye (there were a total of 80 but 4 also met criteria in #1 or #2)

Can you tell us if nay infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

MG: There were 23 who did not meet criteria in #1-3 but who did have surgery:

- 1 had zone II stage 2 with plus disease missing
- 2 had zone II stage 2 no plus disease
- 18 had zone II stage 3 no plus disease
- 1 had zone III stage 3 no plus disease
- 1 had missing zone and stage but plus disease

Thanks

Rose

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301-496-5575  
301-496-3790 (FAX)  
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**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

**Center=A Infant=1 Date of Birth=09/17/05 Gestational Age (weeks)=27 Gestational Age (days)=3**

1	10/26/05	1	2=II	0=No ROP	0=No ROP	N
2	11/09/05	1	2=II	1=Stage 1	1=Stage 1	N
3	11/15/05	1	2=II	1=Stage 1	1=Stage 1	N
4	11/23/05	1	2=II	1=Stage 1	1=Stage 1	N
5	12/08/05	1	2=II	2=Stage 2	2=Stage 2	N
6	12/12/05	1	2=II	2=Stage 2	2=Stage 2	N
7	12/20/05	1	2=II	2=Stage 2	2=Stage 2	N
8	01/04/06	1	2=II	2=Stage 2	2=Stage 2	N
9	01/18/06	1	1=I	3=Stage 3	3=Stage 3	*
10	06/26/06	2	3=III	0=No ROP	0=No ROP	N

N	0=No surgery this day	0=None	2=II	0=No ROP	0=No ROP
N	0=No surgery this day	0=None	2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	2=II	1=Stage 1	3=Stage 3
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
Y	P=Permanently missing	P=Permanently missing	1=I	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	3=III	0=No ROP	0=No ROP

N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None

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# SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA

N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	Y	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

**Center=B Infant=2 Date of Birth=06/01/07 Gestational Age (weeks)=25 Gestational Age (days)=4**

1	07/19/07	1	2=II	0=No ROP	0=No ROP	N
2	08/02/07	1	3=III	0=No ROP	0=No ROP	N
3	09/26/07	1	2=II	3=Stage 3	3=Stage 3	N
4	10/03/07	1	2=II	2=Stage 2	2=Stage 2	N
5	10/11/07	1	2=II	2=Stage 2	2=Stage 2	Y
6	11/08/07	1	2=II	2=Stage 2	2=Stage 2	N
7	11/19/07	1	2=II	2=Stage 2	2=Stage 2	N
8	02/07/08	1	4=Mature	0=No ROP	0=No ROP	N

N	0=No surgery this day	.	2=II	0=No ROP	0=No ROP
N	0=No surgery this day	.	3=III	0=No ROP	0=No ROP
N	0=No surgery this day	.	2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day	.	2=II	2=Stage 2	2=Stage 2
Y	0=No surgery this day	.	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	.	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	.	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	.	4=Mature	0=No ROP	0=No ROP

N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
Y	Y	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.

**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

**Center=B Infant=3 Date of Birth=08/19/08 Gestational Age (weeks)=25 Gestational Age (days)=6**

1	09/25/08	1	1=I	0=No ROP	0=No ROP	N
2	10/02/08	1	1=I	3=Stage 3	3=Stage 3	N
3	10/04/08	1	2=II	0=No ROP	0=No ROP	N
4	10/09/08	1	2=II	1=Stage 1	1=Stage 1	N
5	10/16/08	1	2=II	1=Stage 1	1=Stage 1	N
6	10/23/08	1	2=II	1=Stage 1	1=Stage 1	N
8	11/06/08	1	2=II	3=Stage 3	3=Stage 3	N
9	11/13/08	1	2=II	3=Stage 3	3=Stage 3	N
10	11/20/08	1	2=II	3=Stage 3	3=Stage 3	N
11	11/27/08	1	2=II	2=Stage 2	2=Stage 2	N
12	12/04/08	1	2=II	2=Stage 2	2=Stage 2	N
13	12/18/08	1	2=II	2=Stage 2	2=Stage 2	N
14	01/08/09	1	4=Mature	0=No ROP	0=No ROP	N

N	0=No surgery this day		1=I	0=No ROP	0=No ROP
Y	0=No surgery this day		1=I	3=Stage 3	3=Stage 3
N	0=No surgery this day		2=II	0=No ROP	0=No ROP
N	0=No surgery this day		2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day		2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day		2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day		2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day		2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day		2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day		2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day		2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day		2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day		2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day		4=Mature	0=No ROP	0=No ROP

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# SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA

N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.
N	N	0=No surgery this day	.



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# SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA

Center=C Infant=4 Date of Birth=06/09/06 Gestational Age (weeks)=27 Gestational Age (days)=4

1	07/18/06	1	3=III	3=Stage 3	3=Stage 3	N
2	P	P	P=Permanently missing	P=Permanently missing	P=Permanently missing	*

Y	0=No surgery this day	0=None	1=I	3=Stage 3	3=Stage 3
*	P=Permanently missing	P=Permanently missing	P=Permanently missing	P=Permanently missing	P=Permanently missing

N	Y	0=No surgery this day	0=None
*	*	P=Permanently missing	P=Permanently missing

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**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

**Center=D Infant=5 Date of Birth=11/27/08 Gestational Age (weeks)=26 Gestational Age (days)=4**

1	01/09/09	1	2=II	2=Stage 2	2=Stage 2	N
2	01/30/09	1	2=II	2=Stage 2	2=Stage 2	N
3	02/06/09	1	2=II	3=Stage 3	3=Stage 3	N
4	02/11/09	1	2=II	3=Stage 3	3=Stage 3	N
5	02/17/09	1	2=II	2=Stage 2	2=Stage 2	N
6	02/25/09	1	2=II	3=Stage 3	3=Stage 3	N
7	03/03/09	1	2=II	3=Stage 3	3=Stage 3	N
8	03/09/09	2	2=II	2=Stage 2	2=Stage 2	N
9	03/23/09	2	2=II	2=Stage 2	2=Stage 2	Y
10	03/26/09	2	2=II	2=Stage 2	2=Stage 2	N
11	03/31/09	2	2=II	2=Stage 2	2=Stage 2	N
12	04/07/09	2	2=II	2=Stage 2	2=Stage 2	N
13	04/21/09	2	2=II	1=Stage 1	1=Stage 1	N
14	05/21/09	2	3=III	2=Stage 2	2=Stage 2	N
15	06/11/09	2	3=III	2=Stage 2	2=Stage 2	N

N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
Y	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2

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# SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA

N	0=No surgery this day	0=None	2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	3=III	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	3=III	2=Stage 2	2=Stage 2

N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
Y	Y	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None

**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

**Center=E Infant=6 Date of Birth=06/06/08 Gestational Age (weeks)=25 Gestational Age (days)=0**

1	07/08/08	1	2=II	0=No ROP	0=No ROP	N
2	07/21/08	1	2=II	0=No ROP	0=No ROP	N
3	08/05/08	1	2=II	1=Stage 1	1=Stage 1	N
4	08/18/08	1	2=II	1=Stage 1	1=Stage 1	N
5	08/25/08	1	2=II	1=Stage 1	1=Stage 1	N
6	09/09/08	1	2=II	2=Stage 2	2=Stage 2	Y
7	09/11/08	1	3=III	2=Stage 2	2=Stage 2	N
8	09/29/08	2	3=III	3=Stage 3	3=Stage 3	Y
9	10/13/08	2	4=Mature	0=No ROP	0=No ROP	N

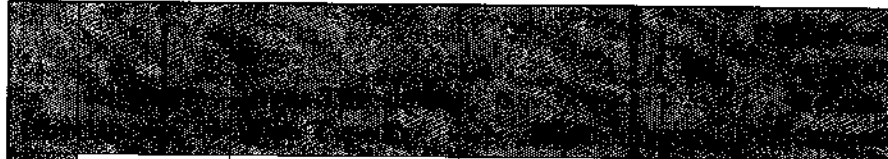
N	0=No surgery this day	0=None	2=II	0=No ROP	0=No ROP
N	0=No surgery this day	0=None	2=II	0=No ROP	0=No ROP
N	0=No surgery this day	0=None	2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	2=II	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	2=II	1=Stage 1	1=Stage 1
Y	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	3=III	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	3=III	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	4=Mature	0=No ROP	0=No ROP

N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
Y	Y	0=No surgery this day	0=None

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# SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA



N	N	0=No surgery this day	0=None
Y	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None

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**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

**Center=F Infant=7 Date of Birth=11/12/05 Gestational Age (weeks)=24 Gestational Age (days)=6**

1	01/11/06	1	2=II	P=Permanently missing	P=Permanently missing	N
2	01/18/06	1	2=II	2=Stage 2	2=Stage 2	N
3	01/24/06	1	2=II	2=Stage 2	2=Stage 2	N
4	01/31/06	1	2=II	2=Stage 2	2=Stage 2	N
5	02/01/06	1	2=II	P=Permanently missing	P=Permanently missing	Y
6	02/05/06	1	2=II	2=Stage 2	2=Stage 2	Y
7	02/07/06	1	2=II	2=Stage 2	2=Stage 2	N
8	02/10/06	1	2=II	2=Stage 2	2=Stage 2	N
9	02/14/06	1	2=II	2=Stage 2	2=Stage 2	N
10	02/21/06	1	2=II	2=Stage 2	2=Stage 2	N
11	02/28/06	1	2=II	2=Stage 2	2=Stage 2	N
12	03/07/06	1	2=II	2=Stage 2	2=Stage 2	N
13	03/21/06	1	2=II	2=Stage 2	2=Stage 2	N
14	03/28/06	1	3=III	0=No ROP	0=No ROP	N

N	0=No surgery this day	0=None	2=II	P=Permanently missing
N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2
Y	0=No surgery this day	0=None	2=II	P=Permanently missing
Y	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2

**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

N	0=No surgery this day	0=None	2=II	2=Stage 2
N	0=No surgery this day	0=None	3=III	0=No ROP

P=Permanently missing	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
P=Permanently missing	Y	Y	0=No surgery this day	0=None
2=Stage 2	Y	Y	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
2=Stage 2	N	N	0=No surgery this day	0=None
0=No ROP	N	N	0=No surgery this day	0=None

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# SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA

Center=F Infant=8 Date of Birth=06/16/08 Gestational Age (weeks)=25 Gestational Age (days)=5

1	08/06/08	1	2=II	2=Stage 2	2=Stage 2	N
2	08/13/08	1	2=II	2=Stage 2	2=Stage 2	N
3	08/20/08	1	2=II	3=Stage 3	3=Stage 3	Y
4	08/21/08	1	2=II	3=Stage 3	3=Stage 3	Y
5	08/22/08	1	2=II	3=Stage 3	3=Stage 3	Y
6	08/25/08	1	2=II	3=Stage 3	3=Stage 3	Y

N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
Y	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
Y	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
Y	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
Y	6=Other	0=None	2=II	3=Stage 3	3=Stage 3

N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
Y	Y	0=No surgery this day	0=None
Y	Y	0=No surgery this day	0=None
Y	Y	0=No surgery this day	0=None
Y	Y	6=Other	0=None



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# SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA

Center=F Infant=9 Date of Birth=01/29/09 Gestational Age (weeks)=26 Gestational Age (days)=0

1	03/11/09	1	1=I	0=No ROP	0=No ROP	N
2	03/19/09	1	1=I	0=No ROP	0=No ROP	N
3	03/25/09	1	2=II	0=No ROP	0=No ROP	N
4	04/01/09	1	2=II	0=No ROP	0=No ROP	N
5	04/08/09	1	2=II	3=Stage 3	3=Stage 3	Y
6	04/15/09	1	2=II	3=Stage 3	3=Stage 3	Y
7	04/22/09	1	P=Permanently missing	P=Permanently missing	P=Permanently missing	N

N	0=No surgery this day	0=None	1=I	0=No ROP	0=No ROP
N	0=No surgery this day	0=None	1=I	0=No ROP	0=No ROP
N	0=No surgery this day	0=None	2=II	0=No ROP	0=No ROP
N	0=No surgery this day	0=None	2=II	0=No ROP	0=No ROP
Y	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
Y	6=Other	0=None	2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	P=Permanently missing	P=Permanently missing	P=Permanently missing

N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
Y	Y	0=No surgery this day	0=None
Y	Y	6=Other	0=None
N	N	0=No surgery this day	0=None

**SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA**

**Center=G Infant=10 Date of Birth=02/24/08 Gestational Age (weeks)=24 Gestational Age (days)=2**

1	04/08/08	1	1=I	0=No ROP	0=No ROP	N
2	04/22/08	1	1=I	2=Stage 2	2=Stage 2	N
3	04/29/08	1	1=I	2=Stage 2	2=Stage 2	N
4	05/06/08	1	1=I	2=Stage 2	3=Stage 3	N
5	05/13/08	1	1=I	2=Stage 2	3=Stage 3	N
6	05/20/08	1	1=I	3=Stage 3	3=Stage 3	N
7	05/27/08	1	1=I	3=Stage 3	3=Stage 3	N
8	06/03/08	1	2=II	3=Stage 3	3=Stage 3	N
9	04/15/08	1	1=I	0=No ROP	0=No ROP	N
10	06/10/08	1	2=II	3=Stage 3	3=Stage 3	N
11	06/24/08	1	2=II	2=Stage 2	2=Stage 2	N
12	07/08/08	1	2=II	2=Stage 2	2=Stage 2	N
13	07/22/08	2	2=II	2=Stage 2	2=Stage 2	N
14	11/19/08	2	4=Mature	0=No ROP	0=No ROP	N
15	04/22/09	2	4=Mature	0=No ROP	0=No ROP	N

N	0=No surgery this day	0=None	1=I	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	1=I	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	1=I	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	1=I	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	1=I	2=Stage 2	3=Stage 3
Y	0=No surgery this day	0=None	1=I	3=Stage 3	3=Stage 3
Y	0=No surgery this day	0=None	1=I	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	1=I	1=Stage 1	1=Stage 1
N	0=No surgery this day	0=None	2=II	3=Stage 3	3=Stage 3
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2

## SUPP10 DATA FOR SUPPORT INFANTS WITHOUT ROP SURGERY RECORDED WHO MET ROP SURGERY CRITERIA

N	0=No surgery this day	0=None	2=II	2=Stage 2	2=Stage 2
N	0=No surgery this day	0=None	4=Mature	0=No ROP	0=No ROP
N	0=No surgery this day	0=None	4=Mature	0=No ROP	0=No ROP

N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	Y	0=No surgery this day	0=None
N	Y	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None
N	N	0=No surgery this day	0=None

**From:** [Gantz, Marie](#)  
**To:** [Vaucher, Yvonne](#); [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#)  
**Cc:** [Das, Abhik](#)  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 12:23:46 PM

---

I have sent Yvonne a couple of very minor edits. Otherwise, I think the paper looks good. One additional minor point - in the first paragraph of the results section, it says 35 of the 68 who were LTFU had unknown survival, but it does not state explicitly that the other 33 were known to be alive (not dead). I think that might be leading to confusion, prompting Wally's first question, below. Maybe we could make that clearer.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

**From:** Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
**Sent:** Friday, May 25, 2012 11:27 AM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil  
**Cc:** Gantz, Marie  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

All,  
As soon as I have Marie's edits I will make changes and resend.

Yvonne

---

**From:** Wally Carlo, M.D. [[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)]  
**Sent:** Friday, May 25, 2012 7:51 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne  
**Cc:** Gantz, Marie  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Hi Rose, Yvonne, and Marie:

I have minor suggestions that can easily be accepted (or rejected if you do like them).

1. Are the babies lost to follow up but known to have died counted in those who had the primary outcome known? I do not think they are being counted in the 93%. I think they should be counted if they are not being counted.
2. The first paragraph of the Discussion should include a sentence about mortality difference by saturation group as mortality is the a component of the primary outcome. I would put it before NDI data as most people would consider it the most important component of the composite primary outcome.
3. We should add Ben Stenson's NEJM reference to the second paragraph of the Discussion as their results more than double our patient population and are consistent in terms of mortality.
4. I would change the order of the last paragraph of the Discussion to state the primary outcome before the mort effect by oxygen group and would drop the subgroup CPAP results.

I hope this helps. I could not do track changes as I am in a conference in Italy with limited email access.

Wally

"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

I

I'd like to send today - would this be possible??

Thanks

Rose

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

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]

Sent: Thursday, May 24, 2012 9:03 PM

To: Higgins, Rosemary (NIH/NICHD) [E]

Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Rose,

Here is the latest. After Maries final check and Wally's comments I think we can send it on to the PIs.

Yvonne

---

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 10:00 PM  
To: Vaucher, Yvonne  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 9:57 PM  
To: 'Gantz, Marie'  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Marie,

Here is the latest and I hope the now correct version of the Combined Outcome SUPPORT paper. I used the corrected copy that you sent me on 4/16 so it should include all your corrections plus the few additional comments and tables you sent later on 5/1. The references are updated. I added age at FUP and FUP rates to Table 1. Please

review the first para of the results. I did move things around and say things a bit differently.

I tried to address Wally's issues. Should we look at the FUP rate differently? Wally and Abhik had some issues about how we calculated it. Do we need to say anything more specific about the differences in the FUP cohorts in SGA, NEC, PNS status?

If we want to compare the demographics for all 1234 children with the primary composite outcome of Death or NDI (Table 1) we will need to run the demographics for this entire group. Table 1 includes only the 990 who were seen in FUP.

The abstract word count is 250 (NEJM limit 250) and paper body word count is 2626 (NEJM limit 2700).

Thanks so much for your careful review. It is really appreciated!

From: Vaucher, Yvonne  
Sent: Wednesday, May 23, 2012 9:48 PM  
To: 'Wally Carlo, M.D.'  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Wally,

Here is the latest version I think with everyone's corrections. I hope this version addresses your concerns. I changed the order of the first para in the Results and began the para with a sentence about the importance of the study. I think it is fine to give the FUP rate as 94%. It does assume that all children LTFU with unknown survival lived which would yield the most conservative estimate of the FUP rate. The FUP rate is really very high and I don't think anyone will criticize it. I eliminated all reference to BOOST and the oximeter algorithm, "specific visual outcomes", ANS. The p values are all presented to two decimal places since none are <0.001 per the NEJM guidelines.

I think it is ready to go out to the other PIs. We can address any other issues in the meantime.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**From:** Gantz, Marie  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 11:27:39 AM

---

Wally, to answer your first question, all those known to have died are considered to have the primary outcome. Those missing the primary outcome were either known to be alive but did not have a FU visit, or they were completely lost to FU and we did not know whether they were alive.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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

From: Wally Carlo, M.D. [mailto:[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)]  
Sent: Friday, May 25, 2012 10:52 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Vaucher, Yvonne'  
Cc: Gantz, Marie  
Subject: RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

Hi Rose, Yvonne, and Marie:

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Thanks  
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Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal  
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-----Original Message-----

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Thursday, May 24, 2012 9:03 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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differently.

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UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**From:** Wally Carlo, M.D.  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Vaucher, Yvonne"  
**Cc:** Gantz, Marie  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 11:10:56 AM

---

I think NEJM uses 3 decimals for p values and a 0 as a decimal when the percentages are whole numbers but other % data are presented with a decimal point.

Wally

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I'd like to send today - would this be possible??

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

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Sent: Wednesday, May 23, 2012 9:48 PM  
To: 'Wally Carlo, M.D.'  
Subject: FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812

**From:** [Wally Carlo, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); ["Vaucher, Yvonne"](#)  
**Cc:** [Gantz, Marie](#)  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 11:10:37 AM

---

I forgot to mention that the sentence on mort by oxygen group in the results should not have the conditional word "Although..). Indeed, as a factorial design, each intervention is independent. In addition, we did not find and interaction so the term "Although" is misleading,  
Wally

"Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

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I'd like to send today - would this be possible??  
Thanks  
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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](mailto:higginsr@mail.nih.gov)

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

**From:** Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
**Sent:** Thursday, May 24, 2012 9:03 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
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**Subject:** FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Gantz, Marie  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Friday, May 25, 2012 9:52:06 AM

---

Rose:

I was surprised to see that as well. We can pull all the data from the SUPP10 forms for each of these babies for you to review. Is that what you had in mind?

Thanks

Abhik

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, May 25, 2012 9:49 AM  
**To:** Das, Abhik  
**Subject:** FW: ROP data from SUPPORT TRIAL FOR DSMC

Abhik

I am a little concerned that we had 23 infants who got ROP surgery, but didn't meet the criteria- we should look at these cases in a little more detail (as well as see if this is site dependent)>

Is it possible to get the SUPP 10 forms on each of these infants – this will help to try to figure out why they had surgery and didn't reach the usual "Threshold" definition??

We need this to be able to explain this to the DSMC.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Thursday, May 24, 2012 5:15 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi Marie,

There are quite a few more cases of treatment before documented criteria for treatment than I had expected.

As we go back to the DSMC with this, I think it would be important to be able to better explain it.

Also, just to confirm with you. Infants who might have had ROP disease worse than Type 1 would also be considered treated appropriately. Did you exclude any infants because they had stage 4a or 4b or stage 5?

If it is going to take a lot of time, please discuss it with Dr. Das first. He and Dr. Higgins and I can discuss whether to go forward.

I do think it will be important to understand and be able to account for at least some of them -- and the fuller clinical ROP picture is likely to do that.

Therefore, I would like to request that you provide the more detailed data.

I also volunteer to individually review the ROP printouts from the subgroups listed below: (there is a nice de-identified format that was used for INS-2 that you could use that gives me basically two pages per infant -- one for each eye)

- 5 who met criteria for surgery, but were not recorded as having had surgery (123-127=5)
- 23 who did receive surgery, but did not meet criteria for surgery

Thanks!

Dale

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Thursday, May 24, 2012 1:39 PM  
**To:** Phelps, Dale  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Dale, do you still need the more detailed data you requested?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-251-8255

---

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Thursday, May 24, 2012 4:18 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Das, Abhik  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Thank you Marie,

The answers provide very interesting data for discussion.

We will have some work to do with the Ophthalmologists in the inositol Study.

Particularly: treating in zone II without evidence of plus disease.

One the cases below not meeting criteria is unlikely enough that it is probably a keying error, but I would not want to go back at this point in time to do a query.

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, May 24, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

Hi all, I included answers to Rose's questions below, based on my preliminary look at the SUPPORT data. I will send more complete answers to Dale's questions when I have them.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery 127 (based on Wally's paper, this looks like 132) MG: 132 includes infants with severe ROP as defined in the paper who did not have surgery recorded.

Can you tell us how many had each of these categories:

1. **type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);**

MG: 22 met these criteria in at least one eye

2. **zone I, stage 3 ROP without plus disease;**

MG: An additional 6 met these criteria in at least one eye (there were a total of 11 but 5 also met criteria for type I ROP in #1)

3. **zone II, stage 2 or 3 ROP with plus disease.**



MG: An additional 76 met these criteria in at least one eye (there were a total of 80 but 4 also met criteria in #1 or #2)

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

MG: There were 23 who did not meet criteria in #1-3 but who did have surgery:

1 had zone II stage 2 with plus disease missing

2 had zone II stage 2 no plus disease

18 had zone II stage 3 no plus disease

1 had zone III stage 3 no plus disease

1 had missing zone and stage but plus disease

Thanks

Rose

**Rosemary D. Higgins, MD**  
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**Cc:** [Gantz, Marie](#)  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 9:46:06 AM

---

Ok. I will send my comments today.

Wally

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

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
**To:** "&apos;Vaucher, Yvonne&apos;" <[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)>  
**Cc:** "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)>, "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>  
**Sent:** Fri, May 25, 2012 13:42:54 GMT+00:00  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012

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**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Vaucher, Yvonne](#)  
**Cc:** [Wally Carlo, M.D.](#)  
**Subject:** RE: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Friday, May 25, 2012 9:44:05 AM

---

I'm checking over it now. Will let you know when I'm finished.

Marie

Marie Gantz, Ph.D.  
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RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Combined SUPPORT ND Outcome paper Ver 05.23.2012  
**Date:** Thursday, May 24, 2012 9:05:03 PM  
**Attachments:** [Table 3 Vision Outcome\\_MG04262012YV0522.docx](#)  
[Appendix A\\_B\\_042512\\_MGYV0522.docx](#)  
[Table 2CPAP\\_MG04262012YV0522.docx](#)  
[Consort Figure Correct\\_MP\\_0523.doc](#)  
[Table 1\\_04112012\\_MG0426YV0523.docx](#)  
[CombPaperNEJM\\_04\\_13\\_2012\\_MPYV\\_MG0416RH0514YEV0523 \(2\).docx](#)

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Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619-543-3759  
FAX: 619-543-3812



**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower	Higher	ARR	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002

## Appendix A: Outcomes for treatment groups by gestational age strata

### CPAP vs. Surfactant

<u>24 0/7-25 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

<u>26 0/7-27 6/7 weeks Gestational Age</u>	CPAP	Surfactant	ARR*	p
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level $\geq$ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

**LOWER VS. HIGHER OXYGEN SATURATION TARGETS**

<u>24 0/7-25 6/7 weeks Gestational Age</u>	Lower	Higher	ARR*	p
Death or NDI-no./total no.(%)	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA-no./total no.(%)	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined-no./total no.(%)	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI-no./total no.(%)	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70-no./total no.(%)	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2-no./total no.(%)	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy-no./total no.(%)	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral -no./total no.(%)	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Hearing impairment-no./total no.(%)	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22

<u>26 0/7-27 6/7 weeks Gestational Age</u>	Lower	Higher	ARR*	P
Death or NDI-no./total no.(%)	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA-no./total no.(%)	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22
Death/NDI determined-no./total no.(%)	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI-no./total no.(%)	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70-no./total no.(%)	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level ≥ 2-no./total no.(%)	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral palsy-no./total no.(%)	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral –no./total no.(%)	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Hearing impairment-no./total no.(%)	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

\*Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms**

<u>CPAP vs. Surfactant</u>	<u>CPAP</u>	<u>SURF</u>	<u>ARR*</u>	<u>p</u>
BSID-III cognitive composite score (adjusted mean)	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score < 85-no./total no.(%)	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 80-no./total no.(%)	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05
<u>Lower vs. Higher Oxygen Saturation Targets</u>	<u>LOWER</u>	<u>HIGHER</u>	<u>ARR*</u>	<u>p</u>
BSID-III cognitive composite score (adjusted mean)	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85-no./total no.(%)	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80-no./total no.(%)	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

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**Table 2: Death and NDI: CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups\***

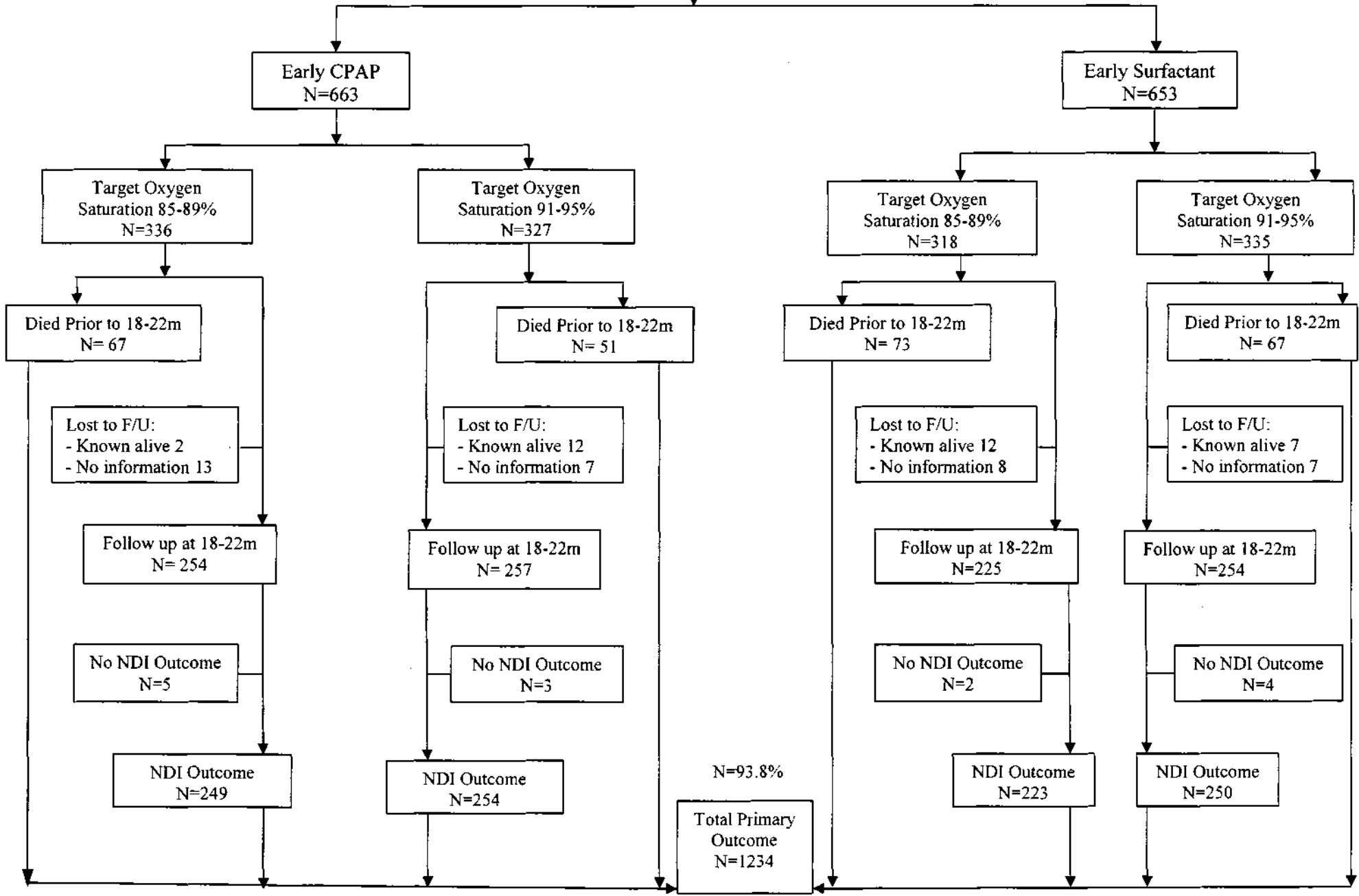
<b><u>a. CPAP vs. Surfactant</u></b>	<b><u>CPAP</u></b>	<b><u>Surfactant</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06



<b><u>b. Lower vs. Higher Oxygen Saturation</u></b>	<b><u>Lower</u></b>	<b><u>Higher</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA-no./total no.(%)	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined-no./total no.(%)	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI-no./total no.(%)	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70-no./total no.(%)	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2-no./total no.(%)	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy-no./total no.(%)	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral-no./total no.(%)	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment-no./total no.(%)	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

SUPPORT TRIAL  
N=1316



Primary Outcome

Primary Outcome

## **Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

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Text: MeSH terms:

Cerebral palsy  
Infant, Newborn  
Infant, Low Birth Weight  
Infant, Extremely Low Birth Weight  
Infant, Premature  
Infant, Extremely Low Gestational Age  
Infant mortality  
Intellectual disability  
Intensive care, neonatal  
Neurodevelopmental outcome  
Oximetry  
Randomized controlled trial  
Continuous Positive Airway Pressure  
Intubation, intratracheal  
Pulmonary surfactants/therapeutic use  
Oxygen inhalation therapy/methods  
Oxygen administration & dosage  
Retinopathy of prematurity, epidemiology  
Child development  
Developmental disabilities, epidemiology  
Psychomotor disorders, epidemiology  
Follow-up studies

## ABSTRACT

**BACKGROUND:** SUPPORT showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS:** Infants born at 24 0/7 to 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary composite outcome was death or NDI at 18-22 months CA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) of all enrolled infants; 93.6% (990/1058) of hospital survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [29.9% (183/613)] groups (RR 0.93, 95% CI 0.78 to 1.1, p=0.38) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)]; oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32, p=0.21). Mortality at follow up was persistently greater in the lower [22.1% (140/633)] compared to the higher [18.2% (118/648)] oxygen saturation group (RR 1.25, 95% CI 1.004 to 1.55, p=0.046).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

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## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>19</sup> BPD,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> SUPPORT demonstrated no difference in the composite outcome of death before discharge or severe retinopathy of prematurity (ROP) between the lower oxygen saturation target group (85-89%) vs. higher oxygen saturation target group (91-95%). However, the risk of ROP among survivors to discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.<sup>24</sup>

The pre-specified follow-up hypotheses of the SUPPORT were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age.

## METHODS

### Study Design

1316 extremely preterm infants, 24 through 27 completed weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation<sup>18</sup>. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation target group) or 91 to 95% (higher oxygenation target group) using a specially designed blinded oximeter. Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

**Comment [MC1]:** To explain why I keep inserting "target" – when the DSMB temporarily stopped the study, there was concern about whether infants were being kept in their assigned ranges, and we emphasized that this was a trial of saturation target ranges rather than actual saturation ranges. We have continued to emphasize that these are target ranges ever since, to avoid any misconception.

### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months CA, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>27</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification; and visual impairment, defined as vision  $< 20/200$ , were based upon examination and parental report.

Certified research staff collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD (physiologic), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

Comment [MG2]: Need to specify that we used two definitions?

### Outcome

The pre-specified primary composite outcome at follow up for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score  $< 70$ , GMFCS  $\geq 2$ , moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality among the entire trial cohort and the individual components of NDI among survivors at follow up. Exploratory secondary outcomes at 18 to 22 months CA included comparisons between treatment arms of death or individual components of NDI, Bayley III cognitive composite scores, and levels of cognitive delay. The primary composite outcome (Death or NDI), and individual components of NDI were also compared for the higher and lower gestational age strata.

### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of children for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two interventions. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted.<sup>28</sup> Missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes. Two-sided p values of < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 8 tests to be significant at the 0.05 level on the basis of chance alone.

## RESULTS

The pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of children enrolled in SUPPORT. (Figure) Two hundred fifty eight children were known to have died before 18-22 months. Survival status could not be determined for 35/68 children lost to follow up. A neurodevelopmental assessment was performed at 18-22 months corrected age for 990/1058 (93.6%) children. NDI was determined for 976/990 (98.6%) of all children seen; 14 had an incomplete evaluation that precluded assigning a NDI status. The follow-up rate and the mean CA at neurodevelopmental assessment and were similar for all treatment groups. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months CA mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%, p=0.01), and more likely to have only public insurance (69 vs. 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers received antenatal steroids. At follow up there were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

**Comment [AD3]:** Shouldn't this comparison be between with 1234 for whom we have outcome and the 82 that we don't?

**Comment [yav 4]:** If so, we need to run the demographic data for all Death or NDI



**Primary outcome:** The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months CA (Table 2 a/b). Results from the sensitivity analysis using multiple imputation were virtually identical to the analysis of the non-missing cases. Neither were there significant differences in the outcome of death or NDI between treatment groups in the higher and lower gestational age strata. (Appendix A) Although there was no difference in death between the CPAP and Surfactant arms, mortality remained significantly higher in the lower compared to the higher saturation target group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death or NDI) among survivors (all p values > 0.7).

**Other outcomes:** The incidences of cognitive impairment (BSID-III cognitive composite score < 70, gross motor function level  $\geq 2$ , moderate/severe cerebral palsy, and blindness among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort (Table 2 a and b) or between the gestational age strata;(Appendix A). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen saturation target group vs. the lower oxygen saturation target group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month CA visit. (Table 3) Neither were there differences between the CPAP and Surfactant arms or between the lower and higher saturation groups in the combined outcome of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix B) Sixty percent (583/977) of children evaluated at 18-22 months CA had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations.

#### **DISCUSSION:**

This trial tested critical outcome hypotheses related to both ventilatory and oxygenation strategies in a very high risk, extremely premature population. We found no significant difference in the primary composite follow up outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant or between those randomized to the lower vs. higher oxygen saturation target groups in the SUPPORT trial. Neither were there significant differences among survivors in any of the treatment arms for NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq 2$ ), hearing impairment, and bilateral blindness. To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which include pre-specified neurodevelopmental outcome at two years of age will not be available until 2014.<sup>29</sup>

Recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>21</sup> In SUPPORT death prior to discharge was increased among neonates randomized to the lower-oxygen-saturation target group. As was published previously, causes of death before discharge between the lower and higher oxygen saturation groups were not different.<sup>24</sup> Mortality remained higher in the lower oxygen saturation target group at 18 to 22 months corrected age as well as in the most immature gestational age stratum of the surfactant administration group..

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>30,31</sup> We previously reported that the lower oxygen saturation target was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) among survivors at discharge.<sup>24</sup> Eye surgery was more frequent in higher

oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at 18 to 22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher saturation groups.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had comprehensive, standardized neurodevelopmental evaluation at 18-24 months CA. The generalizability of this study may be limited by it being center rather than population based and by requiring antenatal consent which is associated with enrollment bias.<sup>32,33</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here.<sup>34</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age; other disabilities may not be evident until later childhood. A sub-cohort of the SUPPORT study will be followed at school age to evaluate longer-term neurodevelopmental outcome.

In summary, mortality was lower in the higher oxygen saturation target group and in the most immature stratum of the Early CPAP group. There were no significant differences in the composite outcome of death or NDI, or in the individual components of NDI at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation targets.

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**Figure1: Consort Diagram for SUPPORT**

**Table 1: Demographic and neonatal characteristics of follow-up cohorts**

**Table 2: Primary outcome (Death or NDI) and component outcomes : CPAP vs. Surfactant and Lower vs. Higher Oxygen Saturation Target Groups**

**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

**Appendix A: Outcomes for treatment groups by gestational age strata**

**Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms**

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Lupton AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.
20. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Haynes RL, Folkert RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.

23. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
27. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
28. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
29. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
30. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
31. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
32. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
33. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
34. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.





**Table 1: Demographics and Characteristics of Follow-up (FUP) Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)

Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < 12 <sup>th</sup> grade-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%) †	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language -no./total no.(%) ‡	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%)†	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	117/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
<u>Corrected age at follow up (months, Mean ± SD)</u>	<u>19.9±2.4</u>	<u>20.1±2.7</u>	<u>19.9±2.4</u>	<u>20.2±2.7</u>

Follow up-no./total no.(%)

\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

511/545(93.8) 479/513(93.4) 479/514(93.2)

551/544(93.9)

\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

¶ Among survivors to 36 weeks postmenstrual age

‡ Only available at 18-22 months corrected age† Among survivors to discharge or transfer

Comparisons of neonatal outcomes are adjusted for stratification by center and gestational age and for familial clustering

**From:** Gabrio, Jenna  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; kurt.schibler@cchmc.org; Michele Walsh; Bradley.Yoder@hsc.utah.edu; ROGER.FAIX@HSC.UTAH.EDU; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy.newman; alaptook@WIHRI.org  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Starlett Williams; fmartinez@ucsd.edu; sharon.gough@hsc.utah.edu; Brenda Vecchio  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - 5/29, Tu, 3:00 PM ET  
**Date:** Thursday, May 24, 2012 3:33:21 PM  
**Attachments:** Secondary analyses SUPPORT SNIPPV (2).doc

---

Dear all,

The SUPPORT call to discuss the secondary analysis proposal has been scheduled for:

**Tuesday, 5/29**  
**3:00pm ET**

Dial:  
Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Michele will be unable to join. Roger will also be on service and unable to join.

Thanks,  
Jenna

---

**From:** Gabrio, Jenna  
**Sent:** Tuesday, May 15, 2012 2:39 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy.newman'; Abbot Laptook (alaptook@WIHRI.org)  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu); 'Brenda Vecchio'  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - Availability Request

Dear all,

Unfortunately we were unable to find a time for this call to discuss the SUPPORT secondary analysis proposal (attached) in the first poll, so we need to look at a later date.

Please provide your availability on this NEW Doodle poll  
(<http://www.doodle.com/28usx4cbpbvexdbi>) for the following dates:

5/29, Tu  
5/30, W  
5/31, Th  
6/1, F

6/4, M  
6/5, Tu  
6/6, W  
6/7, Th  
6/8, F

Thanks,  
Jenna

---

**From:** Gabrio, Jenna  
**Sent:** Wednesday, May 09, 2012 12:50 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy newman'  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu)  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2)

Dear all,

We would like to setup a call to discuss the SUPPORT secondary analysis proposal.

Please provide your availability on this Doodle poll (<http://www.doodle.com/rsy3ndtyd863e5a8>) for the following dates:

5/14, M  
5/15, Tu  
5/16, W  
5/17, Th  
5/18, F

5/21, M  
5/22, Tu  
5/23, W  
5/24, Th  
5/25, F

Thanks,  
Jenna

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 09, 2012 12:41 PM  
**To:** 'Finer, Neil'; Wally Carlo, M.D.; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michele Walsh'; Bradley.Yoder@hsc.utah.edu; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman  
**Cc:** Gabrio, Jenna; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** Secondary analyses SUPPORT SNIPPV (2)

Hi

Attached is a proposal for a SUPPORT secondary analysis. Jenna will set up a call to discuss

Thanks

Rose

Page 1442 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act



Page 1443 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1444 of 2000

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Page 1445 of 2000

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Page 1446 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1447 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1448 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

**From:** Gabrio, Jenna  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - Availability Request  
**Date:** Thursday, May 24, 2012 2:42:28 PM

---

Hi Rose,

Can we do this call on:

**5/29, Tu, 3:00 – 4:00 PM ET—missing Michele, Roger is on service but will do his best to join.**

Brad Yoder and Linda Wright did not respond.

Please let me know if you would like to use this slot or we should look for another time.

Thanks,  
Jenna

---

**From:** Gabrio, Jenna  
**Sent:** Tuesday, May 15, 2012 2:39 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy newman'; Abbot Laptook (alaptook@WIHRI.org)  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu); 'Brenda Vecchio'  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - Availability Request

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(<http://www.doodle.com/28usx4cbpbevxdbi>) for the following dates:

5/29, Tu  
5/30, W  
5/31, Th  
6/1, F

6/4, M  
6/5, Tu  
6/6, W  
6/7, Th  
6/8, F

Thanks,

Jenna

---

**From:** Gabrio, Jenna  
**Sent:** Wednesday, May 09, 2012 12:50 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy newman'  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu)  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2)

Dear all,

We would like to setup a call to discuss the SUPPORT secondary analysis proposal.

Please provide your availability on this Doodle poll (<http://www.doodle.com/rsy3ndtyd863e5a8>) for the following dates:

5/14, M

5/15, Tu

5/16, W

5/17, Th

5/18, F

5/21, M

5/22, Tu

5/23, W

5/24, Th

5/25, F

Thanks,

Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, May 09, 2012 12:41 PM  
**To:** 'Finer, Neil'; 'Wally Carlo, M.D.'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman  
**Cc:** Gabrio, Jenna; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** Secondary analyses SUPPORT SNIPPV (2)

Hi

Attached is a proposal for a SUPPORT secondary analysis. Jenna will set up a call to discuss

Thanks

Rose



**From:** [Truog, William \(MD\)](#)  
**To:** ["Wally Carlo, M.D."; Neil Finer](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: FW: probing the 1300 patient SUPPORT dataset  
**Date:** Tuesday, May 22, 2012 2:51:23 PM

---

Thanks Wally—I appreciate the thoughts and will go from there. I was unsure if those 1316 patients had vast amounts of data collected on their infection status, more than might have been available in the GDB forms.

You answered that.

Of course gestational age at birth trumps everything for BPD risk—at least until you are 7 days of age or more....

Cheers,

Bill T.

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Tuesday, May 22, 2012 12:34 PM  
**To:** Truog, William (MD); Neil Finer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** DRe: FW: probing the 1300 patient SUPPORT dataset

Dear Bill:

As I mentioned to you before reading this email, we have to be careful to use RCT data to do a study that is not focused on the randomization. Furthermore, the data you need to answer the question are available in all GDB patients as SUPPORT did not collect additional infection data.

Thus, GDB data may be better. I would still be concerned that any results to this question are likely to be biased as both infection and pneumonia occur more often in the smallest infants who are likely to get the most severe BPD. I have been careful to depend in statistical adjustments as the models for BPD and many other major neonatal outcomes account generally for the minority of the variance.

I have not discussed this with Rose or Neil but OK forward to their comments as this is only my assessment on the issue.

I hope this is helpful.

Wally

"Truog, William (MD)" <[wtruog@cmh.edu](mailto:wtruog@cmh.edu)> wrote:

Wally,

Here is the email I referred to earlier today.

It's still half baked but I thought I would get your reaction to it.

Bill T.

---

**From:** Truog, William (MD)  
**Sent:** Friday, April 20, 2012 2:48 PM  
**To:** "Wally Carlo, M.D."; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Cc:** Truog, William (MD); Taylor, Jane, B  
**Subject:** probing the 1300 patient SUPPORT dataset

Gentlemen,

Greetings from Kansas City.

I write to you two as the representatives of the SUPPORT subcommittee from the NRN, on behalf of my colleague Dr. Jane Taylor and me, to see if it would be possible to probe the big dataset to determine if

the occurrence of respiratory or other severe infections, however they were defined, was an independent risk factor for moving infants from a predicted more benign outcome to the more severe outcome of moderate/severe BPD or death, using the 5 part BPD/death classification at 36 weeks. In the SPO2 range paper, there is a reference to severe sepsis—it was the same in both high and low saturation groups; otherwise I cannot find in either the primary reports or in the data forms for the multiple secondary studies arising from SUPPORT that are available to me on the private NRN website, that this question has been asked. Maybe I missed it; maybe it's not worth asking; maybe you all did not collect a lot of information about intercurrent infections including "pneumonia" ...but gee whiz, such a large cohort of infants 24-28 weeks....who can resist?

I thought that starting the conversation with you two was the way to go, but please re-direct me if I am wrong.

Perhaps I will see one or both of you in Boston next week.

Cheers and please advise at your convenience...

Bill Truog

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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](mailto:informationsecurityofficer@cmh.edu) and expunge this communication without making any copies. Thank you for your cooperation.

**From:** Phelps, Dale  
**To:** "Kennedy, Kathleen A"; Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Updated ROP Secondary Manuscript  
**Date:** Saturday, May 19, 2012 7:46:55 PM  
**Attachments:** ROP Natural History Study Manuscript (2) DLP.docx

---

Here you go Kathleen,

edits promised from my earlier e-mail. I think my comments will show in purple.. but I tried to add "DLP" to each one just in case.

Dale

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Tuesday, April 10, 2012 9:43 AM  
**To:** Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD); Phelps, Dale  
**Subject:** Updated ROP Secondary Manuscript

I've incorporated the revised figures and comments that were made in preparation of the poster and I've added a draft of the Discussion section. There's still a little more work for Lisa that wasn't done before we finalized the poster. Once Lisa revises the figure and adds the requested data, and you've all given me any additional suggestions you have, I can revise this one more time and send it to the SUPPORT Subcommittee.

I haven't formatted this for any particular journal yet. Do you think Pediatrics would be the best choice?

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

## Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A Kennedy, Lisa A Wrage, Dale L Phelps, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Roger Faix, Abbot Lupton, Kurt Schibler, Michelle Walsh, Brad Yoder, Abhik Das, Marie Gantz, Nancy Newman, Wade Rich

### Abstract

**Introduction:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. However, earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Methods:** ~~This observational study used outcome data from the NICHD Network SUPPORT Trial were used in a secondary observational analysis. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome. Inborn infants 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were included, and ROP eligible. Examinations followed current screening recommendations with follow up until final eye outcome was determined.~~

**Results:** 1316 infants were enrolled of whom, 223 died and 997 of these infants had a definitive ROP outcome. 138 met criteria for severe ROP. 128/138 (93%) with severe ROP had sufficient data (no missing or delayed exams) to determine the age of onset of severe ROP. The postmenstrual age (PMA) at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer; 1.0% (7% of infants with severe ROP) reached severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines. Some infants who are stable enough for back transfer or discharge home are still at risk to develop treatable ROP. A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.

### Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to achieve optimal outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP have not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of the ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2 or 3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution

**Comment [KKA1]:** 2611 words excluding abstract and references

**Comment [KKA2]:** Rose, is there a rule about the order of these authors? I just took this from the list of subcommittee members.

**Comment [O3]:** Stephanie Archer keeps tabs on the authorship and Acknowledgements for all papers. Check with her. DLP

**Comment [KKA4]:** 256 words)

**Comment [O5]:** I think this might miss that final eye outcome was determined, not just bad outcomes. A fine point, but important. You don't have to define severe ROP in the abstract.

**Comment [O6]:** This just looks better for the data, otherwise it looks like about 25% were not followed. I added the 193 early deaths and 30 subsequent deaths prior to eye outcome.

**Comment [O7]:** You may get some pushback on "treatable" ROP. Some may argue that all ROP is treatable. Even infants with total retinal detachments may receive treatment to ensure their face grows normally, or enucleation for intractable pain from glaucoma, etc. I'm ok with it as is, but am trying to think of alternatives since this is a bit imprecise. DLP

**Comment [KKA8]:** Last PubMed search of "ROP AND screening" was done on 2/7/12

**Comment [KKA9]:** Rose, Dale suggested trying to find a more recent reference. I can't see anything from the Network because the 2010 GDB paper reports outcomes by GA not BW. I think this might be the best reference to use if we want to use Network data and compare the CRYO-ROP/LIGHT-ROP era to something more recent. Let me know if you have a better suggestion.

**Comment [KKA10]:** "Chronological age" is what's suggested in the 2004 Pediatrics publication. I've now used that consistently in the manuscript.

of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as seen as Type 1 ROP develops.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This observational study analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27<sup>0/7</sup> weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) to determine if the current ROP screening guidelines were appropriate to identify treatable Type 1 ROP in a contemporary cohort of infants.

## Methods

In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. Extensive ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24<sup>0/7</sup> - 27<sup>6/7</sup> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded at each eye exam: the date of the eye exam, the highest stage of ROP in the and lowest zone of ROP, presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until study endpoint: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks postmenstrual age.

Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

## Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009. See Figure 1. Among surviving infants, 915 (997/1091) had a definitive ROP outcome. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of patient enrollment

**Comment [KKA11]:** Lisa, is this the highest stage in the lowest zone, or the highest stage in any zone and the lost zone with any ROP?

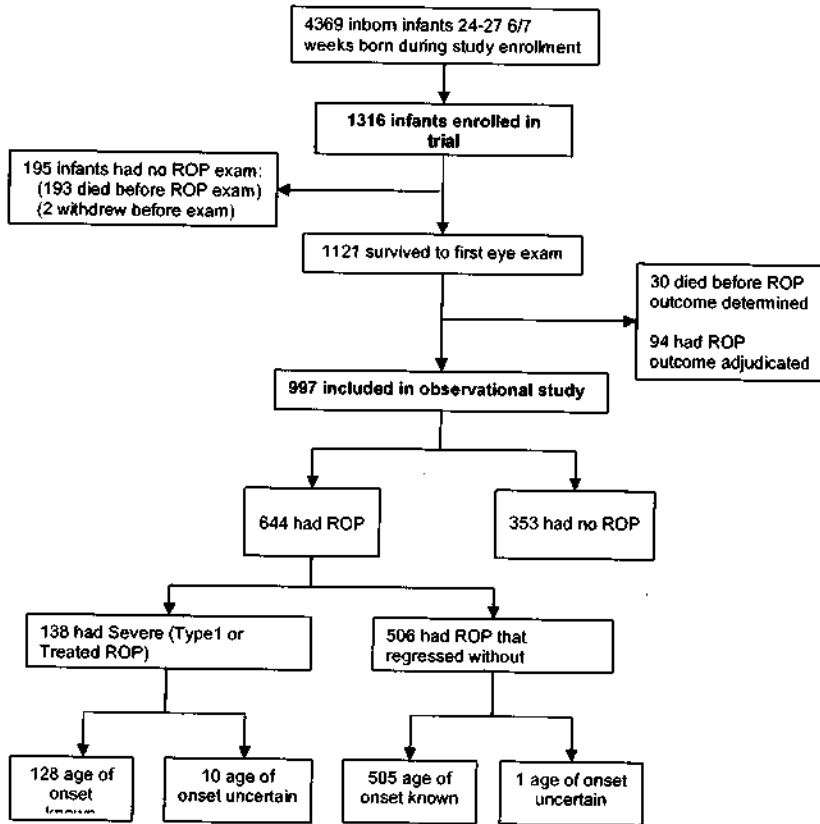
**Comment [O12]:** I corrected this based on the assumption that this is what was collected, but we still need to confirm with Lisa. DLP

**Comment [O13]:** Kathleen, it is interesting that I think NONE of the adjudicated outcomes were judged to have had severe ROP. At least this is my memory after I dug up the supplemental tables that NEJM only put on file. If you think this is interesting enough to include in the paper, I can dig out the actual data. I think it actually does not add anything to the content. DLP

**Comment [KKA14]:** The number who met GA inclusion criteria is still being reviewed. 4369 is based on SUPPORT and GDB data (need to verify that it's all inborn, not some outborns who had GDB data because they were enrolled in other trials). Main SUPPORT papers say that 3546 were assessed for eligibility and 3404 met GA criteria. We need to clarify this. May need to explain the discrepancy.

**Comment [O15]:** These numbers don't add up. 997/1091?? Is the '915' supposed to be 91.5%? (actually, I get 91.3%) DLP

**Formatted:** Font color: Red



The baseline demographic characteristics of the infants are shown in Table 1.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138

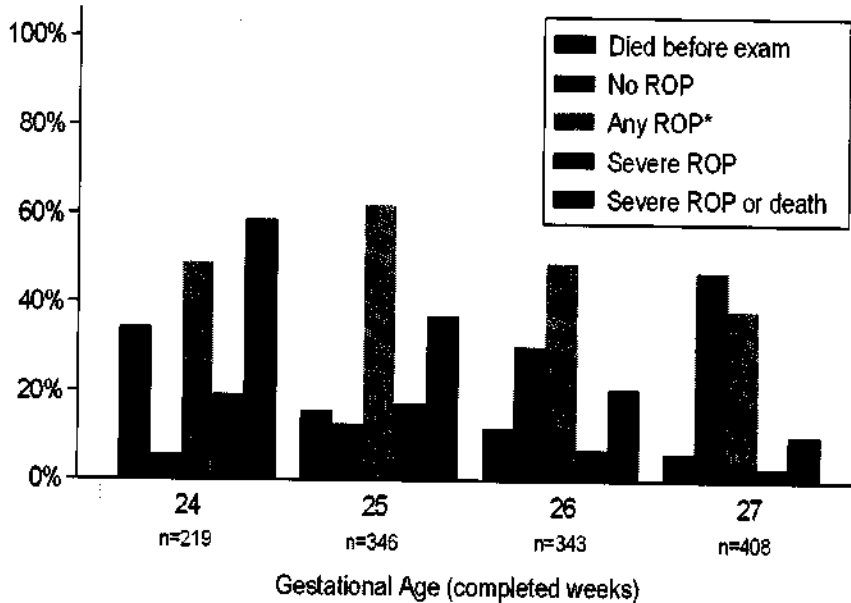
**Comment [KKA16]:** Dale asked about expressing the percents differently (eg risk of ROP among males vs females.) I'm not completely sure what we're trying to convey in this table as it's evolved. The first two columns convey the differences between all enrolled and those who survived to ROP determination. The last 3 columns convey the differences among the groups of infants who did and didn't have ROP. If we want to present the differences in risk by race, gender, ANS, we could do that in a set of figures, like Figure 2, that divides the cohort by these risk factors. I'm not sure that's wise since we really can't talk about incidence here because our cohort suffers from selection bias.

Gestational Age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth Weight [mean (SD)]	830 (193)	849 (190)	943 (173)	798 (179)	708 (148)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal Steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple Birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



**Comment [O17]:** This Figure is most likely to be published in black and white, and I'm afraid that the colors will not reproduce clearly. I would edit it considering black and white publication.--DLP

**Comment [KKA18]:** From 4/4/ email

\*Any ROP includes infants with mild/moderate ROP which regressed + infants with severe (type I/treated) ROP

As expected, the likelihood of surviving without ROP increased with each increasing week of completed gestation at birth (Figure 2).

The incidence of previously reported risk factors for ROP are shown in Table 2.

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on Oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset Sepsis (+ culture) [(n (%))]	76 (21.5)	250 (38.8)	77 (55.8)
Fungal Sepsis [n (%)]	2/352 (0.6)	23/641 (3.6)	8/137 (5.8)
Grade 3-4 Intraventricular Hemorrhage or Periventricular Leukomalacia [n (%)]	29 (8.2)	98/643 (15.2)	29 (21.0)
Proven Necrotizing Enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent Ductus Arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup>Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

**Comment [KKA19]:** Lisa, why are these denominators not the same?

**Comment [KKA20]:** Lisa, why are these denominators not the same?



For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3.

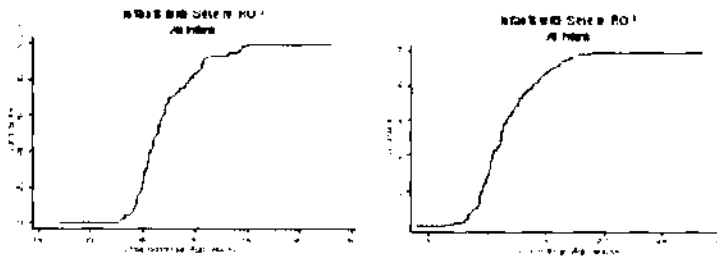
**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	642	29.3	30.4	31.4	32.7	33.9	35.1	37.9	41.0	46.7	4.0	4.6	5.4	6.7	8.0	9.4	11.9	15.3	19.7
Type II ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type I/Treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

<sup>2</sup> Type II ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. Of these infants, (includes 85 infants who had ROP which regressed and 73 went on to infants who developed severe ROP requiring treatment.)

**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Comment [O21]:** Type 2 ROP  
Also, note that in putting the footnote to the table that the '2' for superscript got entered twice.

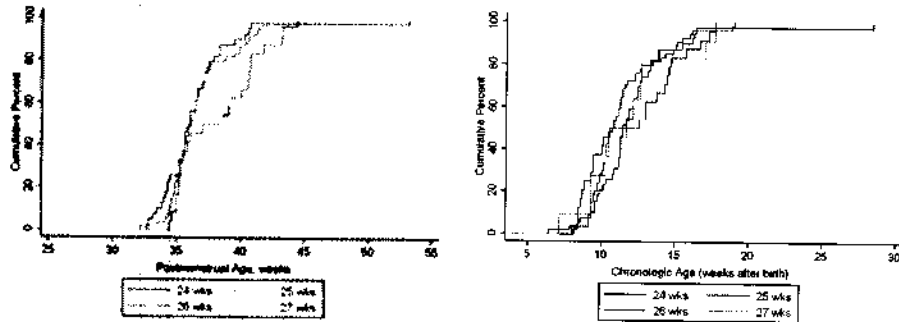
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**Comment [O22]:** Type 2 ROP

**Comment [KKA23]:** From 2/24 email. These were not updated for the poster. Lisa, for the manuscript, we'll need figures without the titles. Could we also label the axes as we've done for the other figures?

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**



**Comment [KKA24]:** From 3/29 email

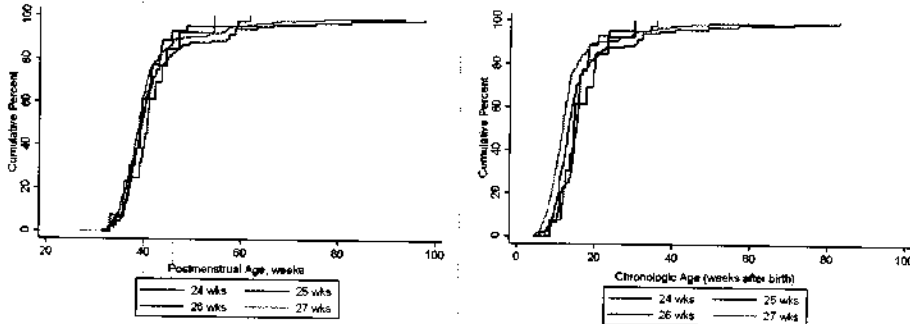
In contrast to prior studies<sup>33,44</sup> our data did not show a clear inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels became mature (to the ora serrata or two consecutive exams with vessels in zone III) are shown in Figure 5 for infants with no ROP and for infants with mild or moderate ROP.

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**Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth**

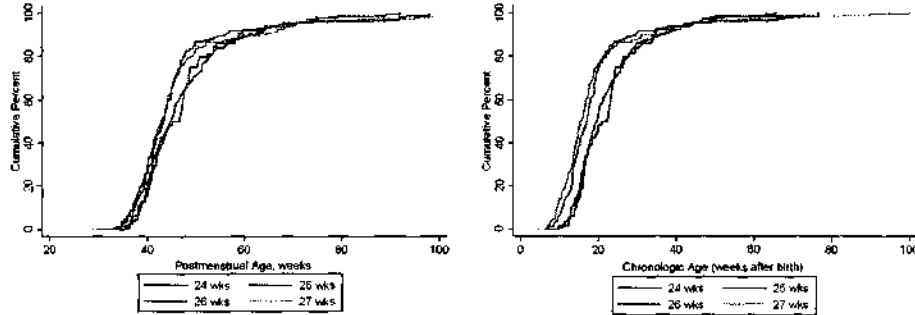
**No ROP**



**Comment [O25]:** As discussed in my earlier e-mail, I really do think we have to be cautious about saying this differs from previous publications. In order to say that, I am convinced we have to take our population and divide it in the same manner as the CRYO-ROP study did: BW >1000g, 750-1000 and <750g. The other point we can make is that the SUPPOR database included only infants of 24-27 weeks, while the CRYO-ROP study included infants of a much wider gestational age spread (xx-xx weeks) because they limited the study based on BW <1251 grams.

**Comment [KKA26]:** From 4/3 email

**Mild/Moderate ROP**



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and	1 (7.1%)	81 (15.4%)

**Comment [KKA27]:** In the email discussion about the poster, it was suggested that these groups be compared for factors that might identify infants as high risk for post-discharge ROP. Factors that were suggested include GA at birth, BW, days on oxygen, PDA, early onset sepsis, late onset sepsis, Candida sepsis, IVH, NEC. If we can get this information, that would be great although I'm skeptical that we'll be able to come up with anything practical that can identify these infants with reasonable specificity.

any stage ROP in any zone		
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

### Conclusion

Current screening guidelines, published in 2006,<sup>11</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity NICU; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### Discussion

In prior ROP natural history studies,<sup>12</sup> less mature infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>11</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>12</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have ~~estimated~~ documented the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion

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Comment [O28]: There was not a plot of each gestational age vs PMA. There was only a plot of 3 different BW groups vs PMA. DLP see note above

Comment [O29]: What was the rate of SGA among the SUPPORT cohort? I think we have to look at that before we say that it was higher in CRYO... I thought the GDB ran about 18% SGA? DLP

Comment [O30]: That has also been true historically in that ROP onset has not been before 4-6 weeks chronologic... also seen in the SUPPORT data. (Table 2)

Comment [KK431]: This might need to be modified when we get some more information.

Comment [O32]: Are you going to add in the table of differences used on the poster? I thought that was neat. DLP

receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>13</sup> The SUPPORT Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>11,13</sup>

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- <sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 117: 572-576, 2006. Erratum (screen gestational age of 30 weeks or less) in: *Pediatrics* 118: 1324, 2006.
- <sup>2</sup> Jeffries A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 15: 667-674, 2010.
- <sup>3</sup> Palmer EA et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 98: 1628-1640, 1991.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 120: 1470-1476, 2002.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 81: 697-706, 1988 and *Arch Ophthalmol* 106: 471-479, 1988.
- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA et al. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 338: 1572-1576, 1998.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 196(2):147 e1-8, 2007.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 102: 233-250, 2004.
- <sup>9</sup> Early Treatment for Retinopathy of Prematurity Cooperative Group. Then incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 116: 15-23, 2005.
- <sup>10</sup> Austeng D, Kallen KBM, Hellstrom A et al. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 128: 1289-1294, 2010.
- <sup>11</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. *Pediatrics* 87: 7-17, 1991.
- <sup>12</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 135:147-152, 1999
- <sup>13</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 129: 480-484, 2012.

**From:** Gantz, Marie  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; Wally, Carlo M.D.; Finer, Neil  
**Cc:** jmd3@case.edu; Das, Abhik  
**Subject:** RE: PAS abstract: analysis of SUPPORT deaths, cause and IH patterns  
**Date:** Thursday, May 17, 2012 12:37:20 PM

---

Rose, you are correct – SGA was not looked at for the primary SUPPORT analysis.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-351-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 17, 2012 11:20 AM  
**To:** 'Walsh, Michele'; Wally, Carlo M.D.; Finer, Neil  
**Cc:** jmd3@case.edu; Das, Abhik; Gantz, Marie  
**Subject:** RE: PAS abstract: analysis of SUPPORT deaths, cause and IH patterns

Michele and Julie

You are correct about the SGA issue. I looked back over the material for the primary NEJM publications and don't think we looked at SGA between the two sat groups and hospital outcome. I have included Marie and Abhik on the email as they may know, but I can't find a record of looking at SGA and death.

You probably saw Lilia DeJesus's paper on SGA from GDB (2006-2008) and these infants have twice the mortality rate as non-SGA infants.

I think this is definitely worth looking at—

Wally and Neil – what do 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](mailto:higginsr@mail.nih.gov)

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Thursday, May 17, 2012 11:07 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally\_Carlo\_M.D.; Finer, Neil  
**Cc:** jmd3@case.edu  
**Subject:** PAS abstract: analysis of SUPPORT deaths, cause and IH patterns

Hi Rose, Wally, Neil:

Julie DiFiore and I were very intrigued by the SUPPORT 2 yr outcomes Presentation saturation arm- where we noted a disproportionate drop out in the SGA infants. I am very intrigued by this and wonder if this may have contributed to the mortality. Would also analyze the intermittent Hypoxia patterns in individual pts who died to look at those impacts. We would like to work on this for a PAS abstract for next year. I leave for ATS and Europe tomorrow- so will have to submit the proposal when I return in June. Would this compete with any existing work?

*Michele Walsh*

**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
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**From:** [Finer, Neil](#)  
**To:** [Walsh, Michele](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally, Carlo, M.D.](#); [imd3@case.edu](mailto:imd3@case.edu)  
**Subject:** Re: PAS abstract: analysis of SUPPORT deaths, cause and IH patterns  
**Date:** Thursday, May 17, 2012 12:06:44 PM

---

This needs doing  
I am OK with it  
I know that Wally was looking at the hypoxia issue so I think Wally needs to comment  
Neil

On May 17, 2012, at 8:07 AM, "Walsh, Michele"  
<[Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)<<mailto:Michele.Walsh@UHhospitals.org>>> wrote:

Hi Rose, Wally, Neil:  
Julie DiFiore and I were very intrigued by the SUPPORT 2 yr outcomes  
Presentation saturation arm- where we noted a disproportionate drop out  
In the SGA infants. I am very intrigued by this and wonder if this  
May have contributed to the mortality. Would also analyze the intermittent  
Hypoxia patterns in individual pts who died to look at those impacts.  
We would like to work on this for a PAS abstract for next year.  
I leave for ATS and Europe tomorrow- so will have to submit the proposal  
When I return in June. Would this compete with any existing work?

Michele Walsh  
Chief Division of Neonatology  
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Professor of Pediatrics  
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by law.



**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Including SGA adjustment in CPAP SUPPORT paper  
**Date:** Thursday, May 17, 2012 11:30:08 AM

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I think so; also see the other emails I just forwarded.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 17, 2012 11:27 AM  
**To:** Das, Abhik  
**Subject:** RE: Including SGA adjustment in CPAP SUPPORT paper

The SGA FU in the low sat arm is low – was there a disproportionate death rate in the SGA infants that randomized to the lower sat arm??

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Thursday, May 17, 2012 11:26 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Including SGA adjustment in CPAP SUPPORT paper

FYI, we have been aware of this. I think we need to be careful with the analyses Michele wants to do, so that we don't undermine the results from our trial!

Thanks

Abhik

---

**From:** Gantz, Marie  
**Sent:** Friday, November 18, 2011 5:27 PM  
**To:** Das, Abhik; 'Vaucher, Yvonne'  
**Subject:** RE: Including SGA adjustment in CPAP SUPPORT paper

One reason I suggested adding the SGA adjustment to the paper is that Table 1 shows that SGA was different between the treatment groups at birth. I would not be surprised if a reviewer noticed that and asked if we had investigated the impact of that difference on the outcomes, so I thought it made sense to provide the information up front. But if the preference is not too, I will go along with

that decision.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Das, Abhik  
**Sent:** Friday, November 18, 2011 5:26 PM  
**To:** 'Vaucher, Yvonne'; Gantz, Marie  
**Subject:** RE: Including SGA adjustment in CPAP SUPPORT paper

I dont have strong feelings about this. So, I am fine with excluding this.  
Thanks

Abhik

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

**From:** Vaucher, Yvonne [yvaucher@ucsd.edu]  
**Sent:** Friday, November 18, 2011 05:14 PM Eastern Standard Time  
**To:** Gantz, Marie; Das, Abhik  
**Cc:** Vaucher, Yvonne  
**Subject:** RE: Including SGA adjustment in CPAP SUPPORT paper

Given Neil's objections to including the SGA adjustment in the paper, I sent the paper to Rose to distribute to the FUP PIs without comments related to the SGA status, analyses.

---

**From:** Vaucher, Yvonne  
**Sent:** Friday, November 18, 2011 1:37 PM  
**To:** 'Gantz, Marie'; Das, Abhik  
**Subject:** Including SGA adjustment in CPAP SUPPORT paper

Marie and Adhik,

Neil questions whether we should even mention SGA at all in the paper since the prespecified outcome did not include this as an adjustment and we did not adjust for many other factors which may also have been different in the treatment arms of the trial cohorts which may also have affected death such as pressors, tocolytics, etc.

yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

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tele: 619-543-3759  
FAX: 619-543-3812

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT trial proposal \_ Patterns of intermittent hypoxia associated with mortality  
**Date:** Thursday, May 17, 2012 11:25:36 AM  
**Attachments:** SUPPORT trial proposal \_ Patterns of intermittent hypoxia associated with mortality.docx

---

Here is Julies very preliminary first draft of how to look at the IH.  
We will refine.

Michele Walsh, MD  
Chief, Division of Neonatology  
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

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

**From:** Juliann Di Fiore [mailto:jmd3@case.edu]  
**Sent:** Thursday, May 17, 2012 10:34 AM  
**To:** Walsh, Michele; Richard Martin  
**Subject:** SUPPORT trial proposal \_ Patterns of intermittent hypoxia associated with mortality

Michele and Richard,

I am still really intrigued by the higher mortality in the low target group. I have been thinking about the possibility of looking at IH patterns in the infants who died compared to survivors. Keeping in mind the limitations of the data set I have written a brief draft of a proposal. It is a fairly large undertaking since I personally will need to analyze all the infants enrolled in the SUPPORT trial (except for ours and San Diego infants with high resolution data). I would also need stats help. Would you see what you think of this brief draft? I think it is worth taking a shot at this cohort.

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) 844-1478

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Page 1473 of 2000

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**From:** [Walsh, Michele](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\)](#) [E]  
**Cc:** [Wally, Carlo, M.D.](#); [Finer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** copy of SUPPORT saturation 20 m outcome slides?  
**Date:** Thursday, May 17, 2012 11:18:11 AM

---

Hi I am presenting a Year in Review Talk at ATS next week;  
And focusing on the SUPPORT trial. May I include a slide  
From Maria's and Tim's presentations on outcomes from the saturation arm?  
If yes pls forward copies of the presentations. Thanks

*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](mailto:michele.walsh@cwru.edu)  
Phone: (216) 844-3387  
Fax: (216) 844-3380

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**From:** Gabrio, Jenna  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; kurt.schibler@cchmc.org; Michele Walsh; Bradley.Yoder@hsc.utah.edu; ROGER.FAIX@HSC.UTAH.EDU; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy.newman; alaptook@WHRI.org  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Starlett Williams; fmartinez@ucsd.edu; sharon.gough@hsc.utah.edu; Brenda Vecchio  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2) - Availability Request  
**Date:** Tuesday, May 15, 2012 2:39:03 PM  
**Attachments:** Secondary analyses SUPPORT SNIPPV (2).doc

---

Dear all,

Unfortunately we were unable to find a time for this call to discuss the SUPPORT secondary analysis proposal (attached) in the first poll, so we need to look at a later date.

Please provide your availability on this NEW Doodle poll (<http://www.doodle.com/28usx4cbpbevyxdbj>) for the following dates:

5/29, Tu  
5/30, W  
5/31, Th  
6/1, F

6/4, M  
6/5, Tu  
6/6, W  
6/7, Th  
6/8, F

Thanks,  
Jenna

---

**From:** Gabrio, Jenna  
**Sent:** Wednesday, May 09, 2012 12:50 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy.newman'  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu)  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2)

Dear all,

We would like to setup a call to discuss the SUPPORT secondary analysis proposal.

Please provide your availability on this Doodle poll (<http://www.doodle.com/rsy3ndtyd863e5a8>) for the following dates:

5/14, M  
5/15, Tu  
5/16, W  
5/17, Th  
5/18, F

5/21, M  
5/22, Tu  
5/23, W  
5/24, Th  
5/25, F

Thanks,  
Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 09, 2012 12:41 PM  
**To:** 'Finer, Neil'; Wally Carlo, M.D.; Kurt Schibler [kurt.schibler@cchmc.org]; 'Michele Walsh'; Bradley.Yoder@hsc.utah.edu; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman  
**Cc:** Gabrio, Jenna; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** Secondary analyses SUPPORT SNIPPV (2)

Hi

Attached is a proposal for a SUPPORT secondary analysis. Jenna will set up a call to discuss

Thanks

Rose

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Page 1480 of 2000

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Page 1481 of 2000

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Page 1482 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act



Page 1483 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

**From:** Phelps, Dale  
**To:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Monday, May 14, 2012 5:11:46 PM

---

Hi Marie,

It might be helpful to understand that one of the most reasonable reasons to do surgery on an eye that does not meet criteria is the circumstance where:

1 eye meets criteria

The fellow eye almost meets criteria, but not quite

General anesthesia is going to be provided to treat the first eye, and it is easier on the infant to treat both eyes at one time with only one anesthetic.

So I am looking for that particular situation.

If you get only a few (less than 6) infants where one eye was treated after meeting criteria and the fellow eye was treated before meeting criteria, we can let it go at that. However, if it is more frequent, we'll want to look at it more closely to see if the data-form can tell us why. (for example, what were the details of the eye examination just prior to treatment for each eye).

The information will help us run the next ROP study better (Inositol).

Thank you very much.

Dale

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Monday, May 14, 2012 1:11 PM  
**To:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

I had started to work on Rose's request, but the additions from Dale will take a bit longer. I will keep you posted.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828.514.8256

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Monday, May 14, 2012 3:23 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie  
**Cc:** Das, Abhik; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

I think that this will have to be done at the eye level.

Among 132 infants who met criteria for the unfavorable ROP outcome in SUPPORT:

- 1) How many received treatment in both eyes, vs only 1 eye? (--- how many eyes treated?)
- 2) Based on eyes from all infants who received surgical treatment in one or both eyes:  
How many eyes met criteria for ETROP Type 1 ROP (or worse) before surgical treatment?  
Surgical Treatment would be laser therapy, cryotherapy or intravitreal injection of Avastin (or similar)

ETROP Type 1 ROP is defined as below:

I would like to review the algorithm Marie writes to translate the data from the dataform please:

(I have to find the SUPPORT eye exam form—can't get on the RTI website at the moment).

“Worse than ETROP Type 1” would be stage 4a, stage 4b or stage 5 ROP (zone does not matter)

- 3) Based on infants:

Among infants who had both eyes treated: How many were:

Both eyes met criteria for ETROP type 1 (or worse)

Only one eye met criteria for ETROP type 1 (or worse)

Dale

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Monday, May 14, 2012 9:52 AM

**To:** Gantz, Marie

**Cc:** 'Das, Abhik'; Phelps, Dale; 'Zaterka-Baxter, Kristin'

**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

Can you look at the SUPPORT data for children who had ROP surgery performed and let us know the following:

Number of infants receiving ROP surgery \_\_\_\_\_ (based on Wally's paper, this looks like 132)

Can you tell us how many had each of these categories:

1. type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph);
2. zone I, stage 3 ROP without plus disease;
3. zone II, stage 2 or 3 ROP with plus disease.

Can you tell us if nay infants underwent surgery and did not meet the above criteria?? If so, what

was their worst ROP status prior to surgery??

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

CDBPM, NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Gabrio, Jenna  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2)  
**Date:** Monday, May 14, 2012 5:06:43 PM

---

Hi Rose,

There aren't any times when both Neil are available for this call. Neil is out of town until 5/24.

These are the best times in this poll:

**5/18, F, 11:00 AM ET**—Missing Neil,

**5/25, F, 10:30 AM ET**—missing Wally, Roger, You need to leave at 11:00 AM ET

I haven't yet heard back from Brad and Linda about their availability.

Also, should Abbot or Myriam and Yvonne be included in this call? I don't think you sent the original message to them.

Do you want to use any of these times, or should I go ahead and repoll for a later date?

Thanks,  
Jenna

---

**From:** Gabrio, Jenna  
**Sent:** Wednesday, May 09, 2012 12:50 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Michele Walsh'; 'Bradley.Yoder@hsc.utah.edu'; 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; 'Wright, Linda (NIH/NICHD) [E]'; 'nancy newman'  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Starlett Williams'; 'fmartinez@ucsd.edu'; (sharon.gough@hsc.utah.edu)  
**Subject:** RE: Secondary analyses SUPPORT SNIPPV (2)

Dear all,

We would like to setup a call to discuss the SUPPORT secondary analysis proposal.

Please provide your availability on this Doodle poll (<http://www.doodle.com/rsy3ndtyd863e5a8>) for the following dates:

5/14, M  
5/15, Tu  
5/16, W  
5/17, Th  
5/18, F

5/21, M

5/22, Tu  
5/23, W  
5/24, Th  
5/25, F

Thanks,  
Jenna

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, May 09, 2012 12:41 PM  
**To:** 'Finer, Neil'; Wally Carlo, M.D.; Kurt Schibler [[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)]; 'Michele Walsh'; [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); 'ROGER.FAIX@HSC.UTAH.EDU'; Das, Abhik; Gantz, Marie; Wright, Linda (NIH/NICHD) [E]; nancy newman  
**Cc:** Gabrio, Jenna; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** Secondary analyses SUPPORT SNIPPV (2)

Hi

Attached is a proposal for a SUPPORT secondary analysis. Jenna will set up a call to discuss

Thanks

Rose

**From:** Phelps, Dale  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"; "Zaterka-Baxter, Kristin"  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Monday, May 14, 2012 4:23:19 PM

---

Marie,

There will be some confusing eye examinations, I'm sure.

Please let me look at the assumptions that you will have to make.

Dale

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Monday, May 14, 2012 1:11 PM  
**To:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

I had started to work on Rose's request, but the additions from Dale will take a bit longer. I will keep you posted.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-4255

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Monday, May 14, 2012 3:23 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie  
**Cc:** Das, Abhik; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC

I think that this will have to be done at the eye level.

Among 132 infants who met criteria for the unfavorable ROP outcome in SUPPORT:

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- 2) Based on eyes from all infants who received surgical treatment in one or both eyes:  
How many eyes met criteria for ETROP Type 1 ROP (or worse) before surgical treatment?  
Surgical Treatment would be laser therapy, cryotherapy or intravitreal injection of Avastin (or similar)

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(I have to find the SUPPORT eye exam form—can't get on the RTI website at the moment).

"Worse than ETROP Type 1" would be stage 4a, stage 4b or stage 5 ROP (zone does not matter)

3) Based on infants:

Among infants who had both eyes treated: How many were:

Both eyes met criteria for ETROP type 1 (or worse)

Only one eye met criteria for ETROP type 1 (or worse)

Dale

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Monday, May 14, 2012 9:52 AM

**To:** Gantz, Marie

**Cc:** 'Das, Abhik'; Phelps, Dale; 'Zaterka-Baxter, Kristin'

**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

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3. zone II, stage 2 or 3 ROP with plus disease.

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

CDBPM, NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Gantz, Marie  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Phelps, Dale; Zaterka-Baxter, Kristin  
**Subject:** RE: ROP data from SUPPORT TRIAL FOR DSMC  
**Date:** Monday, May 14, 2012 12:53:11 PM

---

Will look at this and get back to you.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 14, 2012 12:52 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; 'Phelps, Dale'; Zaterka-Baxter, Kristin  
**Subject:** ROP data from SUPPORT TRIAL FOR DSMC

Marie

The DSMC reviewed our INS-3 protocol and raised a possible concern for ROP surgery possibly being performed prior to an infant meeting threshold ROP.

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2. zone I, stage 3 ROP without plus disease;
3. zone II, stage 2 or 3 ROP with plus disease.

Can you tell us if any infants underwent surgery and did not meet the above criteria?? If so, what was their worst ROP status prior to surgery??

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Myriam Peralta, M.D."  
**Cc:** Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; "Das, Abhik"  
**Subject:** RE: CombPaperNEJM042512  
**Date:** Monday, May 14, 2012 12:46:38 PM

---

Thanks Rose for your comments. Am close and plan to have it done this week. Need to address a few last concerns before sending out to co-authors.

Yvonne

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, May 14, 2012 8:07 AM  
**To:** Vaucher, Yvonne; 'Myriam Peralta, M.D.'  
**Cc:** Finer, Neil; Wally Carlo, M.D.; Gantz, Marie; 'Das, Abhik'  
**Subject:** CombPaperNEJM042512

Here are my suggestions – are you close to having a draft for the SUPPORT subcommittee/co-authors?

Thanks  
Rose

**From:** Bhandari, Vineet  
**To:** [Finer, Neil](mailto:Finer_Neil); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins_Rosemary)  
**Cc:** [Ehrenkranz, Richard](mailto:Ehrenkranz_Richard); [Das, Abhik \(adas@rti.org\)](mailto:Das_Abhik)  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Date:** Saturday, May 05, 2012 11:38:58 AM  
**Attachments:** [Secondary analyses SUPPORT SNIPPV.doc](#)

---

Hello Neil,

OK. The original document is attached for consideration. The only clarification that I would make is that I would combine SNIPPV/NIPPV as the "nasal ventilation group".

If it helps, the analysis proposed is similar to what was reported in Pediatrics 2009 Aug;124(2):517-26. The analysis was done by Shampa Saha and Abhik Das.

If there is anything I can do to expedite the matter, please let me know and I will try and do my best to turn it around as quickly as possible.

Thanks.  
Vineet.

---

**From:** [Finer, Neil \[nfiner@ucsd.edu\]](mailto:nfiner@ucsd.edu)  
**Sent:** Friday, May 04, 2012 10:04 PM  
**To:** Bhandari, Vineet; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** [Ehrenkranz, Richard](mailto:Ehrenkranz_Richard); [Das, Abhik \(adas@rti.org\)](mailto:Das_Abhik)  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

I have the same problem

I remember these discussions but I cannot find any protocol

Can you resend what you wrote and we can reconsider?

I know that you were going to wait till the 2 year follow-up was complete so this is timely

I am sorry that I have no files on this but I had changed computers and I think that the old files were lost

I need to look at my other computer which may have some information on this

Neil

---

**From:** Bhandari, Vineet [<mailto:vineet.bhandari@yale.edu>]  
**Sent:** Thursday, May 03, 2012 9:38 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** [Ehrenkranz, Richard](mailto:Ehrenkranz_Richard); [Das, Abhik \(adas@rti.org\)](mailto:Das_Abhik); [Finer, Neil](mailto:Finer_Neil)  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Hello Rose,

I apologize for the confusion that I have created inadvertently. Ignore the "Response to Reviewers Comments" document as it was in relation to the Benchmarking dataset and as you mentioned, resulted in the PAS abstract and the paper that has already been published in Pediatrics. (I had saved the document in the wrong folder in error).

1. Now, regarding the secondary analysis of the SUPPORT Trial stuff, I am a little surprised that there is no record of it, as I had talked about it with Neil initially at one of the SUPPORT

meetings and later told by him, that it was "approved". I would try and touch base with him at least once a year about it, and he had told me to wait till the follow up was completed and that manuscript was written up.

I spent the last few hours scouring my old files and emails. Unfortunately, I tend to clean up emails >5 years old, and also moved onto to a new email server recently (which did not help matters). I am going to give a listing of dates and copies of emails regarding the same, that I could "find/recover". (I can forward the actual emails, if you wish, but I did not want to clog everybody's inboxes). Perhaps, it will help Neil and/or Abhik to locate some documents. I spoke with Rich, and he has at least found the Secondary Analysis proposal in his file collection.

- (i) Date: 11/12/2004, 11:10 AM. "Hello Rich. I wrote up a (hopefully) succinct request for doing a "Secondary analyses SUPPORT SNIPPV" (do you like that title?). Please review. Your suggestions/comments will be helpful, as always. Then, I will send it over to Neil and hopefully, it will be a go ..."
- (ii) Date: 11/12/2004, 3:45PM. "Hello, Neil, Please find attached a draft of my proposal for secondary analyses of babies receiving SNIPPV as part of the SUPPORT study." [cc'ed to Rich]  
  
Date: 11/15/2004, 12:25 PM. "Hello Vineet, Could you please specify the actual analyses for this secondary? This requires a bit more detail, and should include what you will actually  
(iii) evaluate by which statistic. What is the Primary hypothesis of this Secondary? I realize that you want to use already collected data, but if you don't present in a clear fashion, this will not be considered. Thanks Neil Finer"
- (iv) Date: 11/15/2004, 2:11 PM. "Hello, Neil. Please see attached. Specifically, please see page 2 for the primary and secondary hypotheses of the "secondary analyses" and page 5 for the "statistical analyses". I hope the above is sufficiently detailed. Please let me know if it still does not meet the requirements. Thanks for your help. Vineet."
- (v) Date: 5/4/2011, 4:52 PM. "Hello Neil, It was nice to catch up with you at PAS in Denver.....As the time is coming up for the "follow -up" to be completed, I just wanted to be in the queue.....As with our earlier collaboration, thank you for your support (no pun intended :-)). Regards. Vineet."

Sorry for the long email, but, I am hoping Neil can help me out here....

Thanks.  
Vineet.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 02, 2012 4:38 PM  
**To:** Bhandari, Vineet

**Cc:** Ehrenkranz, Richard; Das, Abhik ([adas@rti.org](mailto:adas@rti.org))  
**Subject:** FW: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Vineet

I have gone back through our files and found an evaluation for a PAS abstract from the Benchmarking dataset for which a manuscript has been published. I have asked RTI and looked through our records and we cannot find a record of approval for this SUPPORT secondary – can you forward us the approval.

Thanks

Rose

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

---

**From:** Bhandari, Vineet [<mailto:vineet.bhandari@yale.edu>]  
**Sent:** Wednesday, May 02, 2012 11:31 AM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Hello Neil (and Rose),

It was nice to catch up with you at PAS in Boston. As I had mentioned to you, I am sending you a copy of my "secondary analysis" proposal of SNIPPV/NIPPV (initially submitted on 11-15-2004) in the SUPPORT study as well as my "response" to comments by the reviewers of the proposal (initially submitted on 6-21-2006). Following this, I was told that it had been "approved". (The only clarification that I would make is that I would combine SNIPPV/NIPPV as the "nasal ventilation group" since we lost our Infant Star ventilators in Dec 2006).

As I believe the "follow-up" is completed, I just wanted to know who should I contact to initiate the analysis.

As with our earlier collaboration, thank you for your support (no pun intended ☺).

Regards.  
Vineet.

**Vineet Bhandari, MD, DM**  
**Associate Professor of Pediatrics, Obstetrics, Gynecology**  
**and Reproductive Sciences**  
**Director, Program in Perinatal Research**  
**Yale University School of Medicine**  
**Yale Child Health Research Center**  
**Room Number: 219**  
**P.O. Box 208081**  
**464 Congress Avenue**  
**New Haven, CT 06520-8081**  
**Phone: 203-785-2613**  
**Fax: 203-737-2805**



Page 1499 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1500 of 2000

Withheld pursuant to exemption

(b)(4)

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Page 1501 of 2000

Withheld pursuant to exemption

(b)(4)

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Page 1502 of 2000

Withheld pursuant to exemption

(b)(4)

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Page 1503 of 2000

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(b)(4)

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Page 1504 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1505 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

**From:** [Finer, Neil](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#); [Gantz, Marie](#); [Wally Carlo, M.D.](#)  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Date:** Friday, May 04, 2012 8:02:29 PM

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Hi Rose

I have no documents about this – but my recollection was that it was near the beginning of SUPPORT.

I have changed computers and the docs I have do not include this

Can we ask Vineet to resubmit?

Neil

---

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#) [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, May 04, 2012 5:43 AM  
**To:** [Finer, Neil](#); [Das, Abhik](#); [Gantz, Marie](#); [Wally Carlo, M.D.](#)  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

Neil

RTI and I cannot find this approval (or review). Perhaps there was email communication by a small number of folks and not the entire subcommittee– if you have something that the SUPPORT subcommittee approved, please send it. Otherwise, we need to have the SUPPORT subcommittee review.

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](mailto:higginsr@mail.nih.gov)

---

**From:** [Finer, Neil](#) [<mailto:nfiner@ucsd.edu>]  
**Sent:** Wednesday, May 02, 2012 6:40 PM  
**To:** [Das, Abhik](#); [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally Carlo, M.D.](#)  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

Hi Vineet

I do remember this

I believe that when the follow-up paper is complete we should be able to give Vineet the go ahead  
Rose, Do you want us to re-review this?

Neil



---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Wednesday, May 02, 2012 9:09 AM  
**To:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

I don't remember either! Also, Yale is no longer in the NRN, though I am not sure whether that is relevant.

Thanks

Abhik

---

**From:** Gantz, Marie  
**Sent:** Wednesday, May 02, 2012 12:03 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; nfiner@ucsd.edu; Wally Carlo, M.D.  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

Rose, I don't think I ever saw these proposals – I have nothing about them in my files. Sorry I can't be more helpful.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-0255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 02, 2012 11:33 AM  
**To:** Das, Abhik; nfiner@ucsd.edu; Wally Carlo, M.D.; Gantz, Marie  
**Subject:** FW: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

My recollection was that we rejected this secondary analysis – can someone help me out here with the history??

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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---

**From:** Bhandari, Vineet [<mailto:vineet.bhandari@yale.edu>]  
**Sent:** Wednesday, May 02, 2012 11:31 AM  
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**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
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Hello Neil (and Rose),

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As I believe the "follow -up" is completed, I just wanted to know who should I contact to initiate the analysis.

As with our earlier collaboration, thank you for your support (no pun intended ☺).

Regards.  
Vineet.

Vineet Bhandari, MD, DM  
Associate Professor of Pediatrics, Obstetrics, Gynecology  
and Reproductive Sciences  
Director, Program in Perinatal Research  
Yale University School of Medicine  
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Room Number: 219  
P.O. Box 208081  
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New Haven, CT 06520-8081  
Phone: 203-785-2613  
Fax: 203-737-2805

**From:** [Finer, Neil](#)  
**To:** [Gantz, Marie](#); [Schmidt, Barbara \(Neonatology\)](#)  
**Cc:** [Robin Roberts](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#); [Robin Whyte](#)  
**Subject:** RE: Reversal of study oximeters from offset to truth  
**Date:** Friday, May 04, 2012 7:54:11 PM  
**Attachments:** [image001.png](#)

---

Hi Barb

My graph was for demonstration purposes only and did not provide the actual conversions as not all values can be converted

Sorry if there was any confusion

Neil

---

**From:** [Gantz, Marie \[mailto:mgantz@rti.org\]](mailto:mgantz@rti.org)  
**Sent:** Friday, May 04, 2012 11:51 AM  
**To:** [Schmidt, Barbara \(Neonatology\)](#); [Finer, Neil](#)  
**Cc:** [Robin Roberts](#); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov); [Das, Abhik](#); [Robin Whyte](#)  
**Subject:** RE: Reversal of study oximeters from offset to truth

Barbara,

The graph you included in your email appears to match the algorithm we used to convert from display to actual values for SUPPORT (see attached document).

Marie

**Marie Gantz, Ph.D.**  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
833-254-8255

---

**From:** [Schmidt, Barbara \(Neonatology\) \[mailto:barbara.schmidt@uphs.upenn.edu\]](mailto:barbara.schmidt@uphs.upenn.edu)  
**Sent:** Friday, May 04, 2012 1:10 PM  
**To:** [Gantz, Marie](#); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Cc:** [Robin Roberts](#); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov); [Das, Abhik](#); [Robin Whyte](#)  
**Subject:** Reversal of study oximeters from offset to truth

Dear Marie and Neil,

Below is a copy of the explanation of the masking algorithm from our COT protocol. At the time of our grant application to CIHR in 2005, Masimo - via Dr. Sayre - confirmed this figure to be correct.

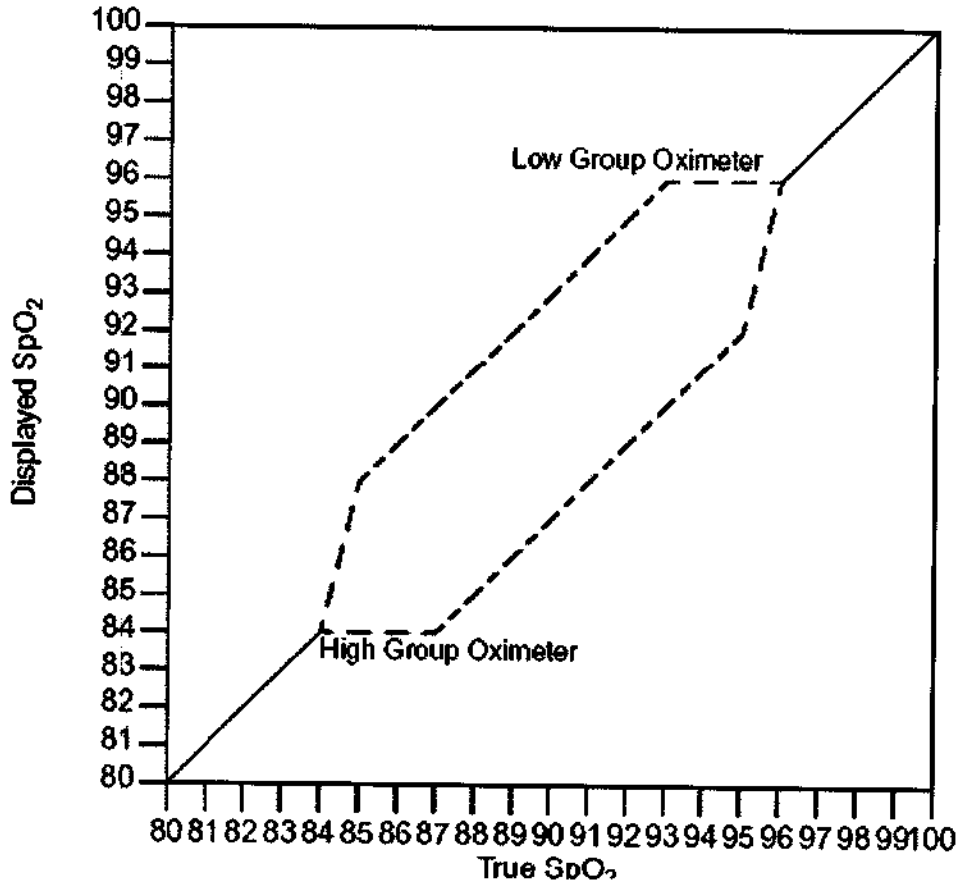
However, during his presentation last Saturday in Boston, Neil showed a figure that was slightly different from the one shown below. Obviously, it will be crucial to try and "reverse" the offset data as best as possible, and to do it the

same way in all of our trials.

Please let us know if you spot any errors in the graph below.

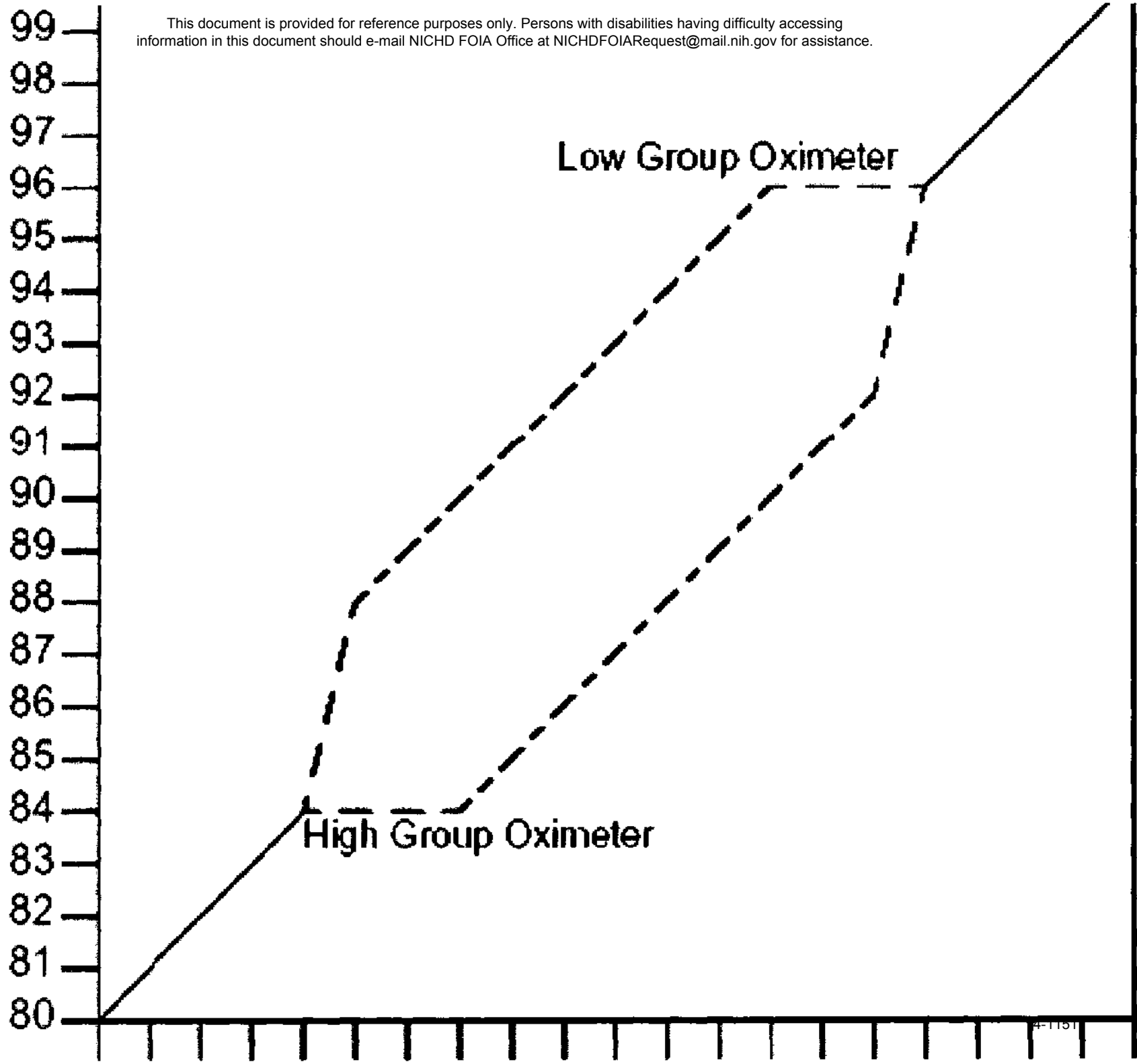
With thanks and best regards

Barbara



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Displayed SpO<sub>2</sub>



Low Group Oximeter

High Group Oximeter

**From:** [Finer, Neil](#)  
**To:** [Cole, Cynthia](#); [Ola D. Saugstad](#); [vkumar3@buffalo.edu](#); [Higgins, Rosemary \(NIH/NICHD\) \(E\)](#); [Inogee@jhmi.edu](#)  
**Subject:** RE: PAS Meeting  
**Date:** Friday, May 04, 2012 7:36:47 PM

---

It was a privilege to be part of this  
Great to see you again Cynthia  
Be well  
Neil

---

**From:** Cole, Cynthia [<mailto:Cynthia.Cole@bmc.org>]  
**Sent:** Friday, May 04, 2012 3:46 PM  
**To:** Ola D. Saugstad; [vkumar3@buffalo.edu](#); Finer, Neil; [higginsr@mail.nih.gov](#); [Inogee@jhmi.edu](#)  
**Subject:** RE: PAS Meeting

Dear Vasanth, Larry, Ola, Neil, and Rose,  
In addition to the PAS oxygenation session being a great experience, it was also fun!  
Vasanth, you are highly commended for organizing such a successful program. One of the technical assistants assessed at least 1300 people attended the session (based on ballroom seating & conservative estimate of people standing). Wow!  
It was an honor to participate in this session and to learn from each of you.

Kindest regards to each of you.  
- Cynthia

Cynthia H. Cole, MD, MPH  
Division of Neonatology  
Department of Pediatrics  
Boston Medical Center  
771 Albany St.  
Dowling 4N  
Boston, MA 02118  
Of: 617-414-5461  
F: 617-414-7297

---

**From:** Ola D. Saugstad [<mailto:odsaugstad@rr-research.no>]  
**Sent:** Friday, May 04, 2012 4:06 PM  
**To:** [vkumar3@buffalo.edu](#); [nfiner@ucsd.edu](#); [higginsr@mail.nih.gov](#); Cole, Cynthia; [Inogee@jhmi.edu](#)  
**Subject:** SV: PAS Meeting

Dear Vasanth, Larry, Neil, Rose and Cynthia,

First of all I want to thank you for a great experience talking in the same session as you at PAS. I have received positive feedback from so many. It was stimulating indeed to listen to all the great talks.

Thanks to Vasanth and Larry for including me.

Warm regards

Ola

Ola Didrik Saugstad MD PhD FRCPE  
Professor of Pediatrics  
Director Department of Pediatric Research  
Oslo University Hospital, Rikshospitalet, University of Oslo Norway

Mailing address: Pediatrisk Forskningsinstitutt Rikshospitalet 0027 Oslo Norway

Phone +47 23072790/94

Fax +47 23072780

Cell phone (b)(6)

---

**Fra:** vkumar3@buffalo.edu [mailto:vkumar3@buffalo.edu]

**Sendt:** lø 21.04.2012 15:06

**Til:** Ola D. Saugstad; nfiner@ucsd.edu; higginsr@mail.nih.gov; Cynthia.Cole@bmc.org; Inogee@jhmi.edu

**Emne:** PAS Meeting

Dear Ola, Neil, Rose, Cynthia and Larry,

Next week we all will be actually at the meeting and I can't believe that it is here.

I am sure we all want this to be a great learning and sharing experience and to see whether this can provide the energy and the oompoh to take this debate a step forward by both research and application through collaboration.

Couple of things - I have received presentation from Rose (thanks Rose). All presentations need a disclosure slide (I am sorry to tell this to all the excellent and professional speakers - PAS wants me to do that); Now that the deadline for submission has passed, I would appreciate if the speakers send me the presentations, so that there is a nice sync and continuity among the presenters / and also not much of duplications. We have some time to work on this too. I have included my presentation as a pdf with this email.

Let me know if I have to make any changes too. I have included couple of my studies too. Once we get to see the presentations, I thought at least the US based speakers (I am ok if Ola can join) can group for a short phone based communication to clear anything that they may have. or is there any other way to do this?

Larry is busy on Monday am - so that time is not available.

Vasanth

This electronic transmission may contain information that is privileged, confidential and exempt from disclosure under applicable law. If you are not the intended recipient, please notify me immediately as use of this information is strictly prohibited.

**From:** Wally Carlo, M.D.  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Finer, Neil"; Das, Abhik; Gantz, Marie  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Date:** Friday, May 04, 2012 9:02:05 AM

---

I do not remember that the group received the concept.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 (b)(6)

---

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**Sent:** Friday, May 04, 2012 7:43 AM  
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Neil

RTI and I cannot find this approval (or review). Perhaps there was email communication by a small number of folks and not the entire subcommittee— if you have something that the SUPPORT subcommittee approved, please send it. Otherwise, we need to have the SUPPORT subcommittee review.

Thanks  
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**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

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Thanks

Abhik

---

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**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

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**Importance:** High

My recollection was that we rejected this secondary analysis – can someone help me out here with the history??

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Rose

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Regards.  
Vineet.

Vineet Bhandari, MD, DM  
Associate Professor of Pediatrics, Obstetrics, Gynecology  
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Director, Program in Perinatal Research  
Yale University School of Medicine  
Yale Child Health Research Center  
Room Number: 219  
P.O. Box 208081  
464 Congress Avenue  
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Fax: 203-737-2805

**From:** Gantz, Marie  
**To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]; mcw3@po.cwru.edu  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Date:** Thursday, May 03, 2012 2:35:21 PM

---

I don't remember this either, but November 2004 was just a few months after I joined RTI, and I don't think I was involved in evaluating secondary studies at that time.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-0255

---

**From:** Das, Abhik  
**Sent:** Thursday, May 03, 2012 2:28 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'; Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]; 'mcw3@po.cwru.edu'  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

I don't remember this at all, and I did look through my emails and folders, but couldn't find anything!

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 03, 2012 2:23 PM  
**To:** 'wcarlo@peds.uab.edu'; Gantz, Marie; Archer, Stephanie (NIH/NICHD) [E]; 'mcw3@po.cwru.edu'  
**Cc:** Das, Abhik  
**Subject:** Fw: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Do any of you recall this? Talking to Neil would not meet the network's approval process for a secondary analysis approval. I am not sure the SUPPORT subcommittee granted approval. I thought we directed this to Benchmarking.  
Let me know if I have dropped the ball on this one. I have included Michele as she was quite involved during the time when Neil's wife was so ill.

Thanks for your help

Rose

---

**From:** Bhandari, Vineet [mailto:vineet.bhandari@yale.edu]  
**Sent:** Thursday, May 03, 2012 12:37 PM

**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Ehrenkranz, Richard <richard.ehrenkranz@yale.edu>; Das, Abhik (adas@rti.org) <adas@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>  
**Subject:** RE: Secondary analysis SUPPORT Study: SNIPPV/NIPPV

Hello Rose,

I apologize for the confusion that I have created inadvertently. Ignore the "Response to Reviewers Comments" document as it was in relation to the Benchmarking dataset and as you mentioned, resulted in the PAS abstract and the paper that has already been published in Pediatrics. (I had saved the document in the wrong folder in error).

1. Now, regarding the secondary analysis of the SUPPORT Trial stuff, I am a little surprised that there is no record of it, as I had talked about it with Neil initially at one of the SUPPORT meetings and later told by him, that it was "approved". I would try and touch base with him at least once a year about it, and he had told me to wait till the follow up was completed and that manuscript was written up.

I spent the last few hours scouring my old files and emails. Unfortunately, I tend to clean up emails >5 years old, and also moved onto to a new email server recently (which did not help matters). I am going to give a listing of dates and copies of emails regarding the same, that I could "find/recover". (I can forward the actual emails, if you wish, but I did not want to clog everybody's inboxes). Perhaps, it will help Neil and/or Abhik to locate some documents. I spoke with Rich, and he has at least found the Secondary Analysis proposal in his file collection.

- (i) Date: 11/12/2004, 11:10 AM. "Hello Rich. I wrote up a (hopefully) succinct request for doing a "Secondary analyses SUPPORT SNIPPV" (do you like that title?). Please review. Your suggestions/comments will be helpful, as always. Then, I will send it over to Neil and hopefully, it will be a go ..."
- (ii) Date: 11/12/2004, 3:45PM. "Hello, Neil, Please find attached a draft of my proposal for secondary analyses of babies receiving SNIPPV as part of the SUPPORT study." [cc'ed to Rich]

Date: 11/15/2004, 12:25 PM. "Hello Vineet, Could you please specify the actual analyses for this secondary? This requires a bit more detail, and should include what you will actually

- (iii) evaluate by which statistic. What is the Primary hypothesis of this Secondary? I realize that you want to use already collected data, but if you don't present in a clear fashion, this will not be considered. Thanks Neil Finer"
- (iv) Date: 11/15/2004, 2:11 PM. "Hello, Neil. Please see attached. Specifically, please see page 2 for the primary and secondary hypotheses of the "secondary analyses" and page 5 for the "statistical analyses". I hope the above is sufficiently detailed. Please let me know if it still does not meet the requirements. Thanks for your help. Vineet."

- (v) Date: 5/4/2011, 4:52 PM. "Hello Neil, It was nice to catch up with you at PAS in Denver.....As the time is coming up for the "follow -up" to be completed, I just wanted to be in the queue.....As with our earlier collaboration, thank you for your support (no pun intended :-)). Regards. Vineet."

Sorry for the long email, but, I am hoping Neil can help me out here....

Thanks.  
Vineet.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 02, 2012 4:38 PM  
**To:** Bhandari, Vineet  
**Cc:** Ehrenkranz, Richard; Das, Abhik (adas@rti.org)  
**Subject:** FW: Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Vineet

I have gone back through our files and found an evaluation for a PAS abstract from the Benchmarking dataset for which a manuscript has been published. I have asked RTI and looked through our records and we cannot find a record of approval for this SUPPORT secondary – can you forward us the approval.

Thanks  
Rose

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

---

**From:** Bhandari, Vineet [mailto:vineet.bhandari@yale.edu]  
**Sent:** Wednesday, May 02, 2012 11:31 AM  
**To:** nfiner@ucsd.edu  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Importance:** High

Hello Neil (and Rose),

It was nice to catch up with you at PAS in Boston. As I had mentioned to you, I am sending you a copy of my "secondary analysis" proposal of SNIPPV/NIPPV (initially submitted on 11-15-2004) in the

SUPPORT study as well as my "response" to comments by the reviewers of the proposal (initially submitted on 6-21-2006). Following this, I was told that it had been "approved". (The only clarification that I would make is that I would combine SNIPPV/NIPPV as the "nasal ventilation group" since we lost our Infant Star ventilators in Dec 2006).

As I believe the "follow -up" is completed, I just wanted to know who should I contact to initiate the analysis.

As with our earlier collaboration, thank you for your support (no pun intended ☺).

Regards.

Vineet.

**Vineet Bhandari, MD, DM**  
Associate Professor of Pediatrics, Obstetrics, Gynecology  
and Reproductive Sciences  
Director, Program in Perinatal Research  
Yale University School of Medicine  
Yale Child Health Research Center  
Room Number: 219  
P.O. Box 208081  
464 Congress Avenue  
New Haven, CT 06520-8081  
Phone: 203-785-2613  
Fax: 203-737-2805

**From:** Gantz, Marie  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Boilerplate | Gantz, SUPPORT Oxygenation and ROP  
**Date:** Thursday, May 03, 2012 12:50:07 PM

---

Thanks, Stephanie.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-251-6255

---

**From:** Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]  
**Sent:** Thursday, May 03, 2012 12:35 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Boilerplate | Gantz, SUPPORT Oxygenation and ROP

Hi Marie,

Attached is the boilerplate for your SUPPORT ROP paper. I never got a response from Dallas about their acknowledgements, but they were given ample opportunities to respond. I would proceed as-is. If we got anything from them in the meantime, we can make changes when the paper proofs are ready.

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](mailto:archerst@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Monday, April 09, 2012 11:01 AM  
**To:** 'Krisa Van Meurs (vanmeurs@stanford.edu)'; Bethany Ball; 'Neil Finer'; 'Wade Rich'; 'Pablo Sanchez'; 'Luc Brion (luc.brion@utsouthwestern.edu)'; 'Diana Vasil'  
**Cc:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Boilerplate | Gantz, SUPPORT Oxygenation and ROP

Please send your concurrence for the attached boilerplate. If we do not receive it by Friday, April

13<sup>th</sup>, we will proceed with it as-is.

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](mailto:archerst@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, January 10, 2012 10:24 AM  
**To:** 'Michele Walsh (Michele.walsh@cwru.edu)'; Kurt Schibler [kurt.schibler@cchmc.org]; Krisa Van Meurs (vanmeurs@stanford.edu); Ivan.Frantz@childrens.harvard.edu; Neil Finer (nfiner@ucsd.edu); Charles Bauer (cbauer@peds.med.miami.edu); 'Shahnaz Duara (sduara@miami.edu)'; Pablo.Sanchez@UTSouthwestern.edu; 'Michael O' Shea (moshea@wfubmc.edu)'  
**Cc:** Cathy Grisby (cathy.grisby@uc.edu); 'Bethany Ball'; Wade Rich (wrich@ucsd.edu); Diana Vasil  
**Subject:** FW: Boilerplate | Gantz, SUPPORT Oxygenation and ROP

Please send in your concurrence for the attached boilerplate.

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](mailto:archerst@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, December 23, 2011 1:33 PM  
**To:** Neil Finer (nfiner@ucsd.edu); 'Shahnaz Duara (sduara@miami.edu)'; Charles Bauer (cbauer@peds.med.miami.edu); Carl D'Angio (carl\_dangio@urmc.rochester.edu); Dale Phelps (dale\_phelps@urmc.rochester.edu); 'Michael O' Shea (moshea@wfubmc.edu); Abbot Laptok (alaptok@wihri.org); Abhik Das (adas@rti.org); Barbara Stoll (barbara\_stoll@oz.ped.emory.edu); Brenda Poindexter (bpoindexter@iupui.edu); Ed Bell (edward-bell@uiowa.edu); Ed Donovan (edward.donovan@cchmc.org); Ivan Frantz (IFrantz@tufts-nemc.org); Kathleen Kennedy (Kathleen.A.Kennedy@uth.tmc.edu); Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Michele Walsh (Michele.walsh@cwru.edu); Pablo Sánchez (Pablo.Sanchez@UTSouthwestern.edu); Richard Ehrenkranz (richard.ehrenkranz@yale.edu); Roger Faix (roger.faix@hsc.utah.edu); Ron Goldberg



(goldb008@mc.duke.edu); Seetha Shankaran (sshankar@med.wayne.edu); Wally Carlo (wacarlo@uab.edu)  
**Cc:** Wade Rich (wrich@ucsd.edu); Bethany Ball (mbball@leland.stanford.edu); Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu); 'Kim Fisher (kimberley.fisher@duke.edu)'; 'Joanne Finkle, J.D.'  
**Subject:** Boilerplate | Gantz, SUPPORT Oxygenation and ROP

Dear PIs,

Attached is an acknowledgements boilerplate for Marie Gantz's SUPPORT paper, "Oxygen Saturations and retinopathy of extremely prematurity in preterm infants." This paper is still being drafted; a copy will be forwarded to the PIs once it is ready for review.

As stated on the boilerplate, this paper includes:

- **SUPPORT recruitment 2005-2009**

This paper does NOT include Follow-up, but it does include the ROP outcomes. So **please add in your site ophthalmologist's full name and degrees in the Acknowledgements for your site.**

As always, please look over the attached boilerplate to make sure that:

- All relevant centers are included
- All relevant personnel are included with full names and degrees

Please send me your responses by **Friday, January 6<sup>th</sup>**.

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](mailto:archerst@mail.nih.gov)

**From:** Myriam Peralta, M.D.  
**To:** "Vaucher, Yvonne"; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org; adas@rti.org; jgabrio@rti.org  
**Cc:** Finer, Neil  
**Subject:** RE: PAS congrats  
**Date:** Wednesday, May 02, 2012 11:12:04 AM

---

Thank you to everyone in the team and in the network who made this study possible.

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

**From:** Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
**Sent:** Tuesday, May 01, 2012 9:26 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org; adas@rti.org; jgabrio@rti.org  
**Cc:** Finer, Neil; Myriam Peralta, M.D.  
**Subject:** RE: PAS congrats

All,

Thanks so much for your help and encouragement!

Yvonne

---

**From:** Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
**Sent:** Tuesday, May 01, 2012 11:51 AM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org; adas@rti.org; jgabrio@rti.org  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; Vaucher, Yvonne  
**Subject:** PAS congrats

Yvonne and Myriam.

You both did an excellent job presenting the SUPPORT trial. Thanks so much for your hard work.

Wally

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

**From:** "Vaucher, Yvonne" <yvaucher@ucsd.edu>  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "&apos;mgantz@rti.org&apos;"; <mgantz@rti.org>, "&apos;adas@rti.org&apos;"; <adas@rti.org>, "&apos;jgabrio@rti.org&apos;"; <jgabrio@rti.org>  
**Cc:** "Finer, Neil" <nfiner@ucsd.edu>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu>, "Vaucher, Yvonne" <yvaucher@ucsd.edu>  
**Sent:** Thu, Apr 26, 2012 00:55:30 GMT+00:00  
**Subject:** Latest version of combined CPAP\_Oximeter ND Outcome paper

Dear All,

Attached is the latest version of the combined CPAP/Oximeter SUPPORT Outcome paper with tables(3), appendices(2), figure(1).

The word limits are congruent (just) with the NEJM request (250 for abstract, <2700 for text). Tables and figures are within the limit (5) References are in NEJM style.

The Figure is still a work in progress and your suggestions are appreciated. The one attached is complicated but

combines both CPAP and Oximeter patient allocations in a single figure. Marie, could you complete the numbers in each group as they are different than the ones in our separate papers?

The correct MeSH terms are a mystery to me, several are borrowed from the original papers. Does a librarian guru at the NEJM review/correct these?

Yvonne

**From:** Bhandari, Vineet  
**To:** [nfner@ucsd.edu](mailto:nfner@ucsd.edu)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD)  
**Subject:** Secondary analysis SUPPORT Study: SNIPPV/NIPPV  
**Date:** Wednesday, May 02, 2012 11:31:10 AM  
**Attachments:** [Secondary analyses SUPPORT SNIPPV.doc](#)  
[RESPONSE to Nasal Ventilation COMMENTS.doc](#)  
**Importance:** High

---

Hello Neil (and Rose),

It was nice to catch up with you at PAS in Boston. As I had mentioned to you, I am sending you a copy of my "secondary analysis" proposal of SNIPPV/NIPPV (initially submitted on 11-15-2004) in the SUPPORT study as well as my "response" to comments by the reviewers of the proposal (initially submitted on 6-21-2006). Following this, I was told that it had been "approved". (The only clarification that I would make is that I would combine SNIPPV/NIPPV as the "nasal ventilation group" since we lost our Infant Star ventilators in Dec 2006).

As I believe the "follow -up" is completed, I just wanted to know who should I contact to initiate the analysis.

As with our earlier collaboration, thank you for your support (no pun intended ☺).

Regards.

Vineet.

Vineet Bhandari, MD, DM  
Associate Professor of Pediatrics, Obstetrics, Gynecology  
and Reproductive Sciences  
Director, Program in Perinatal Research  
Yale University School of Medicine  
Yale Child Health Research Center  
Room Number: 219  
P.O. Box 208081  
464 Congress Avenue  
New Haven, CT 06520-8081  
Phone: 203-785-2613  
Fax: 203-737-2805

Page 1527 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1528 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1529 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1530 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act



Page 1531 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1532 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 1533 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

## RESPONSE to COMMENTS:

1. *The total number of infants receiving nasal ventilation was 176, of which, 155 (88%) were from 2 of the 16 network sites. There was no difference in the primary outcome (BPD) in the main Benchmarking trial. If a difference is seen, how would one correct for the impact of other practices and strategies of care?*

In view of the data provided regarding the number of patients who received nasal ventilation at each site, we will analyze our data, thus:

- (a) SNIPPV at Yale/UCSD vs. NCPAP at Yale/UCSD
- (b) SNIPPV at Yale/UCSD vs. NCPAP at all sites.

We would collect and correct for all the variables that are known to be associated with BPD for which data is collected (1).

2. *There is no citation of the nasal SIMV meta analysis paper (Davis PG, Lemyre B, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2001;(3):CD003212.*

That paper had been cited in the text on page 2, just before the section outlining "hypotheses".

3. *Could caffeine administration be a confounder in the analyses?*

We do not think use of methylxanthines would be a confounder in these analyses since they are widely used in extubated infants on NCPAP and, all studies published on SNIPPV have used them.

4. *How is RDS defined?*

RDS will be defined as respiratory distress requiring surfactant in the first 24 hours of life.

5. *How are "growth parameters" defined? Can you be specific about which growth parameters you intend to evaluate?*

The following "growth parameters" will be looked at:

- (a) Weight, head circumference at birth.
- (b) Weight, head circumference, and length at 36 weeks postmenstrual age and/or at discharge.
- (c) Weight, head circumference, and length at 18-22 months corrected age.
- (d) Using the formula as described in the paper by Patel AL et al (2), we will also calculate growth velocity based on the time it took for the baby to regain birth weight.

6. *The committee was concerned that the skew of data to only 2 centers, together with the overall low numbers was going to yield limited power. Site differences will also be difficult to adjust for or explore. A Sample size analysis is needed before the committee could support going forward.*

If we assume the BPD rate to be 35% and postulate a decrease to 20% by using SNIPPV, we would need 150 patients in each group to pick up a statistically significant difference at 80% power. If we assume the BPD rate to be 26%, and postulate a decrease to 15% by using SNIPPV, we would need 210 patients in each group to pick up a statistically significant difference at 80% power. It might be mentioned that the 2 studies that have looked at the BPD rates when using SNIPPV, using the 36 weeks

definition (albeit, not “physiological”), have reported a decrease from 53% to 35% (3), and from 73% to 40% (4). Another study had “babies discharged on supplemental oxygen” decrease from 75% to 47% (5).

In order to decrease the issue of variability in site differences, we will analyze our data, thus:

- (c) SNIPPV at Yale/UCSD vs. NCPAP at Yale/UCSD
- (d) SNIPPV at Yale/UCSD vs. NCPAP at all sites.

We would like to mention that this would be largest data set of which we are aware that can attempt to answer the question if SNIPPV can decrease BPD, albeit in a retrospective fashion. This would help us decide if it would be worthwhile to consider a randomized controlled trial.

7. *The author should work with Dr. Finer who has previously expressed interest in this topic.*

We would be glad to work with Dr. Finer, if he is so inclined. However, since UCSD is no longer a part of the NICHD NRN, so we are not sure how this can be arranged.

8. *The author should be aware that mode of ventilation is assigned 4 times daily from day 1-7 in the first 6 months of the trial, and then only on day 1, 3 and 7. How will the authors classify nSIMV if it is given at only one time point in the day. What about kids treated with this modality, or CPAP, from the start, vs as an form of support after extubation from MV.*

We are attempting to compare the babies “exposed” to SNIPPV vs. NCPAP in terms of total duration – days or part thereof, if data has been collected for the same. At Yale (and as far as I know at UCSD), a baby is either on SNIPPV or not (just like NCPAP); so, we should have the “total duration” (just like NCPAP), at least from these 2 sites. The data from these 2 centers will be analyzed separately, as mentioned earlier.

As for the other centers, we will collect information of the “duration”, as best collected, after confirming how SNIPPV is being given at each site.

For this study, it does not matter if babies get SNIPPV right from the start – as what we are trying to establish is if the duration of exposure to SNIPPV makes a difference in BPD.

9. *For the power analysis for the sample size, bpd = 45% was used. In the bench study BPD at 36 wks by physiologic definition, bpd was only 26%. The power analysis needs to be done with these lower estimates. In peer review, the benchmarking study is being criticized for looking for an effect of 14% in the main bench trial. So a 15% effect size from 26% (eg > 50% relative reduction) would preclude the analysis from showing any effect.*

Please see response to comment# 6.

## References

1. Akram Khan M, Kuzma-O'reilly B, Brodsky NL, Bhandari V. Site-specific characteristics of infants developing bronchopulmonary dysplasia. *J Perinatol* 2006.
2. Patel AL, Engstrom JL, Meier PP, Kimura RE. Accuracy of methods for calculating postnatal growth velocity for extremely low birth weight infants. *Pediatrics* 2005;116(6):1466-73.
3. Khalaf MN, Brodsky N, Hurley J, Bhandari V. A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. *Pediatrics* 2001;108(1):13-7.
4. Kulkarni A, Ehrenkranz RA, Bhandari V. Effect of introduction of synchronized nasal intermittent positive-pressure ventilation in a neonatal intensive care unit on bronchopulmonary dysplasia and growth in preterm infants. *Am J Perinatol* 2006;23(4):233-40.
5. Jackson JK, Vellucci J, Johnson P, Kilbride HW. Evidence-based approach to change in clinical practice: introduction of expanded nasal continuous positive airway pressure use in an intensive care nursery. *Pediatrics* 2003;111(4 Pt 2):e542-7.

**From:** [Finer, Neil](#)  
**To:** [Wally Carlo, M.D.](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [mgantz@rti.org](#); [adas@rti.org](#); [jgabrio@rti.org](#)  
**Cc:** [Myriam Peralta, M.D.](#); [Vaucher, Yvonne](#)  
**Subject:** RE: PAS congrats  
**Date:** Wednesday, May 02, 2012 12:21:18 AM

---

Thank you Myriam and Yvonne  
I understand that these presentations went very well  
Congratulations to you both and to everyone who helped make this possible  
We had to miss this to catch our flight home  
Neil

---

**From:** [Wally Carlo, M.D. \[mailto:WCarlo@peds.uab.edu\]](#)  
**Sent:** Tuesday, May 01, 2012 11:51 AM  
**To:** [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [mgantz@rti.org](#); [adas@rti.org](#); [jgabrio@rti.org](#)  
**Cc:** [Finer, Neil](#); [Myriam Peralta, M.D.](#); [Vaucher, Yvonne](#)  
**Subject:** PAS congrats

Yvonne and Myriam.

You both did an excellent job presenting the SUPPORT trial. Thanks so much for your hard work.

Wally

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

**From:** "Vaucher, Yvonne" <[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)>  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>, "&apos;mgantz@rti.org&apos;" <[mgantz@rti.org](mailto:mgantz@rti.org)>, "&apos;adas@rti.org&apos;" <[adas@rti.org](mailto:adas@rti.org)>, "&apos;jgabrio@rti.org&apos;" <[jgabrio@rti.org](mailto:jgabrio@rti.org)>  
**Cc:** "Finer, Neil" <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>, "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>, "Myriam Peralta, M.D." <[MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)>, "Vaucher, Yvonne" <[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)>  
**Sent:** Thu, Apr 26, 2012 00:55:30 GMT+00:00  
**Subject:** Latest version of combined CPAP\_Oximeter ND Outcome paper

Dear All,

Attached is the latest version of the combined CPAP/Oximeter SUPPORT Outcome paper with tables(3), appendices(2), figure(1).

The word limits are congruent (just) with the NEJM request (250 for abstract, <2700 for text). Tables and figures are within the limit (5) References are in NEJM style.

The Figure is still a work in progress and your suggestions are appreciated. The one attached is complicated but combines both CPAP and Oximeter patient allocations in a single figure. Marie, could you complete the numbers in each group as they are different than the ones in our separate papers?

The correct MeSH terms are a mystery to me, several are borrowed from the original papers. Does a librarian guru at the NEJM review/correct these?

Yvonne



**From:** Finer, Neil  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SCT poster on weighted SUPPORT analysis  
**Date:** Wednesday, May 02, 2012 12:19:22 AM

---

Many thanks for this Marie  
Neil

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Tuesday, May 01, 2012 2:06 PM  
**To:** Finer, Neil  
**Cc:** Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

Neil, attached is a comparison of the outcomes in the SUPPORT population, the weighted SUPPORT data, and the actual eligible population. These were the outcomes used in Wade's most recent paper comparing SUPPORT and eligible, non-enrolled infants. In general, the outcomes in the weighted data tend to fall between the SUPPORT outcomes and actual eligible group outcomes. The BPD and death/BPD outcomes, however, are much closer to what was actually seen in the overall eligible population than what was actually seen in SUPPORT.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6256

---

**From:** Gantz, Marie  
**Sent:** Tuesday, May 01, 2012 2:22 PM  
**To:** 'Finer, Neil'  
**Cc:** Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

Neil, we can look at the overall incidence of the outcomes in the weighted data from SUPPORT and compare them to what was actually observed among all eligible infants. I have requested that information from Darryl who did the weighting and weighted analysis. I think it is beyond the scope of this poster, since our goal was to see if the weighting changed the incidence of the outcomes in the treatment groups. Also, in order to compare the weighted outcomes to those observed in non-enrolled infants we have to use the modified version of the outcomes based on GDB data that were used in Wade's most recent paper. I'll keep you posted when I get the results from Darryl. In the meantime, I have attached the version of the poster that I intend to send for production. I have modified the conclusion slightly to try to be more clear.

Marie

Marie Gantz, Ph.D.

Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Friday, April 13, 2012 8:10 AM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

Hi Marie

I understand what your analyses did and the rationale behind it

My question has to do with whether using such an analysis can you calculate what the overall occurrence of the outcomes would be predicted for the total eligible population – not by study interventions but after doing the study intervention analyses can you then calculate the overall incidence of say death or BPD or death or ROP or death IVH/PVL for these 2 populations – Actual SUPPORT and Eligibles?

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This may be beyond the scope but I was wondering what these numbers would look like

Thanks

Neil

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**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, April 12, 2012 7:55 AM  
**To:** Finer, Neil  
**Cc:** Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
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Marie

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**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Saturday, April 07, 2012 9:28 AM  
**To:** Gantz, Marie

**Cc:** Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

Hi Marie

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**Sent:** Friday, April 06, 2012 12:48 PM  
**To:** Das, Abhik; Rich, Wade  
**Cc:** [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov); Finer, Neil  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

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**Sent:** Friday, April 06, 2012 1:25 PM  
**To:** Rich, Wade; Gantz, Marie  
**Cc:** [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov); Finer, Neil  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

Wade:

I will let Marie answer you specifically, but I think there may be a broader philosophical issue here. If we cannot infer some patterns for what we did not observe, based on what we did observe, then the whole field of statistics and the exercise of any sort of statistical inference may as well be suspect, and Marie and I are wasting our time in this field! We make such inferences all the time when we apply the results of relatively small and tightly controlled clinical trials with strict eligibility criteria to change clinical practice for a much broader population. We do that by using historical weather and climate data to forecast the weather and broader climate change, and we do that to predict the performance of the stock market and other economic indicators based on current and historic data (ok, the last one may not be a good example in the light of the last few years!). In my mind, we are doing a similar mathematical/statistical modeling exercise here. Also, our method is limited by what data we have in the GDB (as is all analyses). Theoretically, it is possible that we don't have data on some unknown factors that were different between the enrolled and un-enrolled babies and that adjustment for such a factor would have produced a different treatment effect. Perhaps we can allude to such a limitation in the conclusions.

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Abhik

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**To:** Gantz, Marie; Das, Abhik  
**Cc:** [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov); Finer, Neil  
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trials. Just because we got an answer, and the answer suggests that the non-enrolled and the modified enrolled are similar, does that mean the answer is correct ?

Wade

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**From:** Gantz, Marie [mailto:[mgantz@rti.org](mailto:mgantz@rti.org)]  
**Sent:** Thursday, April 05, 2012 4:45 AM  
**To:** Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
**Cc:** Das, Abhik; Creel, Darryl  
**Subject:** SCT poster on weighted SUPPORT analysis

Wade and Rose,

A draft of the poster of weighted SUPPORT results for the SCT conference is attached. Please let me know if you have any comments or suggestions.

Rose, I am supposed to have the poster to the group at RTI that will produce it by May 1. Given that deadline, when do you need the final version for NICHD clearance?

Thanks,  
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**From:** Vaucher, Yvonne  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org; adas@rti.org; igabrio@rti.org  
**Cc:** Finer, Neil; Myriam Peralta, M.D.  
**Subject:** RE: PAS congrats  
**Date:** Tuesday, May 01, 2012 10:27:01 PM

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All,

Thanks so much for your help and encouragement!

Yvonne

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**From:** Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
**Sent:** Tuesday, May 01, 2012 11:51 AM  
**To:** Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org; adas@rti.org; igabrio@rti.org  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; Vaucher, Yvonne  
**Subject:** PAS congrats

Yvonne and Myriam.

You both did an excellent job presenting the SUPPORT trial. Thanks so much for your hard work.

Wally

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

**From:** "Vaucher, Yvonne" <yvaucher@ucsd.edu>  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "&apos;mgantz@rti.org&apos;"; <mgantz@rti.org>, "&apos;adas@rti.org&apos;"; <adas@rti.org>, "&apos;igabrio@rti.org&apos;"; <igabrio@rti.org>  
**Cc:** "Finer, Neil" <nfiner@ucsd.edu>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu>, "Vaucher, Yvonne" <yvaucher@ucsd.edu>  
**Sent:** Thu, Apr 26, 2012 00:55:30 GMT+00:00  
**Subject:** Latest version of combined CPAP\_Oximeter ND Outcome paper

Dear All,

Attached is the latest version of the combined CPAP/Oximeter SUPPORT Outcome paper with tables(3), appendices(2), figure(1).

The word limits are congruent (just) with the NEJM request (250 for abstract, <2700 for text). Tables and figures are within the limit (5) References are in NEJM style.

The Figure is still a work in progress and your suggestions are appreciated. The one attached is complicated but combines both CPAP and Oximeter patient allocations in a single figure. Marie, could you complete the numbers in each group as they are different than the ones in our separate papers?

The correct MeSH terms are a mystery to me, several are borrowed from the original papers. Does a librarian guru at the NEJM review/correct these?

Yvonne

**From:** [Gantz, Marie](#)  
**To:** [Finer, Neil](#)  
**Cc:** [Das, Abhik](#); [Rich, Wade](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** RE: SCT poster on weighted SUPPORT analysis  
**Date:** Tuesday, May 01, 2012 5:07:11 PM  
**Attachments:** [Compare outcomes in weighted SUPPORT data vs all eligible 05MAY12.doc](#)

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Neil, attached is a comparison of the outcomes in the SUPPORT population, the weighted SUPPORT data, and the actual eligible population. These were the outcomes used in Wade's most recent paper comparing SUPPORT and eligible, non-enrolled infants. In general, the outcomes in the weighted data tend to fall between the SUPPORT outcomes and actual eligible group outcomes. The BPD and death/BPD outcomes, however, are much closer to what was actually seen in the overall eligible population than what was actually seen in SUPPORT.

Marie

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**Sent:** Tuesday, May 01, 2012 2:22 PM  
**To:** 'Finer, Neil'  
**Cc:** Das, Abhik; Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

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**Cc:** higginsr@mail.nih.gov; Finer, Neil  
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**Cc:** Das, Abhik; Creel, Darryl

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Comparison of outcomes in weighted SUPPORT data vs. all eligible GDB infants

Character	Enrolled in SUPPORT (N=1316)	Enrolled in SUPPORT weighted data (N=1029)	Actual eligible GDB population (N=4369)
Death	237 (18.01%)	805 (18.44%)	972 (22.28%)
IVH grade 3-4 (NG03)	165 (12.98%)	555 (13.15%)	664 (16.19%)
PVL (NG03)	48 (3.77%)	173 (4.10%)	192 (4.67%)
IVH 3-4 or PVL (NG03)	192 (15.11%)	637 (15.10%)	753 (18.36%)
Death or IVH3-4 or PVL (NG03)	360 (27.38%)	1230 (28.20%)	1438 (33.08%)
BPD (traditional)	468 (42.24%)	1707 (46.68%)	1597 (45.94%)
BPD (traditional) or death by 36 weeks PMA	676 (51.37%)	2420 (55.39%)	2467 (56.76%)
ROP surgery or retinal detachment while hospitalized (NG03)	110 (10.43%)	374 (10.77%)	388 (11.77%)
Medical or surgical NEC (NG03)	146 (11.32%)	529 (12.37%)	517 (12.26%)
Pneumothorax (NG03)	88 (6.82%)	316 (7.37%)	276 (6.54%)
Postnatal steroids for BPD (NG03)	130 (10.16%)	461 (10.86%)	450 (10.77%)
Days on supplemental oxygen (survivors to NG03 status only) (NG07)	56.72 ± 37.72 (Mean ± SD)	60.39 ± 1.12 (Mean ± SE)	59.15 ± 37.38 (Mean ± SD)
Days on mechanical vent (HFV & CV) (survivors to NG03 status only) (NG07)	21.55 ± 25.08 (Mean ± SD)	23.21 ± 0.84 (Mean ± SE)	23.25 ± 26.12 (Mean ± SD)

**From:** [Gantz, Marie](#)  
**To:** [Finer, Neil](#)  
**Cc:** [Das, Abhik](#); [Rich, Wade](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SCT poster on weighted SUPPORT analysis  
**Date:** Tuesday, May 01, 2012 2:22:29 PM  
**Attachments:** [Gantz SCT 2012 V8.pptx](#)

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**To:** Rich, Wade; Gantz, Marie  
**Cc:** higginsr@mail.nih.gov; Finer, Neil  
**Subject:** RE: SCT poster on weighted SUPPORT analysis

Wade:

I will let Marie answer you specifically, but I think there may be a broader philosophical issue here. If we cannot infer some patterns for what we did not observe, based on what we did observe, then the whole field of statistics and the exercise of any sort of statistical inference may as well be suspect, and Marie and I are wasting our time in this field! We make such inferences all the time when we apply the results of relatively small and tightly controlled clinical trials with strict eligibility criteria to change clinical practice for a much broader population. We do that by using historical weather and climate data to forecast the weather and broader climate change, and we do that to predict the performance of the stock market and other economic indicators based on current and historic data (ok, the last one may not be a good example in the light of the last few years!). In my mind, we are doing a similar mathematical/statistical modeling exercise here. Also, our method is limited by what data we have in the GDB (as is all analyses). Theoretically, it is possible that we don't have data on some unknown factors that were different between the enrolled and un-enrolled babies and that adjustment for such a factor would have produced a different treatment effect. Perhaps we can allude to such a limitation in the conclusions.

Thanks

Abhik

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**From:** Rich, Wade [mailto:wrich@ucsd.edu]  
**Sent:** Friday, April 06, 2012 1:05 PM  
**To:** Gantz, Marie; Das, Abhik  
**Cc:** higginsr@mail.nih.gov; Finer, Neil  
**Subject:** FW: SCT poster on weighted SUPPORT analysis

Hi Marie,

It still seems to me this analysis shows that if the SUPPORT kids were more like kids who were not in SUPPORT, that the overall outcomes would be similar. This seems a bit like circular logic to me. Those infants are only *eligible* for the trial, they did not actually receive the interventions. Why is making the SUPPORT subjects more like them a logical paradigm for generalizability? The support kids DID get more steroids and did get more prenatal care, and were treated under a specific set of management criteria, and you can't take that away, can you?

Also, you have indicated previously that this type of analysis is usually used for other processes, such as polling, etc. I guess rather than stating that this analysis shows that SUPPORT is generalizable, perhaps more emphasis should be put on whether the method even works for clinical trials. Just because we got an answer, and the answer suggests that the non-enrolled and the modified enrolled are similar, does that mean the answer is correct?

Wade

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**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Thursday, April 05, 2012 4:45 AM  
**To:** Rich, Wade; Higgins, Rosemary (NIH/NICHD)  
**Cc:** Das, Abhik; Creel, Darryl  
**Subject:** SCT poster on weighted SUPPORT analysis

Wade and Rose,

A draft of the poster of weighted SUPPORT results for the SCT conference is attached. Please let me know if you have any comments or suggestions.

Rose, I am supposed to have the poster to the group at RTI that will produce it by May 1. Given that deadline, when do you need the final version for NICHD clearance?

Thanks,  
Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-954-8255





# Enrollment Propensity Weighting to Assess the Generalizability of a Randomized Clinical Trial

Marie Gantz<sup>1</sup>, Darryl Creel<sup>1</sup>, Wade Rich<sup>2</sup>, Rosemary Higgins<sup>3</sup> and Abhik Das<sup>1</sup> for the SUPPORT Trial Subcommittee of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network<sup>1</sup>, NRTI International, Rockville, MD; <sup>2</sup>University of California, San Diego, CA; <sup>3</sup>NICHD, Rockville, MD

## Abstract

Randomized trials typically enroll a convenience sample of eligible patients without regard to formal propensity sampling. However, trial results often substantially change clinical practice for the population at large, without systematic evaluation of the generalizability of results.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) used a 2x2 factorial design to test different ventilation and oxygenation strategies for respiratory management of extremely premature babies. The intent and largest of its kind trial demonstrated that a less invasive ventilator strategy may be safe to use and reduced increased mortality at least oxygen saturation.

Because intervention started upon delivery, parental consent was required, restricting the ability to enroll some eligible infants, including those who were born precipitously following the mother's admission. Enrolled babies had significantly higher socioeconomic status and greater exposure to prenatal steroids compared to the non-enrolled, which raised questions about the generalizability of the trial results. We conducted a sensitivity analysis by incorporating enrollment propensity weights so the analysis would better reflect the eligible population.

We used Classification and Regression Trees to model enrollment based on maternal and infant characteristics at delivery. Using the groups created by the trees, we constructed unweighted propensity weights. Then we analyzed the weighted data using models that reduced the variance based on a finite population correction. The results were largely similar to the original unweighted analysis.

Although weighting to reflect the characteristics of the larger population is common in survey statistics, to our knowledge the approach has not been used to explore the generalizability of results from randomized trials conducted on convenience samples of eligible patients. When adequate data on the eligible population are available and enrolled subjects are known to differ from those not enrolled, these methods provide a means to assess the validity of trial results to such differences.

## Background

Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) (clinical trial identifier: NCT00232224)

- Randomized controlled trial conducted by the Eunice Kennedy Shriver NICHD Neonatal Research Network (NRTN)
- 2x2 Factorial design
  - Continuous Positive Airway Pressure (CPAP) vs. surfactant (S) vs. surfactant + CPAP (SC) vs. surfactant + CPAP + pulse oximetry (SCPO) vs. conventional mechanical ventilation (Subjunctive)
  - Oxygen saturation (SpO<sub>2</sub>) target of 85-95% (low) vs. 91-95% (high) and 36 weeks post-menstrual age (PMA)
- Inclusion criteria
  - Born at 600s gestation at 24-32 to 27-67 weeks postmenstrual age (GA)
  - Weight between 400g to 1000g and gestational age with full resuscitation indicated
- Randomization
  - Allocation concealment was obtained from parent(s) and randomization was performed at the delivery suite
  - Surfactant was stratified by study center and GA group (24-32 vs. 25-67 weeks and 25-67 vs. 27-67 weeks)
  - Multiple births were randomized together
- Primary Outcomes and Analysis
  - CPAP vs. Surfactant: Bronchopulmonary dysplasia or death by 36 weeks PMA, using two BPD definitions
  - Traditional definition of BPD (BPD-T): use of supplemental oxygen at 36 weeks PMA
  - Physiologic definition of BPD (BPD-P): unable to wean from supplemental oxygen during at least 4 of 36 weeks
  - Low vs. high SpO<sub>2</sub>: Serious morbidity or mortality (BPD or death) before postmenstrual age 36 weeks
  - Interactions with robust Poisson regression generalized estimating equations (GEE) models, stratified by stratification by center and GA group and to family clustering, analyzed in 2003 (SUPPORT Study Group, 2003)
- Infants Enrolled vs. Eligible but Not Enrolled
  - Eligible infants were defined as the General Data Base of very low birth weight infants cared for at NRTN centers
  - Enrolled infants (N=7,316) differed from those who were eligible but not enrolled (N=3,203) (Rich et al., 2010)
  - Enrolled infants had higher socioeconomic status (parental education), maternal insurance (private/other) and higher exposure to prenatal steroids (95% vs. 84%) (Rich et al. 2010)
  - Differences were attributed to both the maternal and infant characteristics – mother who had previous delivery or had not had time to be approached for consent or to receive at prenatal visits
  - Centers were those that enrollment lists could have impacted the results, especially the BPD outcomes

## Objective

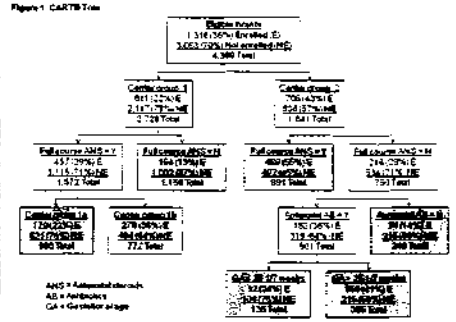
To conduct a secondary analysis in which the intent analysis in SUPPORT was weighted to reflect the characteristics of the entire eligible population. We refer to this type of weighting as enrollment propensity weighting.

## Methods

- Classification and Regression Tree (CART) methods modeled the propensity for enrollment in SUPPORT
- CART created two separate trees for a series of binary splits which create partitions (or groups) based on values of the independent variables of all variables that were given variance of the dependent variable
- Variables were used as independent variables: maternal characteristics (maternal education and insurance, gender, multiple birth, birth weight, GA, race, and Apgar scores at 1 and 5 minutes)
- CART groups were defined based on probability of infants in each terminal branch of the resulting tree
- SUDAAN's WTACROSS procedure was then used to weight the enrollment propensity weights
- CART groups were defined based on gender, GA, any antenatal steroids, and full course of antenatal steroids were predictors in the weight adjustment model
- Propensity weighting, missing values for any antenatal steroids and full course of antenatal steroids were imputed using multiple imputation (MICE, 1993). CARTs group gender, race, and GA were predictors for any antenatal steroids and the same variables plus any antenatal steroids were predictors for full course of antenatal steroids
- SUDAAN's ANALYZE procedure was used to analyze the weighted data
- Models estimated for classification by center and GA group and for family clustering, as in the original analysis
- Models incorporated the adjusted weights and because a finite number of infants were eligible for SUPPORT, appropriately reduced the variance based on a finite population correction

## Results

- CART's Tree
  - CARTs created the 4 365 eligible infants into 7 groups ranging in size from 136 to 1,156 infants (Figure 1)
  - CARTs groups were called or adult center, full course of antenatal steroids, antenatal steroids, and GA
  - The selection of antenatal steroids in most of the 7 CARTs groups ranged from 13% to 56% demonstrating substantial variation in the likelihood of enrollment, or the enrollment propensity, between the groups



## Results (continued)

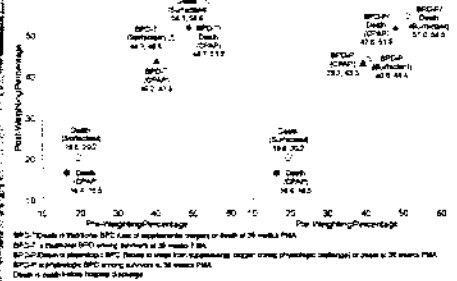
- SUDAAN's WTACROSS procedure
  - 7 antenatal steroids were missing records for both any antenatal steroids and full course, 27 were missing a response to full course only, values were sequentially imputed for any antenatal steroids followed by full course
  - Adjusted propensity weights of the 1,116 enrolled infants summed to a total of 3,373, the number of eligible infants
  - Adjusted propensity weights of the 1,116 enrolled infants summed to a total of 3,373, the number of eligible infants
  - The largest differences between the original and post-weighting proportions of the enrolled infants were in antenatal steroid exposure (36 vs. 56% for any steroids, 17 vs. 56% for full course)

Table 1. Variables Used in Weighting – Pre- and Post-Weighting Means and Percentages

Variable	Pre-Weighting Mean (%)	Post-Weighting Mean (%)
GA 24-32	27.5%	27.5%
GA 25-67	72.5%	72.5%
Adult Center	100%	100%
Antenatal Steroids - Any	13.0%	56.0%
Antenatal Steroids - Full Course	1.0%	56.0%
Female	50.0%	50.0%
Male	50.0%	50.0%
Multiple Birth	10.0%	10.0%
Birth Weight	750g	750g
1st Apgar	8.0	8.0
5th Apgar	9.5	9.5

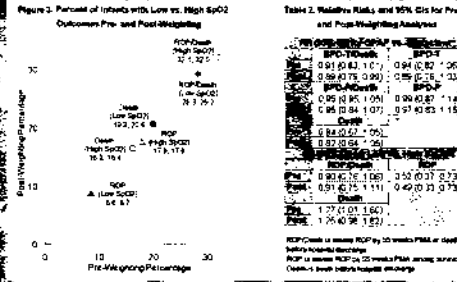
## Comparison of Pre- and Post-Weighting Analysis Results

- The largest difference between pre- and post-weighting results was in the percent of infants with BPD-T or death by 36 weeks PMA for CPAP vs. Surfactant (AS vs. AS + pre-weighting 51.9 vs. 58.6% post-weighting) (Figure 2)
- Although rates of BPD and death increased in both the CPAP and Surfactant groups after weighting, relative rates (RR) and 95% confidence intervals (CI) did not change substantially from the original analysis (Table 2)



## Results (continued)

- Comparison of Pre- and Post-Weighting Analysis Results
  - Results in the Low vs. High SpO<sub>2</sub> groups were very similar pre- and post-weighting, percentages of infants with BPD or death outcomes changed by less than one percent and RR's and CIs were nearly identical (Figure 3, Table 2)



## Conclusions

- When adequate data on the eligible population are available and enrolled individuals are known to differ from those not enrolled, the propensity weighting methods described here provide a means to assess the validity of the results to such differences
- Although the similarity of the results from the SUPPORT study before and after propensity weighting provides no evidence that the original results do not have a substantial bias, the published results of the trial, the final impact of the enrollment bias remains unknown

## References

Rich W, Gantz M, Creel D, Higgins R, Das A, et al. (2010) Enrollment bias in the SUPPORT trial. Pediatrics 126(4):e100-107.

Rich W, Gantz M, Creel D, Higgins R, Das A, et al. (2010) Enrollment bias in the SUPPORT trial. Pediatrics 126(4):e100-107.

Rich W, Gantz M, Creel D, Higgins R, Das A, et al. (2010) Enrollment bias in the SUPPORT trial. Pediatrics 126(4):e100-107.

## Contact Information

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 Presented at Society for Clinical Trials 33rd Annual Meeting, May 2023, 2012, Miami, Florida  
 33rd Annual Meeting Abstracts, 1000-1001

**From:** [Zaterka-Baxter, Kristin](#)  
**To:** [Bethany Ball](#)  
**Cc:** [Krisa Van Meurs](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#)  
**Subject:** RE: SUPPORT Final DSMC Memo  
**Date:** Monday, April 30, 2012 12:07:01 PM

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Thanks for your suggestions Beth, they are very much appreciated. We do want to be as clear as possible in the DSMC summary report while remembering that the DSMC deliberations are strictly confidential as stated in the DSMC Charter and NICHD NRN P&P. Since most folks are at PAS right now, please allow a few days for review and we'll get back to you. We will send a clarification memo about the posting.

Thanks again,  
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP

**RTI International**

*Res Clinical Study Specialist*

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**From:** Bethany Ball [mailto:[mbball@stanford.edu](mailto:mbball@stanford.edu)]  
**Sent:** Monday, April 30, 2012 2:16 AM  
**To:** Zaterka-Baxter, Kristin  
**Cc:** Krisa Van Meurs; Rosemary (NIH/NICHD) [E] Higgins; Das, Abhik  
**Subject:** Re: SUPPORT Final DSMC Memo

Hi Kris

There are a couple of concerns. The first is that we would prefer to submit to our IRB actual minutes (that don't violate the study masking) rather than highly abbreviated statements that leave the DSMC proceedings largely unexplained. Failing that, it would be helpful if memo item 1 was structured with some background and discussion before presenting the decision. Start with:

The data center presented final unmasked data that showed 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 unanticipated increase in mortality and a substantial decrease in severe retinopathy among survivors.

Then present the concerns that were raised, expand the explanation about other oxygenation trials that were underway, and describe the discussion that occurred. Conclude with:

The DSMC agreed it was our obligation to share group-specific mortality data from the oxygen saturation arm of the SUPPORT trial with DSMCs monitoring the safety data for other similarly conducted international trials that are still recruiting patients, without waiting for the

primary papers to be published, to use as those DSMCs see fit. Additionally, they agreed to share the oxygen saturation separation data so that the results can be put in context.

It might also be more accurate to modify the last sentence  
While the DSMC requested some additional information which the Data Center will provide, the Committee determined that the trial should proceed with 18-22 month follow up as originally planned, with no additional actions required on the part of the investigators because all patients have reached the primary outcome, all study interventions have concluded and only follow-up is pending.

We will also need a memo explaining that the minutes were not posted until May 2012.  
Thanks,  
Beth

On Apr 25, 2012, at 1:03 PM, Zaterka-Baxter, Kristin wrote:

Hi Beth,

I am hearing your IRB may have issues with the final Support DSMC Memo. Will this revision clarify why the DSMC recommended we send data to the other DSMCs? This is unfortunate and due to an oversight but I am happy to include this memo in an announcement that it was posted to the NRN website in April 2012 if that is the issue.

Let me know if you would like to chat about it.  
Thanks,  
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP  
**RTI International**  
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<DSMC Addendum Clarification Site Memo20120425uc.doc>

**From:** [Vaucher, Yvonne](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); ["mgantz@rti.org"](#); ["adas@rti.org"](#); ["igabrio@rti.org"](#)  
**Cc:** [Finer, Neil](#); ["wcarlo@peds.uab.edu"](#); ["mperalta@peds.uab.edu"](#); [Vaucher, Yvonne](#)  
**Subject:** Latest version of combined CPAP\_Oximeter ND Outcome paper  
**Date:** Wednesday, April 25, 2012 8:55:29 PM  
**Attachments:** [Table 3 042512.docx](#)  
[Appendix A\\_B 042512.docx](#)  
[Chart \(2\)1.pdf](#)  
[CombPaperNEJM042512.docx](#)  
[Table 1 042512.docx](#)  
[Table 2 042512.docx](#)

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Dear All,

Attached is the latest version of the combined CPAP/Oximeter SUPPORT Outcome paper with tables(3), appendices(2), figure(1).

The word limits are congruent (just) with the NEJM request (250 for abstract, <2700 for text). Tables and figures are within the limit (5) References are in NEJM style.

The Figure is still a work in progress and your suggestions are appreciated. The one attached is complicated but combines both CPAP and Oximeter patient allocations in a single figure. Marie, could you complete the numbers in each group as they are different than the ones in our separate papers?

The correct MeSH terms are a mystery to me, several are borrowed from the original papers. Does a librarian guru at the NEJM review/correct these?

Yvonne

**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower	Higher	ARR	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	493/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.002

## Appendix A: Death and NDI for treatment groups by gestational age strata

### CPAP vs. Surfactant

<u>24 0/7-25 6/7 weeks Gestational Age</u>	CPAP	Surfactant	RR	p
Death or NDI-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral –no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

<u>26 0/7-27 6/7 weeks Gestational Age</u>	CPAP	Surfactant	RR	p
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

**LOWER VS. HIGHER OXYGEN SATURATION TARGETS**

<u>24 0/7-25 6/7 weeks Gestational Age</u>	Lower	Higher	RR	p
Death or NDI-no./total no.(%)	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA-no./total no.(%)	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined-no./total no.(%)	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI-no./total no.(%)	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70-no./total no.(%)	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2-no./total no.(%)	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy-no./total no.(%)	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral -no./total no.(%)	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Hearing impairment-no./total no.(%)	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22



<u>26 0/7-27 6/7 weeks Gestational Age</u>	Lower	Higher	RR	p
Death or NDI-no./total no.(%)	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA-no./total no.(%)	49/366(13.4)	39/365(19.7)	1.28(0.86,1.89)	0.22
Death/NDI determined-no./total no.(%)	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI-no./total no.(%)	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.99
BSID-III cognitive score < 70-no./total no.(%)	17/302(5.6)	16/307(5.2)	0.98(0.49,1.07)	0.95
Gross motor function level ≥ 2-no./total no.(%)	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral palsy-no./total no.(%)	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral-no./total no.(%)	4/306(1.3)	5/311(1.6)	0.83(0.23,3.30)	0.78
Hearing impairment-no./total no.(%)	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering  
(except blindness was not adjusted for study center due to small N)

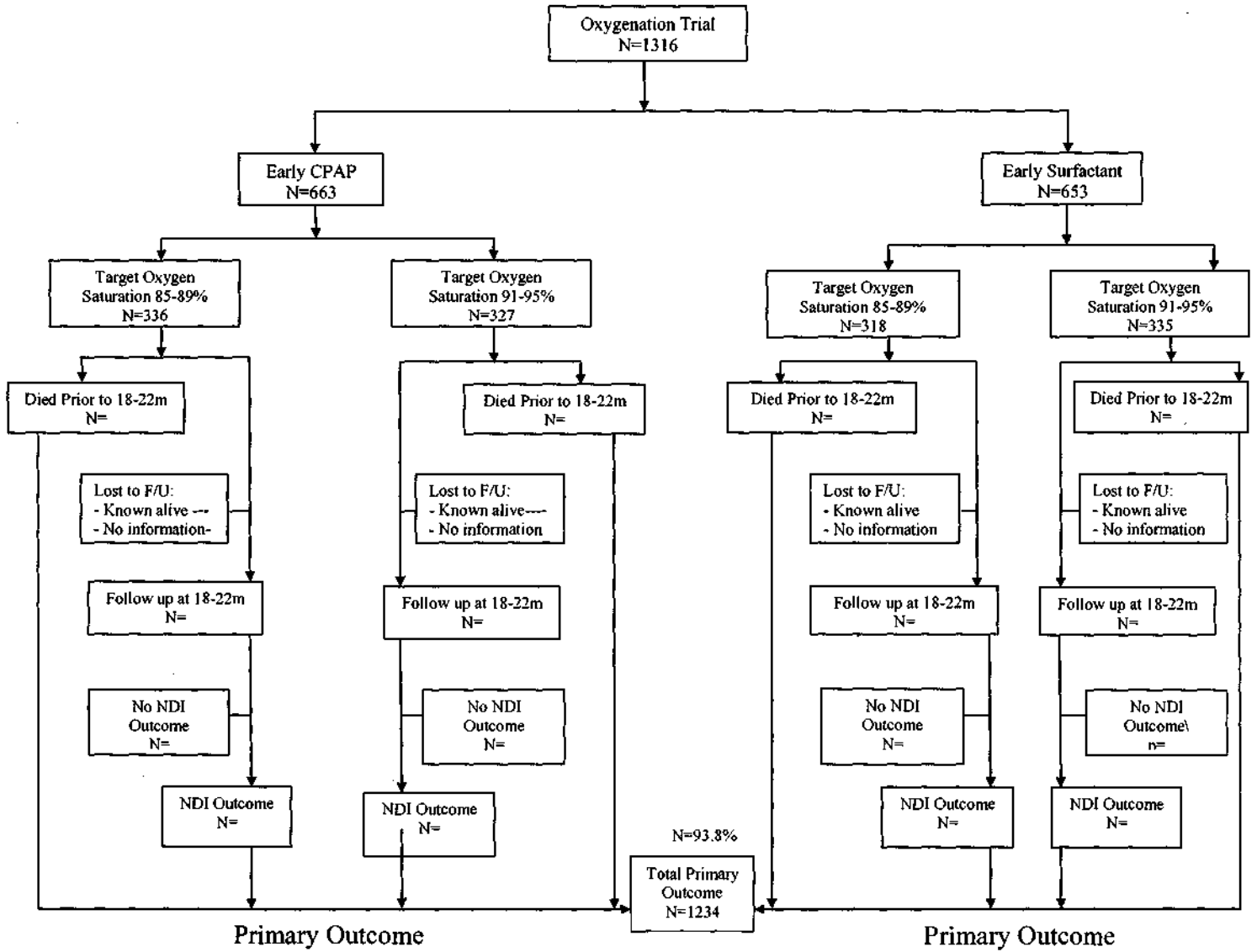
## Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms

### CPAP vs. Surfactant

	CPAP	Surf	RR	p
BSID-III cognitive composite score (mean)	91.3 ± 0.7	90.4 ± 0.8		0.32
BSID-III cognitive composite score < 85-no./total no.(%)	111/502(22.1)	126/472(26/7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 80-no./total no.(%)	65/502(12.0)	81/472(17.2)	0.74(0.55,1)	0.05

### Lower vs. Higher Oxygen Saturation Targets

	Lower	Higher	RR	p
BSID-III cognitive composite score (mean)	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score (median, interquartile range)	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85-no./total no.(%)	105/471(22.3)	132/503	0.85(0.69,1.07)	0.16
BSID-III cognitive composite score < 80-no./total no.(%)	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53



## **Neurodevelopmental Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

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Neurodevelopmental outcome  
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Child development  
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## ABSTRACT

**BACKGROUND:** The SUPPORT trial showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower-oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower- oxygen-saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS** Infants born at 24 0/7 to 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary outcome was a composite of death or NDI at 18-22 months CA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) of all enrolled infants; 93.6% (990/1058) of hospital survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP (27.9% [173/621]) vs. Surfactant (27.9% [173/621]) groups (RR 0.93, 95% CI 0.78 to 1.1,  $p=0.39$ ) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)]; oxygen saturation groups (RR 1.12; 95% CI 0.94 to 1.32;  $p=0.21$ ). Mortality at follow up was persistently greater in the lower (22.1%) compared to the higher (18.2%) oxygen saturation group (RR 1.25; 95% CI, 1 to 1.55,  $p=0.046$ ).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to receive either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

Word Count: 249

## BACKGROUND

Extremely premature infants are at high risk for death and neurodevelopmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and the presence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity, BPD, periventricular leukomalacia, and cerebral palsy.<sup>19-23</sup> Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials.<sup>24</sup> The SUPPORT trial demonstrated no difference in the composite outcome of death or severe retinopathy of prematurity (ROP) before discharge between the lower-oxygen-saturation target group (85-89%) vs. higher-oxygen-saturation target group (91-95%).<sup>24</sup> However, the risk of ROP before discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher oxygen saturation group.

The pre-specified hypotheses of the SUPPORT trial were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age.

## METHODS

### Study Design

1316 extremely preterm infants, 24 through 27 weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation.<sup>18</sup> Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower-oxygen-saturation group) or 91 to 95% (higher-oxygen-saturation group) using a specially designed blinded oximeter. Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months CA, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>25</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>26</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>27</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification; and visual impairment, defined as vision  $< 20/200$ , were based upon examination and parental report.

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD, and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

### Outcome

The pre-specified primary composite outcome at follow up for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score  $< 70$ , GMFCS  $\geq 2$ , moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality among the entire trial cohort and the individual components of NDI (i.e., BSID III cognitive composite score  $< 70$ , GMFCS  $\geq 2$ , moderate/severe cerebral palsy, bilateral blindness and bilateral hearing impairment) among survivors at follow up. Exploratory secondary outcomes included mean cognitive scores, cognitive scores  $< 80$  and  $85$  and visual outcomes, for the entire cohort. In addition we compared the composite outcome of death and NDI and individual components of NDI between treatment groups within each of the two gestational age strata.

### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18, 24</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in composite outcome of death or NDI, using a two-sided significance level of 0.05,



conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

**Comment [MS1]:** Because this is the most conservative outcome rate that could have been used for the power calculations, it does not matter that the initial estimates were based on the Bayley II.

Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted that demonstrated no statistical interaction between the two interventions. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted.<sup>28</sup> Missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes. Two-sided p values of < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 4 tests to be significant at the 0.05 level on the basis of chance alone.

## RESULTS

Of the 1316 infants enrolled in the SUPPORT trial, 250 were known to have died before 18-22 months (Figure). Of the remaining children, 68/1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of the 990 children seen for evaluation, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of enrolled children. The mean CA at neurodevelopmental assessment and the follow-up rates were similar for all treatment arms. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months CA mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups. Sensitivity analysis confirmed that the missing cases would have no impact on study outcomes.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers received antenatal steroids. There were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less

likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant with limited ventilation.

**Primary outcome:** The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months CA in either the entire cohort or between the higher and lower gestational age strata. (Table 2 a and b; Appendix ) There was no difference in death between the CPAP and Surfactant arms. Mortality at follow-up remained significantly higher in the lower compared to the higher saturation group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death, or NDI) among survivors (all p values > 0.7).

**Other outcomes:** The incidences of cognitive impairment (BSID-III cognitive composite score < 70, gross motor function level  $\geq 2$ , moderate/severe cerebral palsy, and blindness among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort or between the gestational age strata (Table 2 a and b; Appendix ). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher-oxygen-saturation group vs. the lower-oxygen-saturation group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month CA visit. (Table 3) Neither were there differences between the CPAP and Surfactant arms or between the lower and higher saturation groups in the combined outcome of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 (Appendix). Sixty percent of children seen in the CPAP/Surfactant arms and in the lower and higher saturation groups were reported as having no difficulties in any of the areas evaluated (i.e., motor, neurosensory or developmental).at 18-22 months CA.

**Comment [MPM2]:** Not sure if we want to include this comment in this paper.

**Comment [yew 3]:** This is an important outcome which need to be recognized by clinicians

#### DISCUSSION:

This trial demonstrated no significant difference in the primary composite outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant or between those randomized to the lower vs. higher oxygen saturation target groups in the SUPPORT trial. Neither were there significant differences among survivors in any of the treatment arms for NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq 2$ ), hearing impairment, and bilateral blindness.

To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which include pre-specified neurodevelopmental outcome at two years of age will not be available until 2014.<sup>29</sup>

The results of recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>21</sup> In the SUPPORT trial death prior to discharge was increased among neonates randomized to the lower-oxygen-saturation group. As was published previously, causes of death before discharge between the lower and higher oxygen saturation groups were not different.<sup>24</sup> Mortality remained lower in the higher-oxygen-saturation target group at 18 to 22 months corrected age. Mortality remained higher as well as in the most immature gestational age stratum of the early intubation with surfactant administration group. Causes of death after discharge are not available.

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>30,31</sup> We previously reported that the lower-oxygen-saturation target was associated with a reduction in the incidence of severe

retinopathy of prematurity (8.6% vs. 17.9%) among survivors at discharge.<sup>24</sup> Eye surgery was more frequent in higher oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at 18-22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher-oxygen- saturation group.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had a comprehensive and standardized neurodevelopmental evaluation at 18-24 months CA. The generalizability of this study may be limited by being center rather than being population based and by requiring antenatal consent which is associated with enrollment bias.<sup>32,33</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN.<sup>4</sup> The present study used the BSID-III for cognitive assessment, whereas previous NRN studies used the BSID-II. As noted by others, inherent changes in BSID-III design and standardization result in a lower incidence of NDI.<sup>34-36</sup> Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age. Other disabilities may be evident in later childhood.<sup>37</sup> A sub-cohort of the SUPPORT study which will be followed at school age to evaluate longer-term neurodevelopmental outcome.

In summary, among survivors at 18-22 months corrected age, there were no significant differences in the composite outcome of death or NDI or in the individual components of NDI between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation limits. However, higher mortality persisted in the lower oxygen saturation target group and in the most immature stratum of the Early CPAP group.

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University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburgh; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

**Figure1: Consort Diagram for SUPPORT**

**Table 1: Demographic and neonatal characteristics of follow-up cohorts**

**Table 2: Death and NDI: CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups**

**Table 3: Visual Outcome for Oxygen saturation target groups**

**Appendix A: Death and NDI for treatment groups by gestational age strata**

**Appendix B: Comparison of Cognitive outcomes for SUPPORT treatment arms**

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Lupton AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobayashi K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. *Pediatr Res* 2001;50:712-9.
20. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol* 2003;62:441-50.
21. Saugstad OD, Aune D. In search of the optimal oxygen saturation for extremely low birth weight infants: a systematic review and meta-analysis. *Neonatology* 2011;100:1-8.
22. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F106-10.



23. Saugstad OD. Surfactant therapy is still on the move. *J Matern Fetal Neonatal Med* 2003;14:145-6.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-69.
25. Bayley. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
26. Amiel-Tison C GJ. *Neurological Development from Birth to Six Years*. Baltimore: The Johns Hopkins University Press; 1998.
27. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
28. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
29. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 2011;11:6.
30. Chen J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. *Curr Opin Pediatr* 2011;23:173-8.
31. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123:311-8.
32. Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 2012;129:480-4.
33. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.
34. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW. Underestimation of developmental delay by the new Bayley-III Scale. *Arch Pediatr Adolesc Med* 2010;164:352-6.
35. Vohr BR SB, Higgins RD, et al. Are Outcomes of Extremely Preterm Infant Improving? Impact of Bayley Assessment of Outcomes. *The Journal of pediatrics* 2012;In press.
36. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between Test Scores Using the Second and Third Editions of the Bayley Scales in Extremely Preterm Children. *J Pediatr* 2012;160:553-8.
37. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005;352:9-19.

**Table 1: Demographics and Characteristics of Follow-up (FUP) Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)

Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < 12 <sup>th</sup> grade-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%) †	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language -no./total no.(%) ‡	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%) †	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	117/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
<u>Corrected age at follow-up (months)</u>	<u>19.9 ± 2.4</u>	<u>20.1 ± 2.7</u>	<u>19.9 ± 2.4</u>	<u>20.2 ± 2.7</u>

\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

¶ Among survivors to 36 weeks postmenstrual age

‡ Only available at 18-22 months corrected age † Among survivors to discharge or transfer

Comparisons of neonatal outcomes are adjusted for stratification by center and gestational age and for familial clustering

**Table 2: Death and NDI: CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups\***

<u>a. CPAP vs. Surfactant</u>	<u>CPAP</u>	<u>Surfactant</u>	<u>ARR*</u>	<u>p</u>
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

<b><u>b. Lower vs. Higher Oxygen Saturation</u></b>	<b><u>Lower</u></b>	<b><u>Higher</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA-no./total no.(%)	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined-no./total no.(%)	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.79
NDI-no./total no.(%)	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70-no./total no.(%)	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2-no./total no.(%)	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.56
Moderate/severe cerebral palsy-no./total no.(%)	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral-no./total no.(%)	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment-no./total no.(%)	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**From:** Zaterka-Baxter, Kristin  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT DSMC  
**Date:** Wednesday, April 25, 2012 1:19:36 PM  
**Attachments:** DSMC Addendum Clarification Site Memo20120425uc.doc

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Hi Rose,

Is this the type of additional information Beth might be looking to include in this memo? I am happy to ask her as well.

Thanks,  
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP

**RTI International**

*Res Clinical Study Specialist*

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Memorandum

November 4, 2009 (Addendum April 25, 2012)

**SUPPORT Trial Final DSMC Review**

TO: SUPPORT PI (co-PI)  
NICHD

FROM: The Data Coordinating Center

SUBJECT: Final DSMC Protocol Review

The NICHD NRN DSMC met on November 4, 2009 in Rockville, MD to discuss the final planned interim analyses for the *Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial)* at 100% primary outcome accrual. Their recommendations and comments are below:

1. The DSMC agreed it was our obligation to share stratified group-specific mortality data from the oxygen saturation arm of the SUPPORT trial with DSMCs monitoring the safety data for other similarly conducted international trials that are still recruiting patients, without waiting for the primary papers to be published, so that to use as those DSMCs can interpret the data see fit. Additionally, we should they agreed to share the oxygen saturation separation data so that the results can be put in context. These data showed 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 unanticipated increase in mortality and a substantial decrease in severe retinopathy among survivors.
2. The DSMC has requested an additional review of the complete 18-22 month Follow Up data when available.

While the DSMC requested some additional information which the Data Center will provide, the Committee determined that the trial should proceed with 18-22 month follow up as originally planned, with no additional actions required on the part of the investigators because the trial has already concluded, with only follow up pending.

cc. Rose Higgins, MD

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Zaterka-Baxter, Kristin"; Das, Abhik](#)  
**Subject:** RE: SUPPORT DSMB meeting reports  
**Date:** Tuesday, April 17, 2012 10:12:00 AM

---

Ok  
Either is fine

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**From:** [Zaterka-Baxter, Kristin \[mailto:kzaterka@rti.org\]](mailto:kzaterka@rti.org)  
**Sent:** Tuesday, April 17, 2012 10:11 AM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#)  
**Subject:** RE: SUPPORT DSMB meeting reports

Hi,

We can, but we've recently (and are updating) this location on the NRN website for DSMC minutes.  
We can post to either or both locations, just let me know which you prefer.

[Administration](#) > [Minutes](#) > **DSMC Minutes**

[6-24 Hour Hypothermia](#)  
[Extended Hypothermia/aEEG Follow-up](#)  
[Hydrocortisone](#)  
[Inositol](#)  
[IPGE1](#)  
[Milk Trial](#)  
[NEST](#)  
[Optimizing Cooling](#)  
[Premie Hypothermia](#)

[Completed Studies](#)



Thanks,  
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Tuesday, April 17, 2012 10:06 AM

**To:** Zaterka-Baxter, Kristin; Das, Abhik

**Subject:** FW: SUPPORT DSMB meeting reports

Can we have a section under each protocol marked DSMC??

This would make it much easier for the coordinators??

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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**From:** Monica Collins [mailto:MCollins@peds.uab.edu]

**Sent:** Monday, April 16, 2012 3:38 PM

**To:** Monica Collins; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]

**Cc:** [ambal@uab.edu](mailto:ambal@uab.edu)

**Subject:** RE: SUPPORT DSMB meeting reports

Dr. Carlo,

Sorry, we also will be sending the Final DSMC Protocol review from 2009. I didn't receive that one either from RTI until today and it just appeared on the website.

---

**From:** Monica Collins

**Sent:** Monday, April 16, 2012 2:20 PM

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

**Cc:** [ambal@uab.edu](mailto:ambal@uab.edu)

**Subject: FW: SUPPORT DSMB meeting reports**

Dr. Carlo,

The IRB called today requesting copies of the DSMB minutes for the SUPPORT study as OHRP had requested the minutes from them (OHRP wants them by Friday). We are collaborating with the IRB to make sure all DSMB meeting minutes had been sent. We found that the IRB had been sent 4 (suspension (2005), reactivation (2006) first interim look (2007), memo about second interim look (without minutes) (2007), tech memo detailing 3<sup>rd</sup> interim look (2008).

We searched my email files, your email files and did not find any more that might have mistakenly not been send. We found none.

We also checked the RTI website and found 2 that had not been sent to us—the prestudy DSMC minutes (2004) that Kris put up on the Website today and the final DSMC review. We will be sending those to the IRB as well. Kris also located the actual minutes for the 2008 meeting. We will be sending them to the IRB. Just wanted to keep you in the loop.

Monica

---

**From:** Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]  
**Sent:** Monday, April 16, 2012 2:05 PM  
**To:** Monica Collins  
**Subject:** RE: SUPPORT DSMB meeting reports

Hi Monica,

You should have the following:

TMs:

SUPP05: 11/22/05 Suspension

SUPP05S: 02/09/06 Reactivation

SUPP12: 12/14/07 Second Planned Interim Analysis (full Site minutes attached and will be posted soon)

SUPP15: 10/07/08 Third Planned Interim Analysis

SUPP17: 11/04/2009 Final Review (attached, soon to be posted)

Full Minutes:

Initial new Study review 12/06/04 (will be posted soon but is attached here)

First Planned DSMC Interim Analysis: 02/06/07

Final DSMC review at 18M FU: 10/15/11

DSMC TMs can be found here on the NRN Private Gateway: [Protocols](#) > [SUPPORT](#) > **Technical Memos**

Full minutes can be found here: [Administration](#) > [Minutes](#) > [DSMC](#) > [Completed Studies](#) > **SUPPORT**

Sorry for the confusion; we have since gone to documenting all DSMC correspondence via technical memos and will post in both places for convenience.

Thanks and let me know if you have any questions.  
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP  
**RTI International**  
*Res Clinical Study Specialist*

3340 Cornwallis Rd  
Research Triangle Park, NC 27709  
Phone: 919-485-7750  
Fax: 919-485-7762

---

**From:** Monica Collins [mailto:MCollins@peds.uab.edu]  
**Sent:** Monday, April 16, 2012 1:23 PM  
**To:** Zaterka-Baxter, Kristin  
**Subject:** SUPPORT DSMB meeting reports

Kris,

Can you verify for me, how many DSMB reports were generated for the SUPPORT trial?—just need to verify that we have all of them as OHRP has requested them by Friday.

**From:** Monica Collins  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** ambal@uab.edu  
**Subject:** FW: SUPPORT DSMB meeting reports  
**Date:** Monday, April 16, 2012 3:19:48 PM  
**Attachments:** [DSMC December 6 2004 Minutes.pdf](#)  
[DSMC Site Minutes 20080130.pdf](#)  
[DSMC Final Site Memo.pdf](#)

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Dr. Carlo,

The IRB called today requesting copies of the DSMB minutes for the SUPPORT study as OHRP had requested the minutes from them (OHRP wants them by Friday). We are collaborating with the IRB to make sure all DSMB meeting minutes had been sent. We found that the IRB had been sent 4 (suspension (2005), reactivation (2006) first interim look (2007), memo about second interim look (without minutes) (2007), tech memo detailing 3<sup>rd</sup> interim look (2008).

We searched my email files, your email files and did not find any more that might have mistakenly not been send. We found none.

We also checked the RTI website and found 2 that had not been sent to us—the prestudy DSMC minutes (2004) that Kris put up on the Website today and the final DSMC review. We will be sending those to the IRB as well. Kris also located the actual minutes for the 2008 meeting. We will be sending them to the IRB. Just wanted to keep you in the loop.

Monica

---

**From:** Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]  
**Sent:** Monday, April 16, 2012 2:05 PM  
**To:** Monica Collins  
**Subject:** RE: SUPPORT DSMB meeting reports

Hi Monica,

You should have the following:

TMs:

SUPP05: 11/22/05 Suspension

SUPP05S: 02/09/06 Reactivation

SUPP12: 12/14/07 Second Planned Interim Analysis (full Site minutes attached and will be posted soon)

SUPP15: 10/07/08 Third Planned Interim Analysis

SUPP17: 11/04/2009 Final Review (attached, soon to be posted)

Full Minutes:

Initial new Study review 12/06/04 (will be posted soon but is attached here)

First Planned DSMC Interim Analysis: 02/06/07

Final DSMC review at 18M FU: 10/15/11

DSMC TMs can be found here on the NRN Private Gateway: [Protocols](#) > [SUPPORT](#) > [Technical Memos](#)

Full minutes can be found here: [Administration](#) > [Minutes](#) > [DSMC](#) > [Completed Studies](#) > **SUPPORT**

Sorry for the confusion; we have since gone to documenting all DSMC correspondence via technical memos and will post in both places for convenience.

Thanks and let me know if you have any questions.  
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP

**RTI International**

*Res Clinical Study Specialist*

3340 Cornwallis Rd  
Research Triangle Park, NC 27709  
Phone: 919-485-7750  
Fax: 919-485-7762

---

**From:** Monica Collins [mailto:MCollins@peds.uab.edu]

**Sent:** Monday, April 16, 2012 1:23 PM

**To:** Zaterka-Baxter, Kristin

**Subject:** SUPPORT DSMB meeting reports

Kris,

Can you verify for me, how many DSMB reports were generated for the SUPPORT trial?—just need to verify that we have all of them as OHRP has requested them by Friday.

Page 1592 of 2000

Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act

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Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act

Page 1594 of 2000

Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act



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Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act

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Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act

Page 1597 of 2000

Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act

Support DSMC Memo  
November 4, 2009



Memorandum

November 4, 2009

**SUPPORT Trial Final DSMC Review**

TO: SUPPORT PI (co-PI)  
NICHD

FROM: The Data Coordinating Center

SUBJECT: Final DSMC Protocol Review

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The NICHD NRN DSMC met on November 4, 2009 in Rockville, MD to discuss the final planned interim analyses for the *Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial)*. Their recommendations and comments are below:

1. (b)(6)
  
2.

While the DSMC requested some additional information which the Data Center will provide, the Committee determined that the trial should proceed with 18-22 month follow up as originally planned.

cc. Rose Higgins, MD

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#); [Maddox, Yvonne \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: "SUPPORT Trial" (HHS Protocol 2U10HD034216)  
**Date:** Monday, April 16, 2012 2:28:00 PM

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FYI- OHRP request for the NRN SUPPORT Trial.

In addition, the Alabama site was contacted last week to provide the DSMC meeting documents provided to the clinical sites and are in the process of working with the data coordinating center to insure they have all of the documents.

Rose

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

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**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Friday, April 13, 2012 2:56 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Thanks! Have a good weekend.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, April 13, 2012 2:53 PM  
**To:** Buchanan, Lisa (HHS/OASH)  
**Subject:** Re: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi

There were no sites outside of the US. Recruitment is complete. However, there is a sub cohort of approximately 500-550 infants enrolled who had neuroimaging who are part of a school age Follow up (FU) study at 6.5-7.5 years of age. The windows are open for FU and will continue through 2016. Data analyses from the 18-22 month FU are in process.

Let me know if you have other questions.

Regards,  
\$rose

**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Friday, April 13, 2012 02:40 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good afternoon Rose,

I have two quick questions regarding the study referenced above. Did this trial involve any sites outside of the US? And are all study activities complete/close for all of the sites?

Thanks,  
Lisa

Lisa Buchanan, MAOM, CIP  
Public Health Analyst  
Division of Compliance Oversight  
Office for Human Research Protections  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852  
Ph: 240-453-8298  
Fax: 240-453-6909

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 01, 2012 1:31 PM  
**To:** Buchanan, Lisa (HHS/OASH)  
**Cc:** Borror, Kristina C (HHS/OASH)  
**Subject:** RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi,  
These were sent and we have confirmed with FED EX that they were delivered – can you confirm that you have them??  
Thanks  
Rose

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

---

**From:** Buchanan, Lisa (HHS/OASH)  
**Sent:** Monday, January 09, 2012 11:40 AM  
**To:** Higgins, Rosemary (NIH/NICHHD) [E]  
**Cc:** Borror, Kristina C (HHS/OASH)  
**Subject:** "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good morning Dr. Higgins,

I am reviewing responses' to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. OHRP has only opened its investigation with the University of Alabama. However, we would like to review the informed consent documents for all of the sites (~20). The data coordinating center, RTI, recommended that we contact you for this information. (See email below.) Would it be possible for you to provide copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPORT study?

Please feel free to contact me if you have any questions regarding this request.

Thanks,  
Lisa

*Lisa Buchanan, MAOM*  
Public Health Analyst, Division of Compliance Oversight  
Office for Human Research Protections  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852  
Ph: 240-453-8298  
Fax: 240-453-6909

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**From:** Borasky, David [mailto:dborasky@rti.org]  
**Sent:** Thursday, August 04, 2011 12:19 PM  
**To:** Borror, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested

Hi Kristina –

We had a chance to discuss your request with the RTI DCC folks this morning and how RTI may be able to help facilitate this for OHRP.

As I mentioned this morning, the RTI IRB does not require the DCC to provide RTI IRB with copies of the approved informed consent documents for each site. I did confirm that the DCC requires sites to submit copies of study approval notices to the DCC, but they do not require submission of copies of site-level informed consent documents to the DCC. Some sites do include them with the approval notices, but this is not done consistently and may not be done every time a consent document is amended at the site level. Therefore, the DCC's records for site-level consent documents are incomplete.

The RTI IRB and the Neonatal Research Network DCC appreciate your desire to expeditiously obtain site-level informed consent documents for the SUPPORT Trial. We believe that the best way to facilitate this is to have OHRP submit a formal request to the Neonatal Research Network steering committee via the NICHD project officer Rosemary Higgins (contact information below) to have the RTI Data Coordinating Center collect copies of the final approved consent forms (as well as whether or not this is the initially approved documents or all versions that were used with participants for the duration of the study) for each of the SUPPORT Trial sites for transmittal to OHRP.

I hope this is a suitable approach.

Best,

Dave

Dr. Higgins contact information:

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

\*\*\*\*\*  
David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

Phone: 919-316-3903  
Fax: 919-316-3897  
E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

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**From:** Borrer, Kristina C (HHS/OASH) [<mailto:Kristina.Borrer@hhs.gov>]  
**Sent:** Friday, July 29, 2011 4:23 PM  
**To:** Borasky, David  
**Cc:** Caddell, Juesta M.  
**Subject:** RE: clarification requested



Dave,

We were wondering if you would be able to get us copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPRT study. Is that possible?

Thanks for your assistance.

Kristina

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**From:** Borasky, David [mailto:dborasky@rti.org]

**Sent:** Monday, July 25, 2011 1:13 PM

**To:** Borrer, Kristina C (HHS/OASH)

**Cc:** Caddell, Juesta M.

**Subject:** RE: clarification requested

Thank you for the quick response Kristina.

RTI was not engaged in the conduct of the SUPPORT clinical protocol nor would have been considered the IRB of record. RTI serves as the network data coordinating center for all sites, and in this role received coded data for analysis.

Therefore, as per your email, we will not submit a response to the letter dated July 18, 2011.

Regards,

Dave

\*\*\*\*\*  
David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

Phone: 919-316-3903

Fax: 919-316-3897

E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

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**From:** Borrer, Kristina C (HHS/OASH) [mailto:Kristina.Borrer@hhs.gov]

**Sent:** Monday, July 25, 2011 1:00 PM

**To:** Borasky, David

**Cc:** Caddell, Juesta M.

**Subject:** RE: clarification requested

Dave,

If RTI is not engaged in the research, we do not require any additional information at this time. We'll let you know if we need anything else.

Kristina C. Borrer, Ph.D.

Director

Division of Compliance Oversight

Office for Human Research Protections

1101 Wootton Parkway, Suite 200

The Tower Building

Rockville, MD 20852  
email: [kristina.borror@hhs.gov](mailto:kristina.borror@hhs.gov)  
Phone: (240) 453-8132  
Fax: (240) 453-6909

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**From:** Borasky, David [mailto:[dborasky@rti.org](mailto:dborasky@rti.org)]  
**Sent:** Monday, July 25, 2011 11:10 AM  
**To:** Borror, Kristina C (HHS/OASH)  
**Cc:** Caddell, Juesta M.  
**Subject:** clarification requested

Good morning Kristina,

On Friday we (RTI) received a letter from you that was addressed to both our signatory official (Ward Sax) and the SO of UAB (Dr. Marchase) related to the SUPPORT trial. However, we noticed that the letter's salutation was only addressed to Dr. Marchase.

For the SUPPORT Trial (and for the entire Neonatal Research Network) RTI serves as the data coordinating center and we have no oversight of the clinical research. We receive and analyze coded data, and do not have access to the code linking subjects to identifiers.

Given our role and that we are not in the salutation, we assume that OHRP does not expect a formal response from RTI. Would you please confirm if our assumption is correct, and if not, provide guidance on what OHRP would want RTI to provide given our role with the SUPPORT Trial? I leave on vacation tomorrow, so if you could reply to all I would appreciate it. Juesta Caddell is the Director of our IRB office and is the HPA on our FWA.

Thank you.

Dave

\*\*\*\*\*  
David Borasky, MPH, CIP  
Office of Research Protection  
RTI International  
3040 Cornwallis Rd  
RTP, NC 27709  
USA

Phone: 919-316-3903  
Fax: 919-316-3897  
E-mail: [dborasky@rti.org](mailto:dborasky@rti.org)

**From:** Susan Hintz  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Support main trial fu  
**Date:** Monday, April 16, 2012 9:43:18 AM

---

Thanks Rose

S

Sent from my iPhone

On Apr 16, 2012, at 6:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> See previous email with draft paper

>

> Rose

>

> Rosemary D. Higgins, MD

> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

> Pregnancy and Perinatology Branch

> CDBPM, NIH

> 6100 Executive Blvd., Room 4B03

> MSC 7510

> Bethesda, MD 20892

> For overnight delivery use Rockville, MD 20852

> 301-435-7909

> 301-496-5575

> 301-496-3790 (FAX)

> higginsr@mail.nih.gov

>

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

> From: Susan Hintz [<mailto:srhintz@stanford.edu>]

> Sent: Monday, April 16, 2012 9:04 AM

> To: Higgins, Rosemary (NIH/NICHD) [E]

> Subject: Support main trial fu

>

> Hi Rose

>

> I am continuing to work/ prepare for PAS presentations and want to make sure I have recent versions of Yvonne's paper and Myriam's. I know they are being combined, but if I could get the versions that were separate that would be great. I have an early version of both - just want to make sure I am recent in my thinking. OF COURSE, it would be confidential - I just want to look at the tables, make sure my comparison of characteristics and FU outcomes in main trial vs. NEURO are correct.

>

> Thanks

>

> S

>

> Sent from my iPhone

**From:** Vaucher, Yvonne  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik  
**Cc:** Myriam Peralta, M.D.; Vaucher, Yvonne  
**Date:** Friday, April 13, 2012 4:26:38 PM  
**Attachments:** Table 3 Vision Outcome.docx  
Table 1 04112012.docx  
Table 2CPAP.docx  
CombPaperNEJM 04\_13\_2012 MPYV.docx

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All,

Please review body of paper and tables for content, readability, accuracy. Ignore references—they are not yet been combined—the reference numbers refer to the original two papers. Am working on appendices; Myriam is working on consort diagram. Word count is ~2600 presently.

Thanks.

Yvonne

---

**From:** Vaucher, Yvonne  
**Sent:** Thursday, April 12, 2012 3:45 PM  
**To:** Finer, Neil  
**Cc:** Vaucher, Yvonne  
**Subject:**

Neil,

Here is the latest version ~ 2500 words. Please read. I want to send this around ASAP  
Thanks.

Yvonne

**Yvonne E. Vaucher, M.D., M.P.H.**  
Division of Neonatal/Perinatal Medicine  
Clinical Professor of Pediatrics  
UCSD School of Medicine

tele: 619;543-3759  
FAX: 619;543-3812

**Table 3: Visual Outcome at 18-22 Months CA for Lower vs. Higher Oxygen Saturation Targets Groups**

	Lower	Higher	ARR	p
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	432/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.001

**Table 1: Demographics and Characteristics of Follow-up (FUP) Cohorts**

	<u>CPAP</u>	<u>Surfactant</u>	<u>Lower Saturation</u>	<u>Higher Saturation</u>
	N=511	N=479	N=479	N=511
Birth weight (grams, Mean ± SD)	849±186	852±193	858±186	844±192
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)	17/479(3.5)**	38/511(7.4)**
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Race				
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)	201/479(42)	176/511(34.4)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)	178/479(37.2)	218/511(42.6)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.5)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)

Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
With both biological parents-no./total no.(%) †	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education < 12 <sup>th</sup> grade-no./total no.(%)	128/506(25.3)	116/469(24.7)	115/479(24.4)	129/504(25.6)
Income < \$30,000/year-no./total no.(%) †	260/493(52.7)	251/461(54.4)	239/456(52.4)	271/498(54.6)
English as primary language -no./total no.(%) ‡	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe retinopathy of prematurity-no./total no.(%)†	62/479(12.9)	58/434(13.4)	38/442 (8.6)***	82/471(17.4)***
Bronchopulmonary dysplasia -no./total no.(%) ¶	193/511(37.8)	187/479(39)	117/479(37)	203/511(39.7)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
Necrotizing enterocolitis -no./total no.(%)	56/511(11)**	30/479(6.3)**	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids-no./total no.(%)	34/508(6.7)**	55/476(11.6)**	41/477(8.6)	48/507(9.5)

\*p<0.02, \*\* p<0.01, \*\*\*p<0.001

¶ Among survivors to 36 weeks postmenstrual age

‡ Only available at 18-22 months corrected age

† Available only for infant who survived to discharge or transfer

**Table 2: Death and NDI: CPAP vs. Surfactant treatment arms and Lower vs. Higher Oxygen Saturation Target Groups\***

<b><u>a. CPAP vs. Surfactant</u></b>	<b><u>CPAP</u></b>	<b><u>Surfactant</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06



<b><u>b. Lower vs. Higher Oxygen Saturation</u></b>	<b><u>Lower</u></b>	<b><u>Higher</u></b>	<b><u>ARR*</u></b>	<b><u>p</u></b>
Death or NDI-no./total no.(%)	185/612(30.2)	171/622(27.5)	1.12(0.94,1.32)	0.21
Death before 18-22 mo CA-no./total no.(%)	140/633(22.1)	118/648(18.2)	1.25(1,1.55)	0.046
Death/NDI determined-no./total no.(%)	612/654(93.6)	622/662(94)	1(0.97,1.03)	0.38
NDI-no./total no.(%)	45/472(9.5)	53/504(10.5)	0.87(0.6,1.28)	0.49
BSID-III cognitive score < 70-no./total no.(%)	34/471(7.2)	38/503(7.6)	0.91(0.58,1.43)	0.69
Gross motor function level ≥ 2-no./total no.(%)	26/479(5.4)	23/511(4.5)	1.17(0.68,2.01)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	20/479(4.2)	20/511(3.9)	1(0.54,1.83)	>0.99
Blindness, bilateral-no./total no.(%)	5/479(1)	6/511(1.2)	0.9(0.28,2.9)	0.86
Hearing impairment-no./total no.(%)	12/479(2.5)	12/511(2.3)	1.16(0.54,2.49)	0.70

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

## **Outcome at 18-22 months of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)**

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## ABSTRACT

**BACKGROUND:** The SUPPORT trial showed no difference in the outcome of death or BPD between infants receiving early CPAP vs. early surfactant. Lower-oxygen saturation targets were associated with a lower rate of severe retinopathy of prematurity but increased mortality. Our pre-specified hypothesis was that early CPAP and lower oxygen saturation targeting would each decrease death or neurodevelopmental impairment (NDI) at 18-22 months corrected age (CA).

**METHODS** Infants born at 24 0/7 to 27 6/7 weeks gestation were randomly assigned using a 2X2 factorial design to early CPAP vs. early surfactant administration and to lower (85-89%) vs. higher (91-95%) oxygen saturation targets. The primary outcome was a composite of death or NDI at 18-22 months CA.

**RESULTS:** Death or NDI was determined for 1234/1316 (93.8%) of all enrolled infants; 93.6% (990/1058) of hospital survivors were evaluated at 18-22 months CA. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant 27.9% [173/621]] groups (RR 0.93, 95% CI 0.78-1.1, p=0.39) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)]; oxygen saturation groups (RR risk 1.12; 95% CI 0.94 to 1.32; p=0.11). Mortality at follow up was persistently greater in the lower (22.1%) compared to the higher (18.2%) oxygen saturation group (RR 1.25; 95% CI, 1 to 1.55, p=0.046).

**CONCLUSION:** We found no significant differences in the composite outcome of death or NDI in extremely premature infants randomized to receive either early CPAP vs. or early surfactant and lower vs. higher oxygen saturation target ranges.

**Comment [MG1]:** This should be "randomized to receive" instead of "received" since this is an ITT analysis and we are not looking at what the infants actually received.

## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks postmenstrual age (PMA), air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Although for many preterm infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity,<sup>1</sup> BPD,<sup>2,3</sup> periventricular leukomalacia,<sup>4</sup> and cerebral palsy.<sup>5</sup> Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials.<sup>6,7</sup> The SUPPORT trial demonstrated no difference in the composite outcome of death or severe retinopathy of prematurity (ROP) before discharge between the lower-oxygen-saturation target group (85-89%) vs. higher-oxygen-saturation target group (91-95%). However, the risk of ROP before discharge was decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73;  $p < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60;  $p = 0.04$ ) in the lower oxygen saturation group compared to the higher-oxygen-saturation group.<sup>6</sup>

The pre-specified hypotheses of the SUPPORT trial were 1) that early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration and 2) that lower compared to higher oxygen saturation targets would each decrease the incidence of death or neurodevelopmental impairment at 18-22 months corrected age.

**Comment [AD2]:** I think we may have to get away from this, because the protocol is a little fuzzy on this aspect.

## METHODS

### Study Design

1316 extremely preterm infants, 24 through 27 weeks gestation, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery with a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth followed by conventional ventilation.<sup>18</sup> Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85 to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group) using a specially designed blinded oximeter. Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months CA, by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>19</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy (CP) defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>20</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>21</sup> Moderate to severe cerebral palsy was defined by a GMFCS  $\geq 2$  plus an abnormal exam as stated above. Hearing impairment, defined as the inability to understand directions of the examiner and communicate with or without amplification; and visual impairment, defined as vision  $< 20/200$ , were based upon examination and parental report.

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, ROP, BPD, and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

### Outcome

The pre-specified primary composite outcome at follow up for this trial was death or neurodevelopmental impairment at 18 to 22 months CA. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score  $< 70$ , GMFCS  $\geq 2$ , moderate or severe CP, hearing or bilateral visual impairment. Other pre-specified outcomes at 18 to 22 months CA were mortality among the entire trial cohort and the individual components of NDI among survivors at follow up. Exploratory secondary outcomes at 18 to 22 months CA were death and components of NDI (i.e., cognitive composite score  $< 70$ , GMFCS  $\geq 2$ , moderate/severe cerebral palsy, bilateral blindness and bilateral hearing impairment).

Comment [AD3]: Wasn't this pre-specified?

Comment [sec 4]: NDI, blindness and CP were pre-specified

### Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18</sup> While the sample size for the study was primarily based on the hospital outcomes (i.e., death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the final sample size for the study was sufficient to detect a 10% absolute reduction in composite outcome of death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering.

Comment [MS5]: See below.

Comment [MS6]: Because this is the most conservative outcome rate that could have been used for the power calculations, it does not matter that the initial estimates were based on the Bayley II.

Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary composite outcome of death or NDI at 18-22 months CA could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Comment [AD7]: Are we actually presenting any unadjusted t tests? If not, we can take this out.

Comment [yav.8]: Yes-Table 1

Analyses of all neonatal and 18-22 month outcomes were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted that demonstrated no for the presence of statistical interaction between the two interventions. To test the impact of characteristics that differed between children with and without follow up, a sensitivity analysis using multiple imputation was conducted (ref). Missing values of the primary outcome were imputed based on treatment assignment, perinatal characteristics and in-hospital outcomes; results were virtually identical to the analysis of the non-missing cases. ~~MARIE ADD HERE\*\*\*\*\*Two-sided p values of < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 4 tests to be significant at the 0.05 level on the basis of chance alone.~~

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<sup>22</sup>Two-sided p values of < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 4 tests to be significant at the 0.05 level on the basis of chance alone.

~~Sensitivity analyses were conducted to assess the impact of loss to follow up on the primary follow up outcome of death or NDI and the two individual components of the outcome. MARIE TO ADD HERE~~

Comment [MG9]: Will describe the methods used when I am done with the analysis.

Comment [yav.10]: Still need.

## RESULTS

Of the 1316 infants enrolled in the SUPPORT trial, 250 were known to have died before 18-22 months (Figure). Of the remaining children, 68/1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of the 990 children seen for evaluation, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of enrolled children. The mean CA at neurodevelopmental assessment and the follow-up rates were similar for all treatment arms. (Table 1)

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months CA mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%, p=0.01), and more likely

to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups. (MARIE-NEED SENSITIVITY ANALYSES)

Comment [AD11]: Shouldn't this comparison be between with 1234 for whom we have outcome and the 82 that we don't?

Comment [yav 12]: We can change this.

**Follow-up Cohort Characteristics:** (Table 1) Almost all mothers received antenatal steroids. There were more SGA children and more children with ROP in the higher vs. the lower oxygen saturation group. Compared to the Surfactant arm, children in the CPAP arm were more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Thirty-two percent of infants in the CPAP arm were intubated in the delivery room and 65% ultimately received surfactant (with limited ventilation).

Comment [MG13]: Can we be sure that they received ventilation, based only on the fact that they received surfactant?

Comment [yav 14]: Per the protocol all those with intubation for surfactant had "limited ventilation"

**Primary outcome:** The composite outcome of death or NDI was not significantly different between the CPAP and surfactant arms or between the lower and higher oxygen saturation target groups at 18-22 months CA in either the entire cohort or between the higher and lower gestational age strata. (Table 2 a and b; Appendix) There was no difference in death between the CPAP and Surfactant arms. Mortality at follow-up remained significantly higher in the lower compared to the higher saturation group. There was no evidence of any statistical interaction between the two interventions for either the composite outcome of death or NDI, or for its components (i.e. death, or NDI) among survivors (all  $p$  values  $> 0.7$ ).

**Other outcomes:** The incidences of cognitive impairment (BSID-III cognitive composite score  $< 70$ , gross motor function level  $\geq 2$ , moderate/severe cerebral palsy), and blindness among survivors were not different between the CPAP vs. Surfactant treatment arms or between the lower vs. higher saturation groups in the entire cohort or between the gestational age strata (Table 2 a and b; Appendix). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher-oxygen-saturation group vs. the lower-oxygen-saturation group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month CA visit. (Table 3) Neither were there significant differences in between the CPAP and Surfactant arms or between the lower and higher saturation groups in the composite combined outcomes of death or individual NDI components, mean cognitive scores, or the percent with cognitive composite scores less than 80 or 85 between the CPAP and Surfactant arms or between the lower and higher saturation groups (Appendix) Sixty percent of children seen in the CPAP/Surfactant arms and \_\_\_\_\_ % of children in the lower and higher saturation groups had had normal neuromotor, neurosensory and developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations, at 18-22 months CA.

Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen target group vs. the lower oxygen target group, the rates of bilateral blindness, blindness of at least one eye or other vision impairment were not significantly different at the 18 to 22 month CA visit. (Table 3)

ADD text for Cog scores, cutoffs (Appendix)

#### DISCUSSION:

This trial demonstrated no significant difference in the primary composite outcome of death or NDI at 18-22 months corrected age between those infants randomized to treatment with early CPAP vs. early intubation and surfactant or between those randomized to the lower vs. higher oxygen saturation target groups in the SUPPORT trial. Neither were there significant differences among survivors in any of the treatment arms for



NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC  $\geq$ 2), hearing impairment, and bilateral blindness.

To our knowledge this is the first large, multicenter, RCT published to date including neurodevelopmental impairment as a pre-specified outcome for these therapeutic alternatives in infants as immature as 24 weeks gestation. Results of additional randomized trials which include pre-specified neurodevelopmental outcome at two years of age will not be available until 2014.<sup>7,15</sup>

The results of recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>2</sup> In the SUPPORT trial death prior to discharge was increased among neonates randomized to the lower-oxygen-saturation group. As was published previously, causes of death before discharge between the lower and higher oxygen saturation groups were not different.<sup>6</sup> Mortality remained lower in the higher-oxygen-saturation target group at 18 to 22 months corrected age. Mortality remained higher as well as in the most immature gestational age stratum of the early intubation with surfactant administration group. Causes of death after discharge are not available

Severe ROP may be associated with poor visual outcomes even with treatment.<sup>17,18</sup> We previously reported that the lower-oxygen-saturation target was associated with a reduction in the incidence of severe retinopathy of prematurity (8.6% vs. 17.9%) among survivors at discharge.<sup>6</sup> Eye surgery was more frequent in higher oxygen saturation target group. Although our study was not designed to collect detailed data on visual function at 18 to 22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness, nystagmus, strabismus or use of corrective lenses between the lower and higher saturation groups

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, and the very high percentage of participants who had a comprehensive and standardized neurodevelopmental evaluation at 18-24 months CA. The generalizability of this study may be limited by the being center rather than being population based and by requiring antenatal consent which is associated with enrollment bias.<sup>23,24</sup> The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. The present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, whereas previous NRN studies used the Bayley, 2<sup>nd</sup> edition. Changes in Bayley test design and standardization may account for the lower incidence of NDI reported here, (REF). Although Bayley scores in this study were higher than previously reported for extremely premature infants, there were no differences between any of the treatment groups. The present study reports results of a single follow-up visit at 18 to 22 months corrected age. Other disabilities may not be evident until later childhood. There is a sub-cohort of the SUPPORT study which will be followed at school age to evaluate longer-term neurodevelopmental outcome.

In summary, mortality was lower in the higher-oxygen-saturation group and in the most immature stratum, of the Early CPAP group. Among survivors at 18-22 months corrected age, there were no significant differences in the individual components of NDI or in composite outcome of death or NDI between extremely preterm infants who were randomized at delivery to either early CPAP or early intubation with surfactant administration and to either lower or higher saturation limits.

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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 are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Rurey, MPH; Brenda L. MacKinnon, RNC; Ellen Nysten, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN;

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowitz, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen; Emily Kushner, MA; Joari Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Alred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Willey Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons,

PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

**Table 1: Demographic and neonatal characteristics of follow-up cohorts**

**Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata**

**Table 3: Death and components of NDI for entire cohort and by gestational age strata**

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris OH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Bayley. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
20. Amiel-Tison C GJ. Neurological Development from Birth to Six Years. Baltimore: The Johns Hopkins University Press; 1998.
21. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
22. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
23. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.

24. Rich W, Finer Neil N, Gantz Marie G, et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. *Pediatrics* 2012;129:480-4.

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**From:** Vaucher, Yvonne  
**To:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Myriam Peralta, M.D.  
**Subject:** RE: Sensitivity analysis results  
**Date:** Tuesday, April 10, 2012 5:48:04 PM

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Marie,

It would be good idea to include a short statement with reference in the paper such that sensitivity analysis using imputation resulted in virtually identical results for the primary outcome. Can you phrase that properly? We are close to the word limit so the shorter the better.

Thanks!

Yvonne

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**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 10, 2012 1:52 PM  
**To:** Gantz, Marie; Vaucher, Yvonne; Das, Abhik; Higgins, Rosemary (NIH/NICHD); Finer, Neil; Myriam Peralta, M.D.  
**Subject:** Re: Sensitivity analysis results

Great, Marie. Thx.

Wally

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

**From:** "Gantz, Marie" <mgantz@rti.org>  
**To:** "Vaucher, Yvonne" <yvaucher@ucsd.edu>, "Das, Abhik" <adas@rti.org>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>, "Finer, Neil" <nfiner@ucsd.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu>  
**Sent:** Tue, Apr 10, 2012 20:50:09 GMT+00:00  
**Subject:** Sensitivity analysis results

I have completed the sensitivity analysis using the multiple imputation approach. Abhik and I talked today and agreed that this approach is probably sufficient to answer the reviewers' concerns that the results of our analysis could have been impacted by the difference in follow up rates related to maternal education and public health insurance. We also decided to restrict the sensitivity analysis to the primary outcome of death or NDI at this time, unless the reviewers subsequently ask us to look at additional outcomes.

I can write up the methods for inclusion in the paper and/or response to the reviewers, but basically death/NDI was imputed based on perinatal characteristics (including maternal education and public insurance) as well as in-hospital outcomes (IVH, BPD, etc.). Five versions of the full data set were imputed, each was analyzed separately using the same method we used for the paper, and then the results were combined into one inference that accounted for both the between- and within-imputation variance. The results were almost identical to the results included in the paper. For CPAP vs. surfactant, the RR and CI (in this case, the mean of the upper and lower CI limits) was 0.93 (0.78, 1.10) the same as the original RR and CI, and for low vs. high SpO2 it was 1.09 (0.92, 1.30) as

opposed to 1.12 (0.94, 1.32).

A reference for using this MI approach to sensitivity analysis in clinical trials is Kenward, M.G. & Carpenter, J. (2007). Multiple imputation: current perspectives. *Statistical Methods in Medical Research*, 16(3): 199-218.

Marie

**Marie Gantz, Ph.D.**  
**Senior Research Statistician**  
**RTI International**  
**[mgantz@rti.org](mailto:mgantz@rti.org)**  
**828-254-6256**

**From:** Vaucher, Yvonne  
**To:** Das, Abhik; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [F]  
**Cc:** Finer, Neil; Myriam Peralta, M.D.  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper  
**Date:** Tuesday, April 10, 2012 1:02:11 PM

---

That looks fine.

---

**From:** Das, Abhik [adas@rti.org]  
**Sent:** Tuesday, April 10, 2012 9:34 AM  
**To:** Vaucher, Yvonne; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD)  
**Cc:** Finer, Neil; Myriam Peralta, M.D.  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

This is how Susan reported follow up outcomes from the PiNO trial. Perhaps we can do something similar to convey all necessary information?

" The follow-up rate for survivors was 90% (91/101) for the iNO group and 91% (102/112) for the placebo group. The primary outcome for this analysis was able to be determined for 198 patients receiving iNO (95%) and 200 receiving placebo (95%)..."

Thanks

Abhik

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

**From:** Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
**Sent:** Tuesday, April 10, 2012 11:47 AM  
**To:** Das, Abhik; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD)  
**Cc:** Finer, Neil; Myriam Peralta, M.D.; Vaucher, Yvonne  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

Marie can you recalculate the rates based on this approach for the paper? If so we should change our PAS slides accordingly.

Yvonne

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**From:** Das, Abhik [adas@rti.org]  
**Sent:** Tuesday, April 10, 2012 6:55 AM  
**To:** Vaucher, Yvonne; Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD)  
**Cc:** Finer, Neil; Myriam Peralta, M.D.  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

I think issues 1-3 are related, and I agree with Wally (and tried to make this point at our call) that the loss to follow up should be calculated on the basis of the proportion of babies among all randomized, that could not be assigned the primary outcome of death or NDI. (I think this is how most Network papers, including the cooling trials, have reported this.) This is a very small number, and comparisons between those with this outcome vs. those missing this outcome would likely turn up very few significant differences because they would be unconfounded by death (which is the problem with the NEC and SGA comparisons currently). I agree with Wally that if we had framed it in this manner then it is unlikely that we would have been asked about sensitivity analyses.

Thanks

Abhik

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Monday, April 09, 2012 12:56 PM  
To: Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD)  
Cc: Finer, Neil; Myriam Peralta, M.D.; Vaucher, Yvonne  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

Thanks Wally for your thoughtful comments on the first draft.

1. The LTFU rate is small. Let's see the imputation results from Marie. I don't think those LTFU will change any conclusions.
2. Re: NEC, SGA: This needs to be in the table and the question will come up so we should formulate an appropriate comment in the paper per Marie and Abhik.
3. There were significant differences in the enrolled and non-enrolled groups. It may affect generalizability. Marie/Abhik-how would you state this? We can comment without specifics and provide the references. Wade's paper is out this month.
4. We can certainly reword. I agree that we should make the importance of the study as clear as possible.
5. We can delete the algorithm discussion.
6. Visual outcomes: unfortunately there were no formal ophthalmologic exams to evaluate refractive errors, etc although as far as NDI is concerned the data is sufficient (blindness) and we did do a history/physical/neurologic exam for obvious problems (e.g. strabismus, nystagmus.) Follow-up at 6-7 years would be very important as there will be visual field defects secondary to laser therapy and one would expect a higher incidence of myopia. It should be feasible to get data for most of the children with ROP since they should be followed regularly by ophthalmology. It would be informative to at least have a case control as ELGANS without ROP are also at higher risk for refractive errors etc.

yvonne

---

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
Sent: Sunday, April 08, 2012 1:31 PM  
To: Das, Abhik; Gantz, Marie; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD)  
Cc: Finer, Neil; Myriam Peralta, M.D.  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

I am enclosing further comments largely on the Results and Conclusions which I had not sent when I send tracked changes. I am in Europe with limited email access so I am sending comments in this email.

1. We may prefer to start the Results with the next to the last sentence of the first paragraph and follow that by adding the other babies followed with neuro assessment and death knowledge and could even total that to be 97.5% this is the real follow up rate (at least for death). We are shooting ourselves by presenting what others will interpret as high loss to FU, which may have made a reviewer ask for sensitivity analysis. At 10% or so NDI rate, I think the loss to FU will only account to about 0.25% of NDI extra.
2. We need to be careful about highlighting the SGA and NEC differences as mortality differed or trended to differ between groups. We also did not analyze NEC/death which would be the better way to report NEC as death tended to differ.
3. We should not in any way imply that high ANS is a limitation of the trial or generalizing the results. ANS is the standard of care. There was no evidence from our trial that the results depended on ANS use.
4. The second sentence of the discussion qualifies the trial so uniquely that it is difficult for regular readers to know the high importance of the trial. The imp to me is that these are two trials of that tested critical hypotheses related to ventilatory and oxygenation strategies in a very high risk population and that we now have very high follow up rates and excellent NDI assessments.
5. I do not think the algorithm should be addressed in the Discussion. We found increased death with the old algorithm and BOOST reports increased death with the new one. To me

death is increased in the low saturation target independent of the algorithm. Raising concerns about the algorithm raises concerns about our results that are not valid.

6. I don't think we should undermine our paper by stating we did not evaluate "specific visual outcomes". We know the rate of blindness is much less than the rates of death.

In summary, I think the paper needs to be improved substantially before resubmission.

Wally

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

From: "Das, Abhik" <adas@rti.org>  
To: "Gantz, Marie" <mgantz@rti.org>, "Vaucher, Yvonne" <yvaucher@ucsd.edu>, "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>  
Cc: "Finer, Neil" <nfiner@ucsd.edu>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu>  
Sent: Thu, Apr 5, 2012 18:59:33 GMT+00:00  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

I have added a few more suggested changes to Marie's revision.

Thanks

Abhik

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

From: Gantz, Marie  
Sent: Thursday, April 05, 2012 11:09 AM  
To: 'Vaucher, Yvonne'; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik  
Cc: Finer, Neil; mperalta@peds.uab.edu  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

My additions and comments are attached. I am working on the sensitivity analyses and we can discuss them on our call tomorrow.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Tuesday, April 03, 2012 10:20 AM  
To: Higgins, Rosemary (NIH/NICHD); Gantz, Marie; wcarlo@peds.uab.edu; Das, Abhik  
Cc: Vaucher, Yvonne; Finer, Neil  
Subject: FW: Boilerplate | SUPPORT FU Combined paper

Here is my first draft at combining the papers, without Marie's comments, so we still need to shorten some but getting there. I am combining the tables. I included only those outcomes described in the original protocol (i.e. Death and NDI and the individual components.

Yvonne

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From: Vaucher, Yvonne  
Sent: Monday, April 02, 2012 9:39 PM  
To: Myriam Peralta, M.D.  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

2867 words (excluding abstract and references) so almost there. We need to get down to 2700 so see if you can cut somewhere.

Yvonne

---

From: Myriam Peralta, M.D. [MPeralta@peds.uab.edu]  
Sent: Sunday, April 01, 2012 6:08 PM  
To: Vaucher, Yvonne  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

Yvonne where you able to put some of the paper together, I can work on it this week if you want to send me what you have and I will work on it some, Also I can start on the letter to respond to the reviewers, thanks.

---

From: Vaucher, Yvonne [yvaucher@ucsd.edu]  
Sent: Saturday, March 31, 2012 2:00 PM  
To: Archer, Stephanie (NIH/NICHD) [E]; Wally Carlo (wacarolo@uab.edu); Finer, Neil; Myriam Peralta, M.D.  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

All,  
Re boilerplate: We can discuss revised title, authors on Friday.

Yvonne

---

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]  
Sent: Wednesday, March 28, 2012 1:15 PM  
To: Wally Carlo (wacarolo@uab.edu); Finer, Neil; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Vaucher, Yvonne  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Boilerplate | SUPPORT FU Combined paper

Attached is a combined author list and boilerplate for the new combined SUPPORT FU paper. The only center that had two different authors on each paper was Indiana (highlighted in yellow in the attachment). Need to decide whether to include both of them, or not, and make necessary adjustments to the author list and acknowledgements (at the moment I have them listed in both).

Stephanie

**From:** [Vaucher, Yvonne](#)  
**To:** [Finer, Neil](#); [Wally Carlo, M.D.](#); [Das, Abhik](#); [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Cc:** [Myriam Peralta, M.D.](#)  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper  
**Date:** Tuesday, April 10, 2012 11:08:58 AM

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Done

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**From:** [Finer, Neil](#)  
**Sent:** Tuesday, April 10, 2012 12:03 AM  
**To:** [Wally Carlo, M.D.](#); [Das, Abhik](#); [Gantz, Marie](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\)](#)  
**Cc:** [Myriam Peralta, M.D.](#)  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

I agree with Wally's points  
Most of these were discussed on the telephone call  
We should not talk about the algorithm and we do not need to reference this  
Neil

**From:** [Wally Carlo, M.D.](#) [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Sunday, April 08, 2012 1:32 PM  
**To:** [Das, Abhik](#); [Gantz, Marie](#); [Vaucher, Yvonne](#); [Higgins, Rosemary \(NIH/NICHD\)](#)  
**Cc:** [Finer, Neil](#); [Myriam Peralta, M.D.](#)  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

I am enclosing further comments largely on the Results and Conclusions which I had not sent when I send tracked changes. I am in Europe with limited email access so I am sending comments in this email.

1. We may prefer to start the Results with the next to the last sentence of the first paragraph and follow that by adding the other babies followed with neuro assessment and death knowledge and could even total that to be 97.5% this is the real follow up rate (at least for death. We are shooting ourselves by presenting what others will interpret as high loss to FU, which may have made a reviewer ask for sensitivity analysis. At 10% or so NDI rate, I think the loss to FU will only account to about 0.25% of NDI extra.
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4. The second sentence of the discussion qualifies the trial so uniquely that it is difficult for regular readers to know the high importance of the trial. The imp to me is that these are two trials of that tested critical hypotheses related to ventilatory and oxygenation strategies in a very high risk population and that we now have very high follow up rates and excellent NDI assessments.
5. I do not think the algorithm should be addressed in the Discussion. We found increased death with the old algorithm and BOOST reported increased death with the new one. To me death is increased in the low saturation target independent of the algorithm. Raising concerns about the algorithm raises concerns about our results that are not valid.
6. I don't think we should undermine our paper by stating we did not evaluate "specific visual outcomes". We know the rate of blindness is much less than the rates of death.

In summary, I think the paper needs to be improved substantially before resubmission.

Wally

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



From: "Das, Abhik" <adas@rti.org<mailto:adas@rti.org>>  
To: "Gantz, Marie" <mgantz@rti.org<mailto:mgantz@rti.org>>, "Vaucher, Yvonne" <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>, "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>  
Cc: "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>, "Myriam Peralta, M.D." <MPeralta@peds.uab.edu<mailto:MPeralta@peds.uab.edu>>  
Sent: Thu, Apr 5, 2012 18:59:33 GMT+00:00  
Subject: RE: Boilerplate | SUPPORT FU Combined paper  
I have added a few more suggested changes to Marie's revision.

Thanks

Abhik

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

From: Gantz, Marie  
Sent: Thursday, April 05, 2012 11:09 AM  
To: 'Vaucher, Yvonne'; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>; Das, Abhik  
Cc: Finer, Neil; mperalta@peds.uab.edu<mailto:mperalta@peds.uab.edu>  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

My additions and comments are attached. I am working on the sensitivity analyses and we can discuss them on our call tomorrow.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org<mailto:mgantz@rti.org>  
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Tuesday, April 03, 2012 10:20 AM  
To: Higgins, Rosemary (NIH/NICHD); Gantz, Marie; wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>; Das, Abhik  
Cc: Vaucher, Yvonne; Finer, Neil  
Subject: FW: Boilerplate | SUPPORT FU Combined paper

Here is my first draft at combining the papers, without Marie's comments, so we still need to shorten some but getting there. I am combining the tables. I included only those outcomes described in the original protocol (i.e. Death and NDI and the individual components.

Yvonne

---

From: Vaucher, Yvonne  
Sent: Monday, April 02, 2012 9:39 PM  
To: Myriam Peralta, M.D.  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

2867 words (excluding abstract and references) so almost there. We need to get down to 2700 so see if you can cut

somewhere.

Yvonne

---

From: Myriam Peralta, M.D. [MPeralta@peds.uab.edu]  
Sent: Sunday, April 01, 2012 6:08 PM  
To: Vaucher, Yvonne  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

Yvonne where you able to put some of the paper together, I can work on it this week if you want to send me what you have and I will work on it some, Also I can start on the letter to respond to the reviewers, thanks.

---

From: Vaucher, Yvonne [yvaucher@ucsd.edu]  
Sent: Saturday, March 31, 2012 2:00 PM  
To: Archer, Stephanie (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu<mailto:wacarlo@uab.edu>); Finer, Neil; Myriam Peralta, M.D.  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

All,  
Re boilerplate: We can discuss revised title, authors on Friday.

Yvonne

---

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]  
Sent: Wednesday, March 28, 2012 1:15 PM  
To: Wally Carlo (wacarlo@uab.edu<mailto:wacarlo@uab.edu>); Finer, Neil; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu<mailto:MPeralta@peds.uab.edu>); Vaucher, Yvonne  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Boilerplate | SUPPORT FU Combined paper

Attached is a combined author list and boilerplate for the new combined SUPPORT FU paper. The only center that had two different authors on each paper was Indiana (highlighted in yellow in the attachment). Need to decide whether to include both of them, or not, and make necessary adjustments to the author list and acknowledgements (at the moment I have them listed in both).

Stephanie

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "vkumar3@buffalo.edu"; "nfiner@ucsd.edu"; "lnogee@jhmi.edu"  
**Subject:** RE: PAS plenary  
**Date:** Monday, April 09, 2012 11:07:00 AM  
**Attachments:** PAS 2012 oxygen talk.ppt

---

Hi

Here is my preliminary draft talk - DO NOT Disseminate as I need NICHD Clearance

Thanks

Rose

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

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

From: vkumar3@buffalo.edu [mailto:vkumar3@buffalo.edu]  
Sent: Saturday, April 07, 2012 8:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; lnogee@jhmi.edu  
Subject: PAS plenary

Rosemary / Finer / Larry,

Attaching the program for the session.

Please go through the titles for the session The time allotted is 20 minutes per speaker I hope we will have a great session with all your help

Once we all submit in the next few days, we can first communicate by email and then may be by phone so that we all know what we are talking about. Please let me know if this needs to be handled differently. I have already sent this info to Ola;

Vasanth

# Oxygen and Infants: Gaps in Knowledge and Opportunities for Research

Rosemary D. Higgins, MD  
Pregnancy and Perinatology  
Branch, NICHD



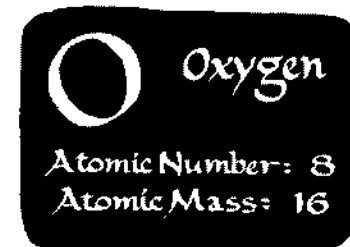
# **TOPICS TO BE COVERED**

- **Basic Science Gaps**
- **Translational Science Gaps**
- **Clinical Science Gaps**
- **Technology Needs**

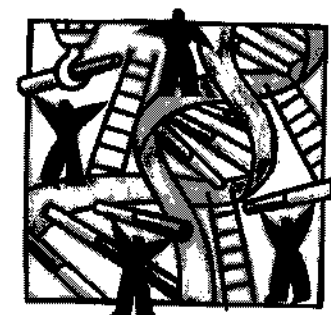
# Basic Science Gaps

- Hypoxia and hyperoxia tolerance
  - Biochemistry
  - Physiology
  - Genetic basis
- Hypoxia and hyperoxia susceptibility
  - Biochemistry
  - Physiology
  - Genetic basis

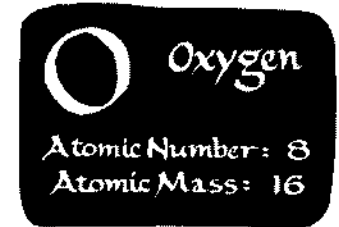
# Biologic Features of Oxygen



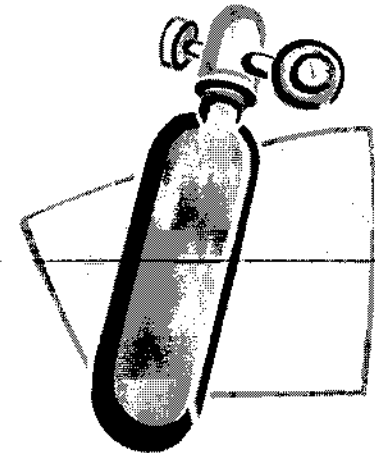
- Susceptibility to injury
- Reactive oxygen species
  - DNA base modifications
  - Strand scission
  - Protein modification



# Biologic Features of Oxygen



- Newborn animals – more tolerant to hyperoxia than adult animals
- Premature infants – more vulnerable to oxygen toxicity
  - Decreased levels of anti-oxidant enzymes and vitamins
  - Decreased trace elements





# Basic Science Gaps

- Hypoxia and reperfusion injury
  - Biochemistry
  - Physiology
  - Genetic basis
- Oxidative stress injury
  - Changes in reactive oxygen species (ROS)
  - Organ specific effects

# Basic Science Gaps

- Role of antioxidants
- Sympathetic nervous system and interactions
- Effects of hypo-and hyper-capnea with hypoxia and hyperoxia

# TOPICS TO BE COVERED

- Basic Science Gaps
- **Translational Science Gaps**
- Clinical Science Gaps
- Technology Needs

# **Translational Science Gaps**

- Oxygen delivery to tissues
- Oxygen consumption by the tissues
- Measurement of oxygen at the tissue level

# Translational Science Gaps

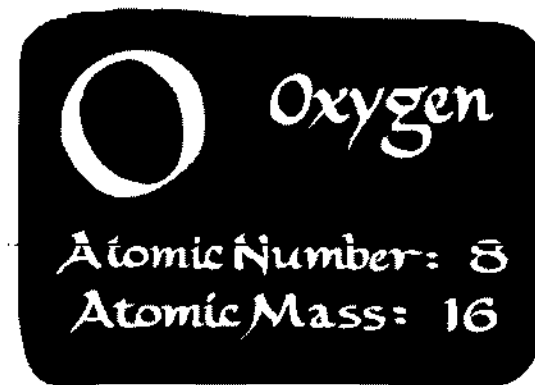
- Placenta function and effect on fetus
  - Normal physiology
  - Normal transport mechanisms
- Placental pathology and effect on fetus
  - Abnormal function
  - Outcomes

# TOPICS TO BE COVERED

- Basic Science Gaps
- Translational Science Gaps
- **Clinical Science Gaps**
- Technology Needs

# Oxygen and Clinical Applications

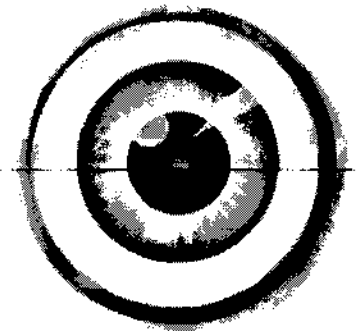
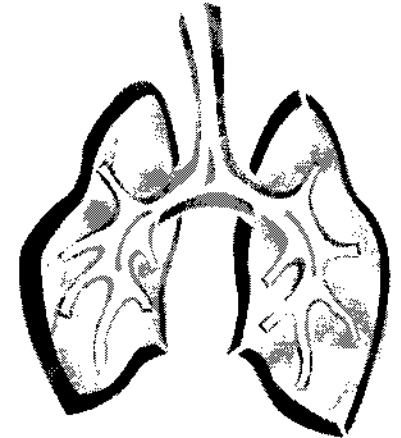
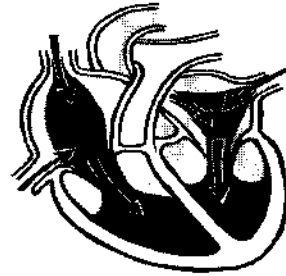
- Oxygen use is considered “routine” for infants
- Definition of “appropriate oxygenation” is NOT clear
- Hypoxia and hyperoxia can have deleterious effects



# Oxygen and Clinical Issues

- PPHN, ROP and BPD are impacted by oxygen

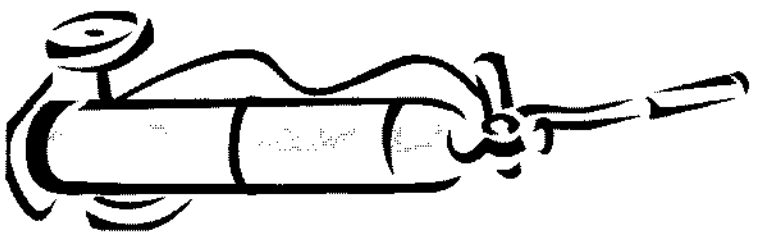
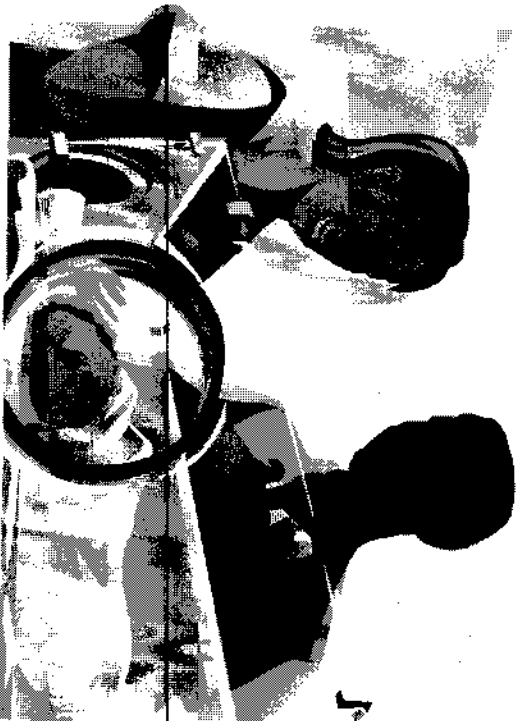
- Biology
- Excess and deficient oxygen
- Practical aspects of oxygen therapy





# Practical Aspects of Oxygen Therapy – Clinical Trials

- STOP ROP
- BOOST
- BOOST II
- BOOST II -UK
- COT
- BOOST NZ
- SUPPORT



# NeOProm: Neonatal Oxygenation Prospective Meta-analysis Collaboration

<b>Trial Acronym</b>	<b>Country</b>	<b>Start date</b>	<b>Recruitment complete</b>	<b>FU data complete</b>
SUPPORT	USA	April 2005	April 2009	April 2011
BOOST II	Australia	Mar 2006	Dec 2010	Dec 2012
BOOST NZ	New Zealand	Sept 2006	Dec 2009	Dec 2011
COT	Canada	Jan 2007	Jul 2010	Jul 2012
BOOST II- UK	UK	Sept 2007	Feb 2011	Feb 2012

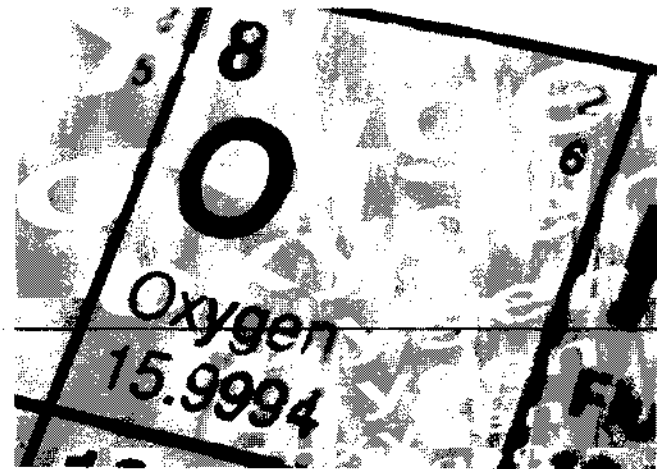
\*Askie LM et al BMC Ped 2011;11:6

# NeOProm

- Prospective meta analysis of oxygen saturation studies
- High saturation arm: 91-95% target range
- Low saturation arm: 85-89% target range
- N = 5000 infants
- Primary outcome – death or major disability at 18 - 24 months of age

# Resuscitation and Oxygen

- Oxygen use with resuscitation – longstanding practice
- High inspired oxygen use – now questioned



# Resuscitation and Oxygen



- PRO

- ILCOR 2006 recommendation pending evidence
- Cyanosis
- Long standing practice

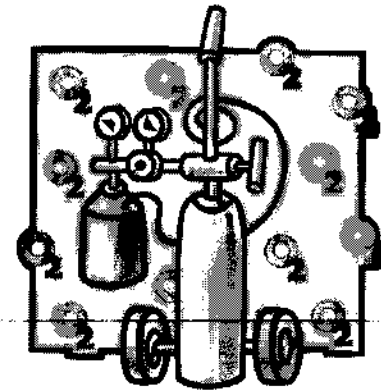
- CON

- Earlier spontaneous respiration
- Reduction in infant mortality
- Reduce oxidant injury
- Increased HR at 90 seconds
- Improved 5-min apgar score

**EXPERT PANEL RECOMMENDED NEED FOR EVIDENCE**

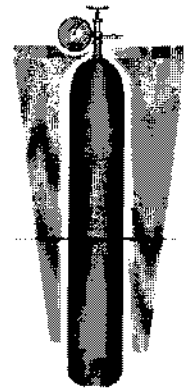
# Resuscitation and Oxygen - GAPS

- Oxygen delivery versus oxygen consumption
- Placental function and effect of labor on fetus



# Resuscitation and Oxygen - GAPS

- Should one use 100% oxygen for resuscitation? %
- What is the ideal amount of oxygen to use for resuscitation? %
- Should different oxygen amounts be used based on gestational age?



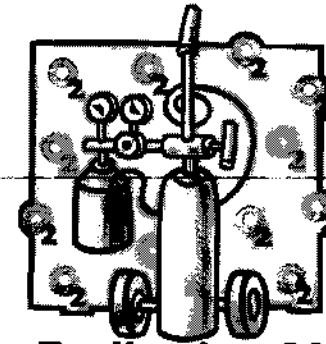
# Resuscitation and Oxygen - GAPS

- How should perinatal events be factored into oxygen use at delivery?
- What is the therapeutic range of inspired oxygen?
- What is the toxic range of inspired oxygen?
- What is the variability in the therapeutic and toxic ranges of inspired oxygen?



# Resuscitation and Oxygen - GAPS

- What outcome variables should be used in designing studies for oxygen use during resuscitation?
  - Survival
  - Vision
  - Pulmonary outcome
  - Neurodevelopment
  - Growth
  - Days on oxygen



**Pediatrics 2007;119:790**

# **TOPICS TO BE COVERED**

- **Basic Science Gaps**
- **Translational Science Gaps**
- **Clinical Science Gaps**
- **Technology Needs**

# Technology Needs

- Measurement of oxygenation at the tissue level
- Feedback devices
  - Keep saturations constant or in a range
  - Oxygen delivery system with Pulse oximetry feedback

# **TOPICS TO BE COVERED**

- **Basic Science Gaps**
- **Translational Science Gaps**
- **Clinical Science Gaps**
- **Technology Needs**

# NICHD ROLE

- **The mission of the NICHD is to ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve their full potential for healthy and productive lives, free from disease or disability, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation.**

# NICHD ROLE

- Research to provide knowledge
- Research to provide evidence base
- Research to provide information for clinical practice



**From:** [Kennedy, Kathleen A](#)  
**To:** [Wrage, Lisa Ann \(wrage@rti.org\)](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [dale\\_phelps@urmc.rochester.edu](#)  
**Subject:** Updated ROP Secondary Manuscript  
**Date:** Tuesday, April 10, 2012 12:44:17 PM  
**Attachments:** [ROP Natural History Study Manuscript.doc](#)

---

I've incorporated the revised figures and comments that were made in preparation of the poster and I've added a draft of the Discussion section. There's still a little more work for Lisa that wasn't done before we finalized the poster. Once Lisa revises the figure and adds the requested data, and you've all given me any additional suggestions you have, I can revise this one more time and send it to the SUPPORT Subcommittee.

I haven't formatted this for any particular journal yet. Do you think Pediatrics would be the best choice?

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

## Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A Kennedy, Lisa A Wrage, Dale L Phelps, Rosemary D Higgins, Neil Finer, Waldemar Carlo, Roger Faix, Abbot Laptook, Kurt Schibler, Michelle Walsh, Brad Yoder, Abhik Das, Marie Gantz, Nancy Newman, Wade Rich

**Comment [KKA1]:** 2611 words excluding abstract and references

**Comment [KKA2]:** Rose, is there a rule about the order of these authors? I just took this from the list of subcommittee members

**Comment [KKA3]:** 256 words

### Abstract

**Introduction:** Timely detection of treatable retinopathy of prematurity (ROP) is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Methods:** This observational study used outcome data from the NICHD Network SUPPORT Trial. Severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome. Inborn infants 24 0/7 to 27 6/7 wks gestational age (GA) with consent prior to delivery were eligible. Examinations followed current screening recommendations.

**Results:** 1316 infants were enrolled. 997 of these infants had a definitive ROP outcome. 138 met criteria for severe ROP. 128/138 (93%) with severe ROP had sufficient data (no missing or delayed exams) to determine the age of onset of ROP. The postmenstrual age (PMA) at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 wks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer; 1.0% (7% of infants with severe ROP) reached severe ROP after discharge.

**Conclusions:** Our contemporary data support continued use of the 2006 guidelines. Some infants who are stable enough for back transfer or discharge home are still at risk to develop treatable ROP. A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.

### Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to achieve optimal outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>3</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age and chronological (postnatal) age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP have not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication. We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as soon as Type 1 ROP develops.

**Comment [KKA4]:** Last PubMed search of "ROP AND screening" was done on 2/7/12

**Comment [KKA5]:** Rose, Dale suggested trying to find a more recent reference. I can't see anything from the Network because the 2010 GDB paper reports outcomes by GA not BW. I think this might be the best reference to use if we want to use Network data and compare the CRYO-ROP/LIGHT-ROP era to something more recent. Let me know if you have a better suggestion.

**Comment [KKA6]:** "Chronological age" is what's suggested in the 2004 Pediatrics publication. I've now used that consistently in the manuscript.



In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This observational study was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27 <sup>6</sup>/<sub>7</sub> weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) to determine if the current ROP screening guidelines were appropriate to identify treatable Type 1 ROP in a contemporary cohort of infants.

### Methods

In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. Extensive ROP outcome data were prospectively collected for all enrolled infants. Inborn infants 24 <sup>0</sup>/<sub>7</sub> - 27 <sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began no later than 33 weeks postmenstrual age. The following data were recorded at each eye exam: the date of the eye exam, the highest stage and lowest zone of ROP, presence of plus disease, whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until study endpoint: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks postmenstrual age.

Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the chronological age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

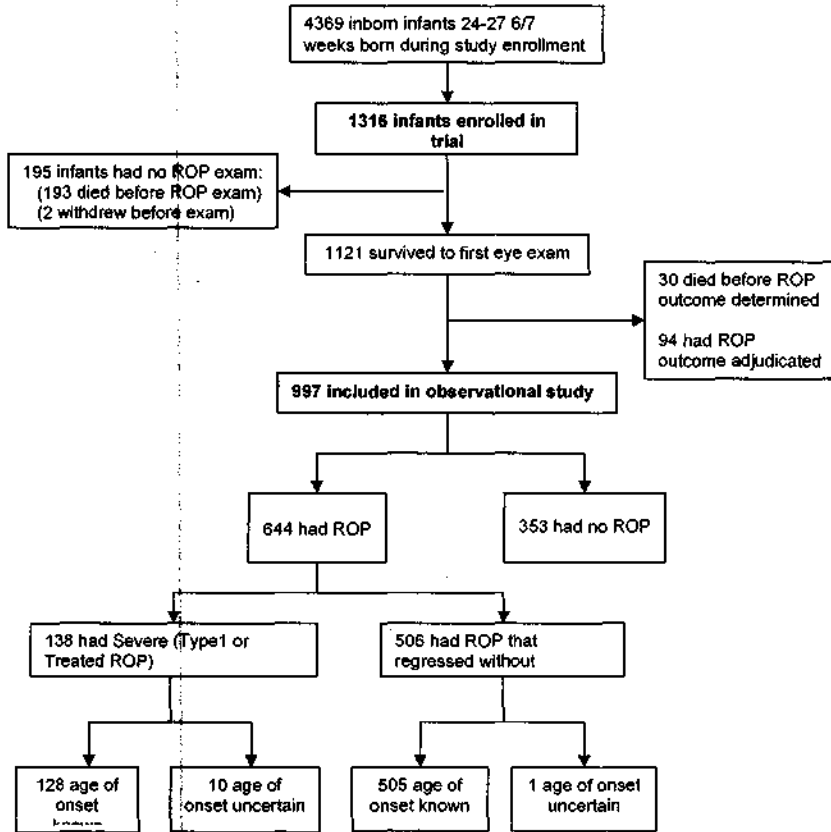
### Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009. See Figure 1. Among surviving infants, 915 (997/1091) had a definitive ROP outcome. Among infants with severe ROP, 93% (128/138) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

Figure 1. Flow diagram of patient enrollment

**Comment [KKA7]:** Lisa, is this the highest stage in the lowest zone, or the highest stage in any zone and the lost zone with any ROP?

**Comment [KKA8]:** The number who met GA inclusion criteria is still being reviewed. 4369 is based on SUPPORT and GDB data (need to verify that it's all inborn, not some outborns who had GDB data because they were enrolled in other trials). Main SUPPORT papers say that 3546 were assessed for eligibility and 3404 met GA criteria. We need to clarify this. May need to explain the discrepancy.



The baseline demographic characteristics of the infants are shown in Table 1.

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
n	1316	997	353	644	138

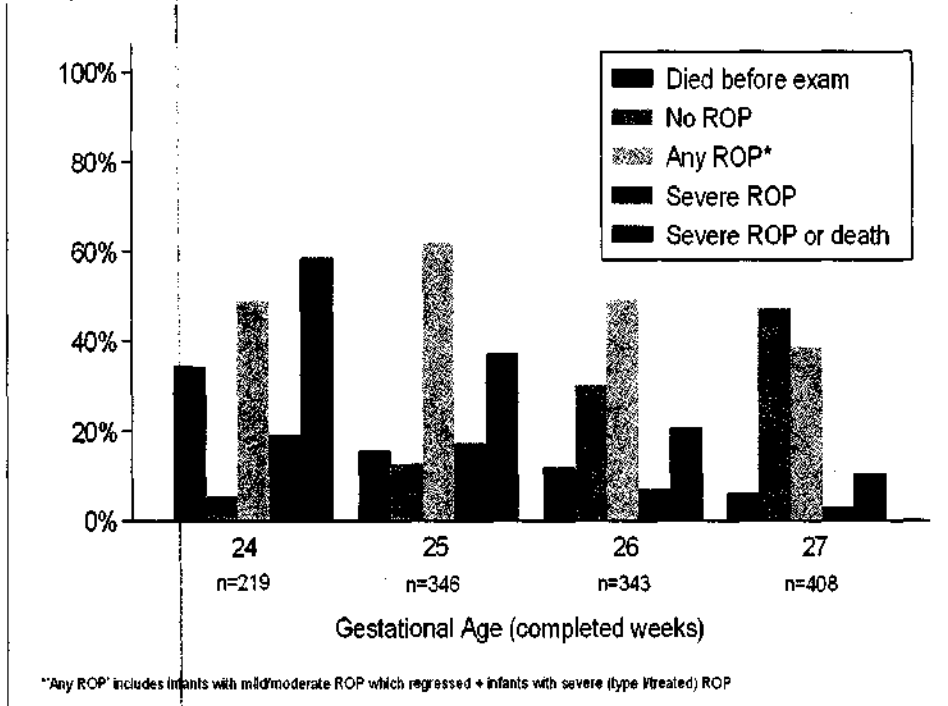
**Comment [KKA9]:** Dale asked about expressing the percents differently (eg risk of ROP among males vs females.) I'm not completely sure what we're trying to convey in this table as it's evolved. The first two columns convey the differences between all enrolled and those who survived to ROP determination. The last 3 columns convey the differences among the groups of infants who did and didn't have ROP. If we want to present the differences in risk by race, gender, ANS, we could do that in a set of figures, like Figure 2, that divides the cohort by these risk factors. I'm not sure that's wise since we really can't talk about incidence here because our cohort suffers from selection bias.

Gestational Age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth Weight [mean (SD)]	830 (193)	849 (190)	943 (173)	798 (179)	708 (148)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
Non-Hispanic White	521 (39.6)	398 (39.9)	125 (35.4)	273 (42.4)	61 (44.2)
Hispanic	259 (19.7)	190 (19.1)	69 (19.6)	121 (18.8)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (1.7)	29 (4.5)	7 (5.1)
Male [n (%)]	712 (54.1)	529 (53.1)	195 (55.2)	334 (51.9)	78 (56.5)
Antenatal Steroids [n (%)]	1265 (96.2)	955 (95.8)	340 (96.3)	615 (95.5)	135 (97.8)
Multiple Birth [n (%)]	337 (25.6)	253 (25.4)	91 (25.8)	162 (25.1)	41 (29.7)

\* Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type I/treated) ROP (n=138)

The risk of ROP by gestational age, in this cohort, is depicted in Figure 2.

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



Comment [KKA10]: From 4/4/ email

As expected, the likelihood of surviving without ROP increased with each increasing week of completed gestation at birth (Figure 2).

The incidence of previously reported risk factors for ROP are shown in Table 2.

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on Oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset Sepsis (+ culture) [n (%)]	76 (21.5)	250 (38.8)	77 (55.8)
Fungal Sepsis [n (%)]	2/352 (0.6)	23/641 (3.6)	8/137 (5.8)
Grade 3-4 Intraventricular Hemorrhage or Periventricular Leukomalacia [n (%)]	29 (8.2)	98/643 (15.2)	29 (21.0)
Proven Necrotizing Enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent Ductus Arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

<sup>1</sup>Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

Comment [KKA11]: Lisa, why are these denominators not the same?

Comment [KKA12]: Lisa, why are these denominators not the same?

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3.

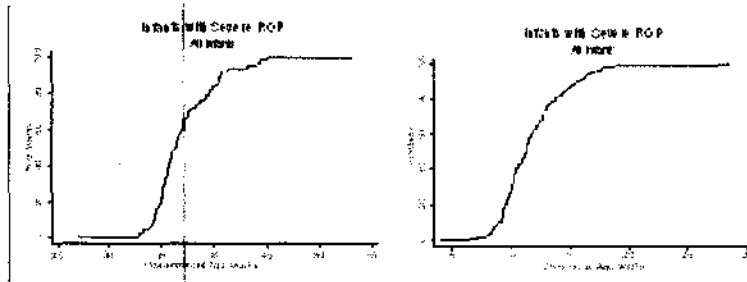
**Table 3. Postmenstrual and chronological age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Chronological Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	642	29.3	30.4	31.4	32.7	33.9	35.1	37.9	41.0	46.7	4.0	4.6	5.4	6.7	8.0	9.4	11.9	15.3	19.7
Type II ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type 1/Treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

<sup>2</sup> Type II ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease (includes 85 infants who had ROP which regressed and 73 infants who developed severe ROP)

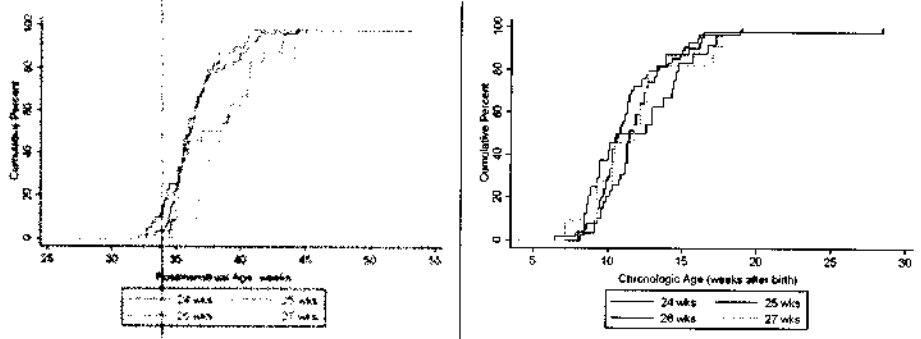
**Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



**Comment [KKA13]:** From 2/24 email. These were not updated for the poster. Lisa, for the manuscript, we'll need figures without the titles. Could we also label the axes as we've done for the other figures?

These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

**Figure 4. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**

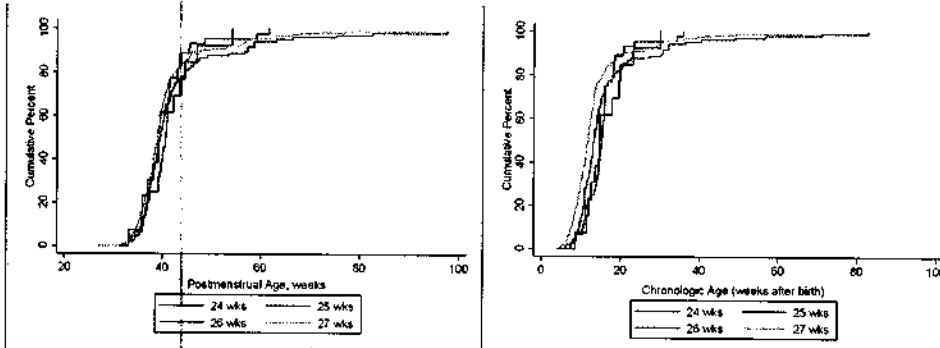


Comment [KKA14]: From 3/29 email

In contrast to prior studies,<sup>3,4</sup> our data did not show a clear inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. The age at which the retinal vessels became mature (to the ora ferrata or two consecutive exams with vessels in zone III) are shown in Figure 5 for infants with no ROP and for infants with mild or moderate ROP.

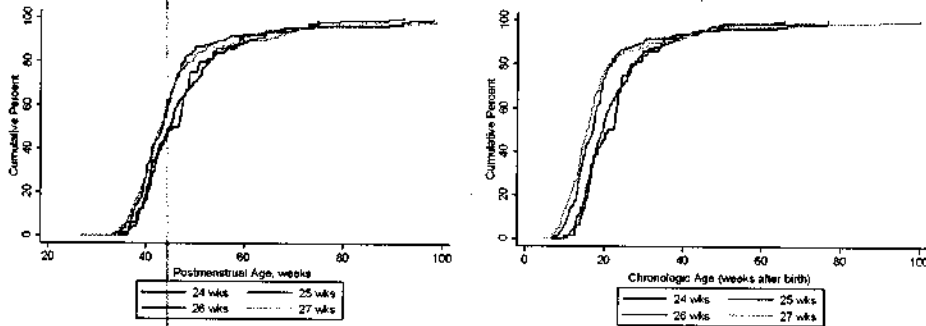
Figure 5. Postmenstrual and chronological age of mature vessels by gestational age at birth

No ROP



Comment [KKA15]: From 4/3 email

Mild/Moderate ROP



In general, retinal vessels matured several weeks later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

**Comment [KKA16]:** In the email discussion about the poster, it was suggested that these groups be compared for factors that might identify infants as high risk for post-discharge ROP. Factors that were suggested include GA at birth, BW, days on oxygen, PDA, early onset sepsis, late onset sepsis, Candida sepsis, IVH, NEC. If we can get this information, that would be great although I'm skeptical that we'll be able to come up with anything practical that can identify these infants with reasonable specificity.

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Conclusion**

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity NICU; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### Discussion

In prior ROP natural history studies,<sup>3</sup> less mature infants developed treatable ROP at a later chronological age than more mature infants, such that the incidence curves for each week of completed gestation overlapped when plotted by postmenstrual age. This relationship was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$ g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>11</sup> Although both the CRYO-ROP and SUPPORT studies used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT study relied more heavily on early ultrasound criteria. If the CRYO-ROP study more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>12</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA. This distinction is important because the current ROP screening guidelines allow for screening to begin at 31 weeks PMA even for infants 22-23 weeks gestation at birth; this could result in delayed diagnoses of treatable ROP if PMA is not the best predictor of onset in these infants. There are no large published studies to support or refute whether extrapolation of data from more mature infants is appropriate for these less mature infants.

We have not identified any other studies that have documented the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

**Comment [KKA17]:** This might need to be modified when we get some more information.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>13</sup> The SUPPORT Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at even higher risk of ROP.

Future studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>13</sup>

<sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of



- 
- premature infants for retinopathy of prematurity. *Pediatrics* 117: 572-576, 2006. Erratum (screen gestational age of 30 weeks or less) in: *Pediatrics* 118: 1324, 2006.
- <sup>2</sup> Jeffries A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 15: 667-674, 2010.
- <sup>3</sup> Palmer EA et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 98: 1628-1640, 1991.
- <sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 120: 1470-1476, 2002.
- <sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 81: 697-706, 1988 and *Arch Ophthalmol* 106: 471-479, 1988.
- <sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA et al. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 388: 1572-1576, 1998.
- <sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 196(2):147 e1-8, 2007.
- <sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 102: 233-250, 2004.
- <sup>9</sup> Early Treatment for Retinopathy of Prematurity Cooperative Group. Then incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 116: 15-23, 2005.
- <sup>10</sup> Austeng D, Kallen KBM, Hellstrom A et al. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 128: 1289-1294, 2010.
- <sup>11</sup> Phelps DL, Brown DR, Tung B et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less; *Pediatrics* 87: 7-17, 1991.
- <sup>12</sup> Donovan EF, Tyson JE, Ehrenkranz RA et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr* 135:147-152, 1999
- <sup>13</sup> Rich W, Finer NN, Gantz MG et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics* 129: 480-484, 2012.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT CPAP SLIDES PAS2012  
**Date:** Monday, April 09, 2012 9:00:00 AM  
**Attachments:** CPAPSUPPORT NRNFormatPAS2012\_0406NRNReview.pptx

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**From:** Vaucher, Yvonne [mailto:[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)]  
**Sent:** Friday, April 06, 2012 9:12 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Finer, Neil; Vaucher, Yvonne  
**Subject:** SUPPORT CPAP SLIDES PAS2012

Rose,

Here are the slides for PAS which were modified from the Hot Topics slides.

Myriam and I discussed the paper today and made it through to the discussion which we will finish on Monday.

Yvonne

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# NICHD NEONATAL RESEARCH NETWORK

...for the support study group  
...Neelam K. Vaidya and Waldemar C. Cabeler  
...for the support study group  
...for the support study group



This presentation will motivate a discussion of the use of off-label experimental or investigational use of a drug.

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# Primary Hypothalamic-Pituitary (PPAP) would increase survival with neuroprotection at 36 weeks post-menstrual age (PMA)

SUPPORT Study Group, NEJM 2019; 382:1420-9

NICHD

NEONATAL RESEARCH NETWORK

of death or BPD at 36 weeks PMA

of death or BPD in the composite primary outcome

of death or BPD in the composite primary outcome

of death or BPD in the composite primary outcome

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of death or BPD in the composite primary outcome

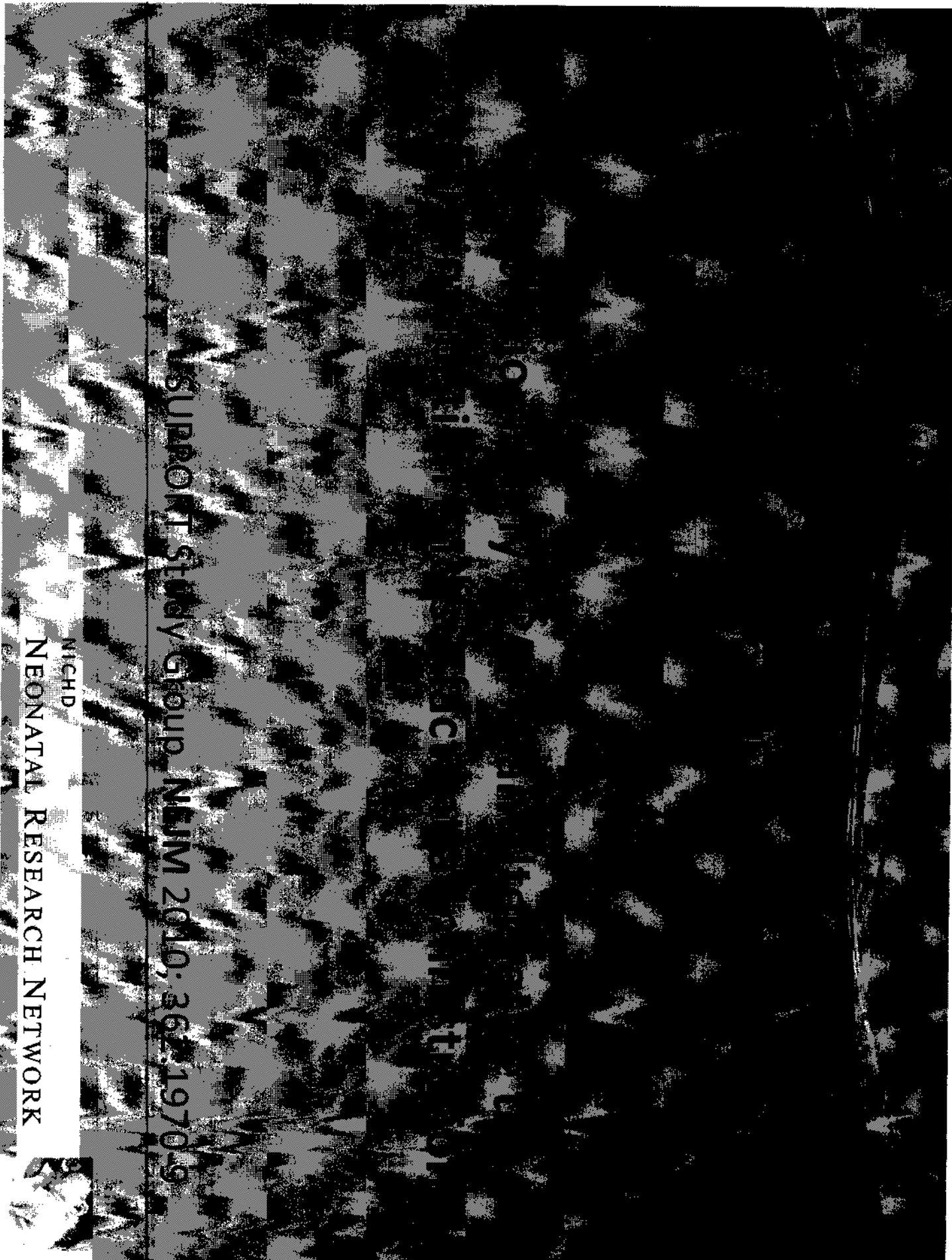
of death or BPD in the composite primary outcome

SUPPORT Study Group: NEMZ010; 3621970-9

NICHD

NEONATAL RESEARCH NETWORK





SUPPORT STUDY GROUP NEJM 2010; 362:1970-9

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Original study powered to detect a 10% absolute difference in death or NDI at 18-22 months corrected age

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- **Parental questionnaires**
- **Medical history**
- **Gross Motor Function Classification System (GMFCS)**
- **Amalgam Tissue Reaction Examination**

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...from some ... on ...

...rate ... ( ... )

Blind in both eyes (vision < 20/200)

• Hearing impairment with or without amplification

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adjusted  $p < 0.05$

estimating a quadratic model; adjusted means and 95% CI for continuous variables were estimated using linear mixed models.

Statistical significance was determined using a two-tailed test. All analyses were performed using SAS (SAS Institute Inc., Cary, NC).

	2007	2008
Multiples	27%	23%
Mothers married	47.7%	46.1%
Public Insurance	51.3%	53.7%
Maternal Education < 12th grade	25.3%	24.7%
English primary language	83.5%	84.3%

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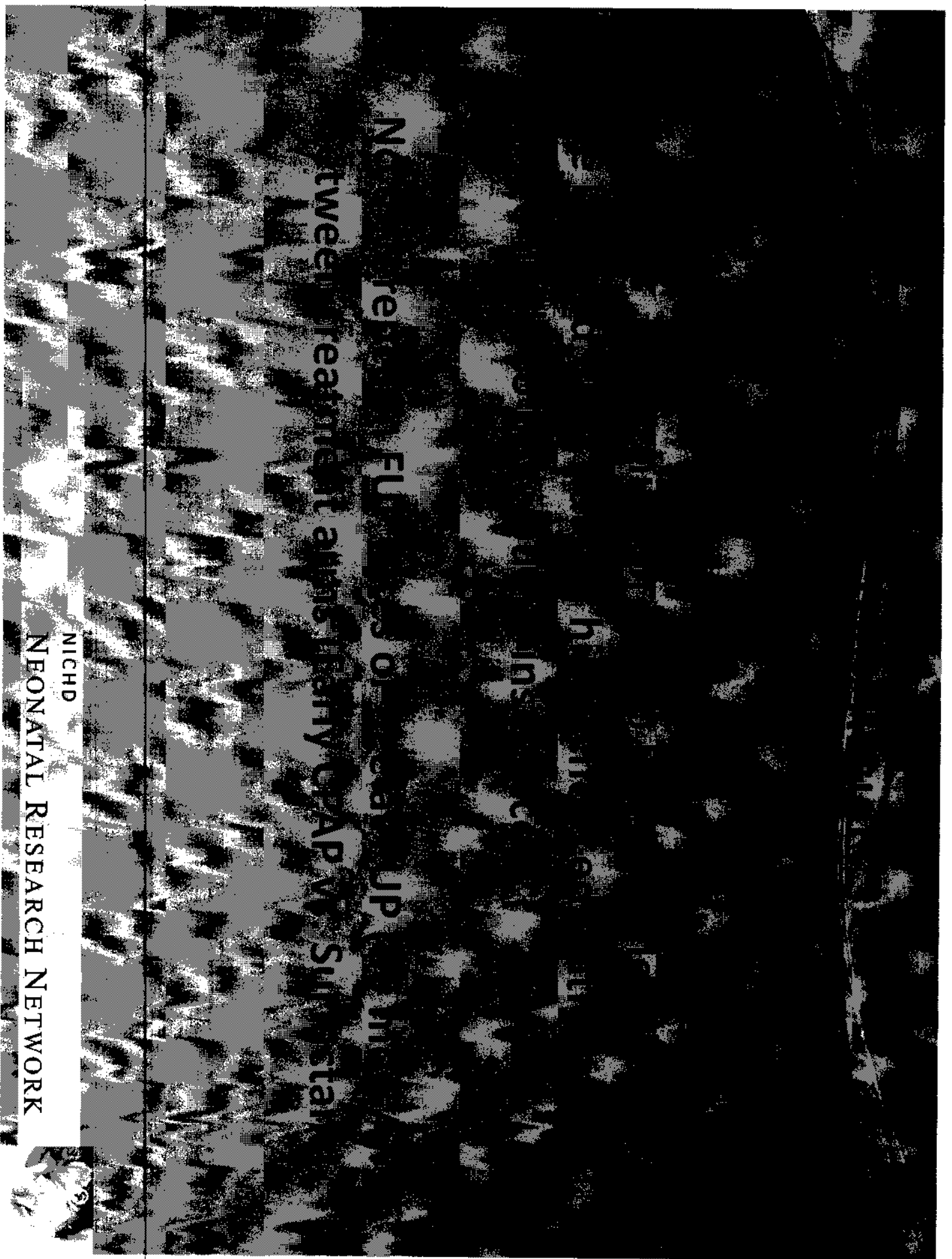
- Neonatal Stage
- Late gestation
- Postnatal steroids

11.8%      11.8%  
32.1%      32.2%  
6.7%      11.6%\*\*

p < 0.02;      p < 0.001

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Reported composite outcome (Death or ND) determined for 93.8% (1234/1316)

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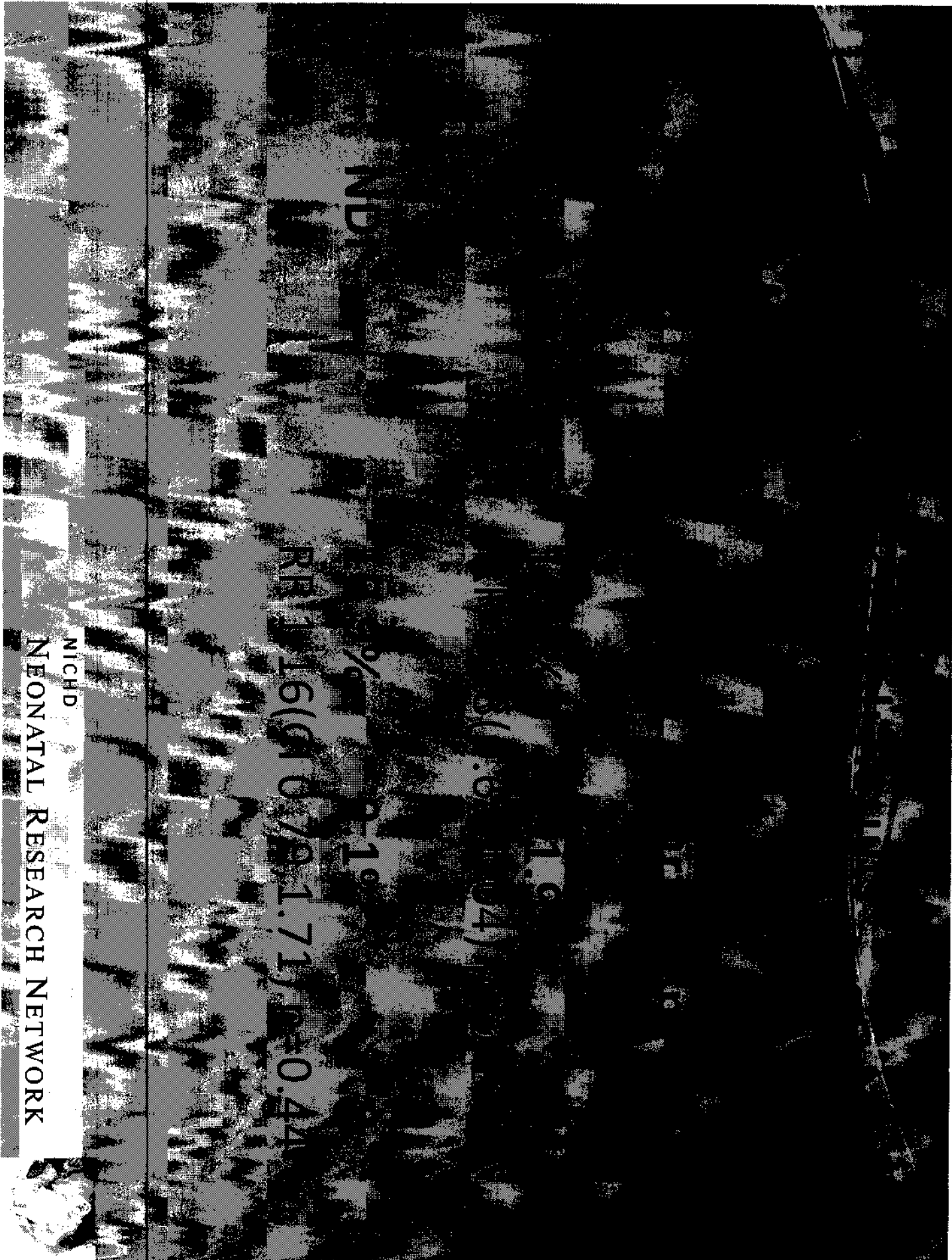


RR 0.93 (95% CI 0.78, 1.1)  $\rho=0.38$

2V. ...

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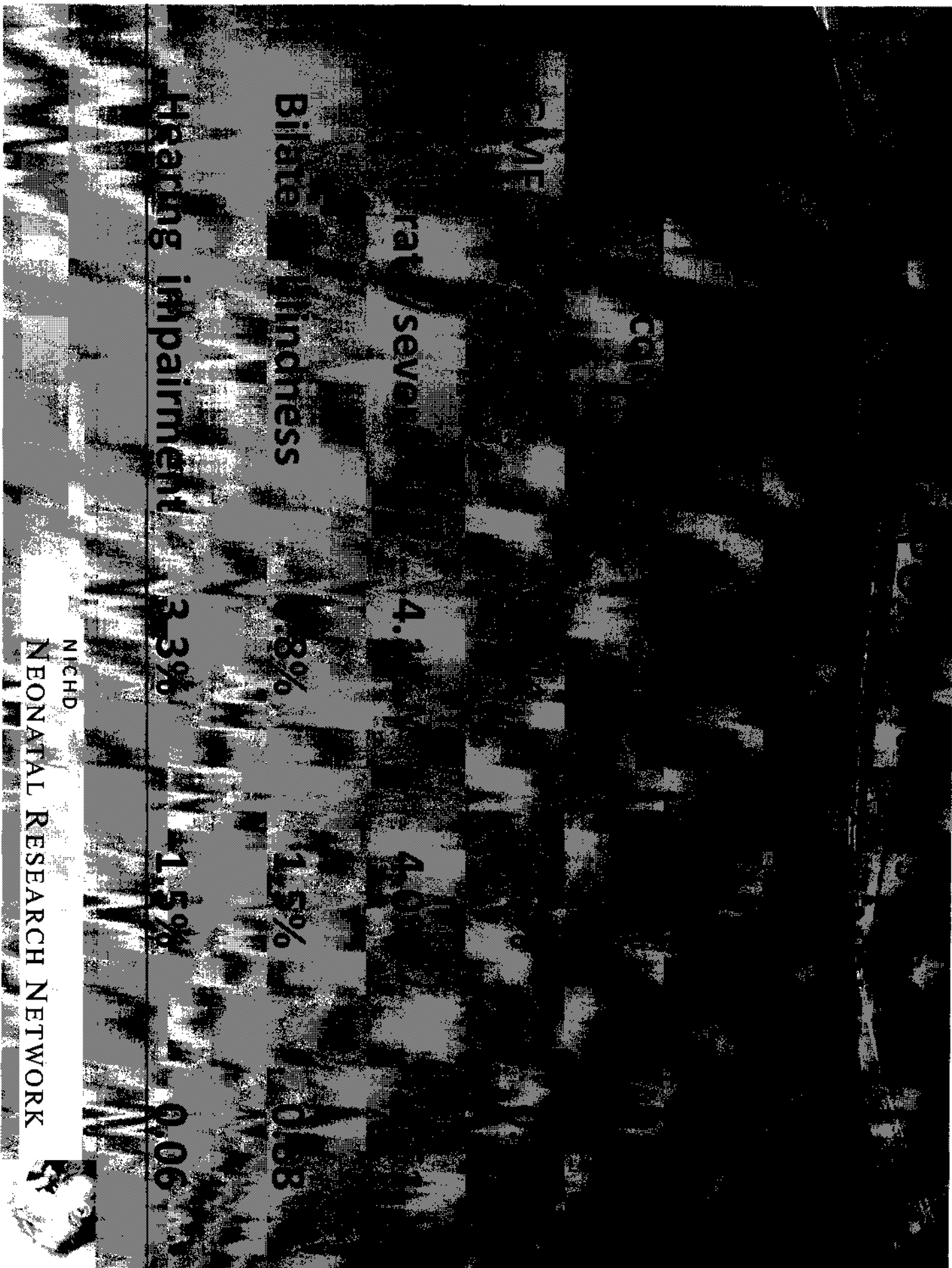
MD

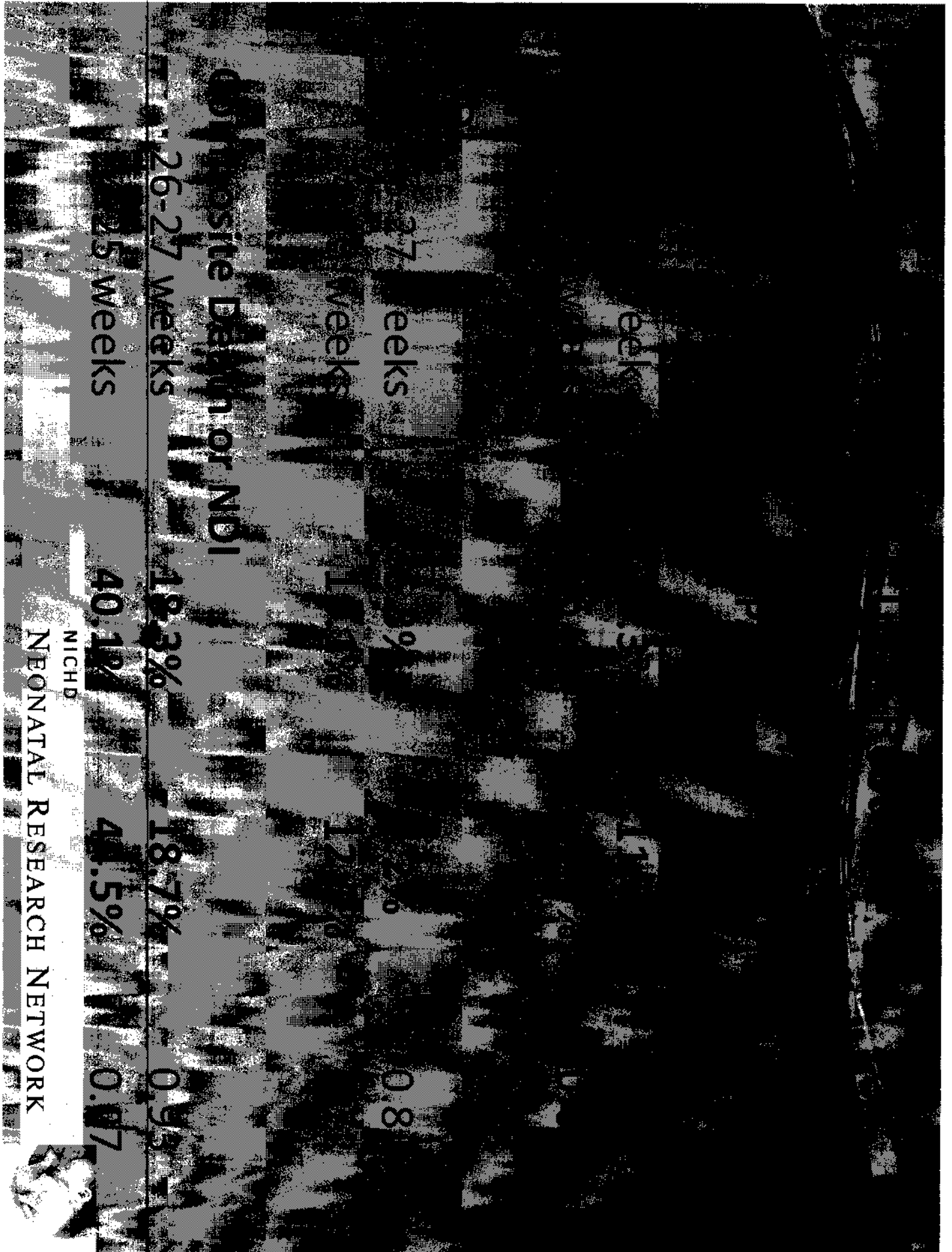
PRN 16(910791.71)R=0.44

8(0.6.104)

19

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- Large, multi-center, multi-site, multi-national, multi-disciplinary research network
- Comprehensive, standardized follow-up assessment
- Excellent follow-up rate

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● Study not powered for individual low birth weight outcomes

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Early... alternative respiratory strategy in extremely premature infants born at 24-27 weeks gestation

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- University of California - San Diego
- University of Alabama at Birmingham
- Tufts Medical Center

- Wake Forest University
- Wayne State University
- Yale University

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Oxygen trial PAS presentation 2012.pptx  
**Date:** Friday, April 06, 2012 3:54:00 PM  
**Attachments:** [Oxygen trial PAS presentation 2012.pptx](#)

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---

**From:** Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]  
**Sent:** Friday, April 06, 2012 3:51 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Oxygen trial PAS presentation 2012.pptx

Here is the PAS slides, thank you





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# Neurodevelopmental Outcome of Extremely Preterm Infants in the SUPPORT trial: Pulse Oximetry Trial

Myriam Peralta-Carcelen; Yvonne E. Vaucher;  
Neil N. Finer; and Waldemar A. Carlo;  
for the SUPPORT Study Group  
of the NICHD Neonatal Research Network



# Disclosures

Myriam Peralta-Carcelen

Dr. Peralta-Carcelen has no financial relationships to disclose or Conflicts of Interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

This presentation will not involve discussion of unapproved or off-label, experimental or investigational use of a drug.

RESEARCH NETWORK



# Background

Oxygen supplementation is vital therapy for survival in many preterm infants with respiratory disorders

However, oxygen supplementation may increase risk of retinopathy of prematurity and BPD

There have been concerns that a restrictive oxygen practice can increase mortality and neurodevelopmental impairment



# SUPPORT trial: Design

1316 – 24 to 27 weeks GA infants

Randomized to lower oxygen saturation target group

85-89% vs. higher oxygen saturation target group 91-95%

Targets initiated within 2 hours after birth and continued up to 36 weeks postmenstrual age as long as oxygen supplementation or respiratory support was administered

SUPPORT study group NEJM 2010; 362: 1959-1969

RESEARCH NETWORK



# SUPPORT trial: Design

1316 Underwent randomization

654 were assigned to SpO<sub>2</sub> 85-89%

662 were assigned to SpO<sub>2</sub> of 91-95%

336 were assigned to early CPAP

318 were assigned to early surfactant

327 were assigned to early CPAP

335 were assigned to early surfactant

SUPPORT study group NEJM 2010; 362: 1959-1969

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# SUPPORT trial: Results

Severe retinopathy of prematurity (ROP) or death did not differ significantly between the two groups

However death before discharge was higher in the lower oxygen saturation target group (19.9% vs. 16.2 %, RR 1.27 95% CI, 1.01 to 1.60; P=0.04 )

Severe ROP among survivors to discharge was reduced in the lower oxygen saturation target group (8.6% vs. 17.9% RR 0.52; 95% CI 0.37 to 0.73; P<0.001)

SUPPORT study group NEJM 2010; 362: 1959-1969

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# Hypothesis for Follow Up phase

The composite outcome of death or neurodevelopmental impairment will be decreased in the lower oxygen saturation target group compared to the higher oxygen saturation target group at 18 to 22 months corrected age.

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# Assessments at 18-22 months

Masked neurodevelopmental examiners, certified yearly

Bayley Scales of Infant and Toddler Development 3<sup>rd</sup> edition: Cognitive Composite Score

Modified Gross Motor Function Classification System (GMFCS)

Neurologic examination (Amiel Tison)

Standard questionnaires and medical history provided by parent or primary caregiver





# Definitions

Neurodevelopmental Impairment (NDI) defined  
as **any** of:

Bayley III cognitive composite score < 70

GMFCS  $\geq$  2

Moderate to Severe Cerebral Palsy (CP)

Hearing impairment

Bilateral visual impairment (<20/200)



# Outcomes

Primary: Death or NDI at 18 to 22 months corrected age

Other outcomes at 18 -22 m corrected age:

Death

NDI

CP

Blindness

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# Data collection and analysis

Data collected in standard forms transmitted to and analyzed by RTI International

## Analysis

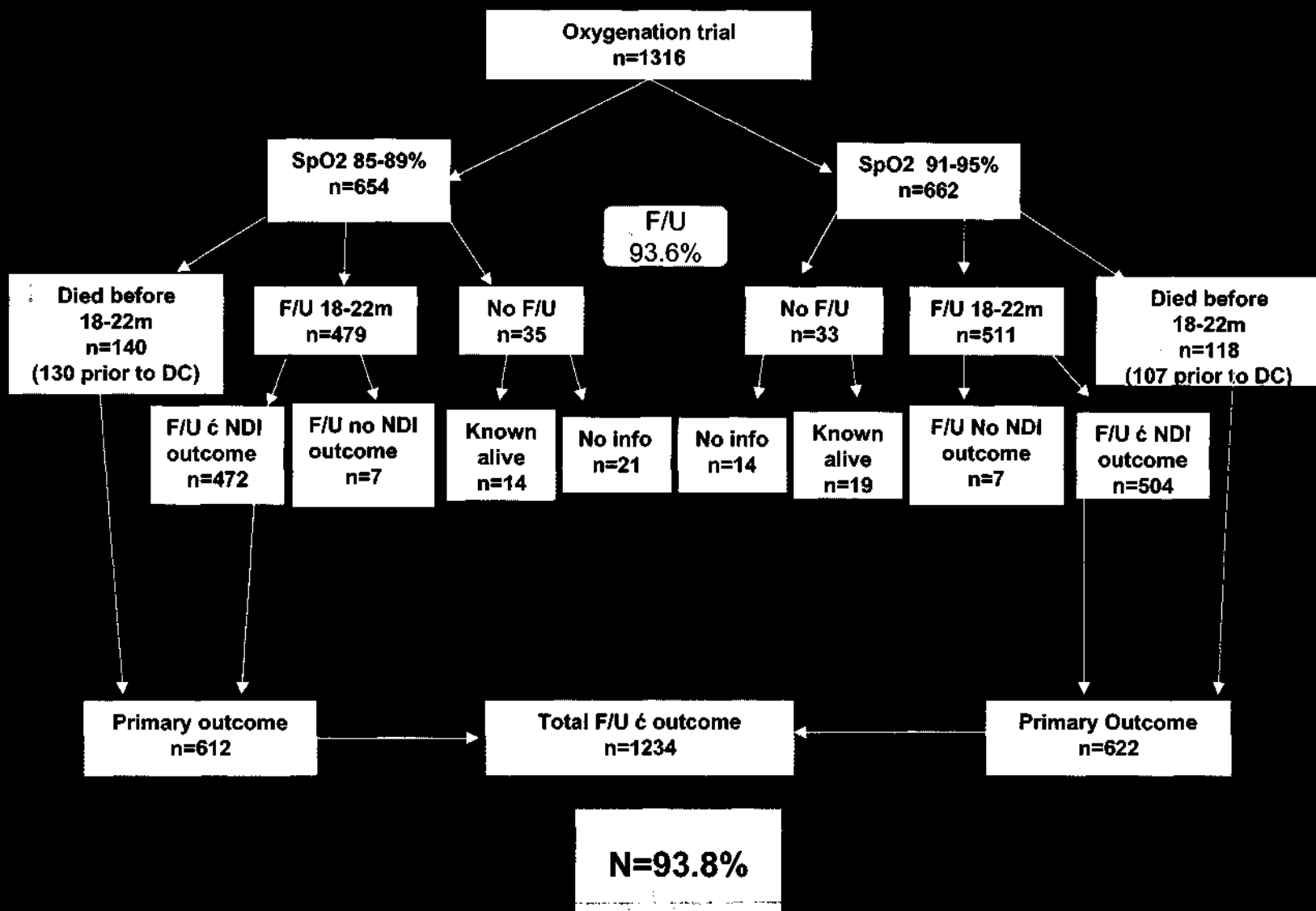
Intention to treat

Adjusted for GA stratum, center, familial clustering (multiples assigned to same group)

2 sided  $P < 0.05$  considered statistically significant

Adjusted relative risks and 95% CI for categorical variables were estimated using robust Poisson regression in a generalized-estimating-equation model; adjusted means and 95% CI for continuous variables were estimated using linear mixed models





# Baseline infant characteristics

Characteristic	Trial Cohort		Cohort with FU visit	
	85-89% N=654	91-95% N=662	85-89% N=479	91-95% N=511
Birth weight - g	835	825	858	844
Gestational age - wk	26	26	26	26
SGA – (%)	6.3	8.3	3.5*	7.4*
Male sex (%)	52.1	56.0	50.1	55.2
Race (%)				
Non hispanic black	39.3	35.0	42.0	34.4
Non hispanic white	37.0	42.1	37.2	42.7
Hispanic	20.2	19.2	18.0	19.0



# Baseline maternal characteristics

Characteristic	Trial Cohort		Cohort with FU visit	
	85-89% N=654	91-95% N=662	85-89% N=479	91-95% N=511
Maternal education < HS	24.9	27.0	24.4	25.6
Public Health Insurance	54.8	52.7	52.8	52.1
Mother married	43.6	46.6	46.3	47.6
Antenatal steroids	96.8	95.6	96.5	95.3
Cesarean section	67.4	66.8	69.3	65.6
Multiple births	24.6	26.6	25.9	25.0

NATIONAL RESEARCH NETWORK



# Perinatal characteristics

Characteristic	Trial Cohort		Cohort with FU visit	
	85-89% N=654	91-95% N=662	85-89% N=479	91-95% N=511
CPAP (%)	51.4	49.4	53.0	50.3
Surfactant (%)	48.6	50.6	47.0	49.7
Postnatal steroids (%)	9.6	10.7	8.6	9.5
BPD (%)	38.0	41.7	37.0	39.7
Severe ROP (%)	8.6*	17.9*	8.6*	17.4*
IWH grade 3 or 4 or PVL	15.6	15.6	11.7	11.8
NEC	11.9	10.8	8.8	8.6
LO sepsis/meningitis	36.5	35.6	32.4	32.5



# Primary Outcomes at 18-22 months corrected age

Outcome (%)	85-89% N=654	91-95% N=662	Adjusted RR	P-value
Outcome determined	93.6	94.0	1.0 (0.97, 1.03)	0.79
NDI or Death	30.2	27.5	1.12 (0.94, 1.32)	0.21
Died by 18-22 mo	22.1	18.2	1.25 (1, 1.55)	0.046

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# Outcomes of Survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
NDI	9.5	10.5	0.87(0.6, 1.28)	0.49
Bayley III cognitive < 70	7.2	7.6	0.91(0.58, 1.43)	0.69
GMFCS $\geq 2$	5.4	4.5	1.17(0.68, 2.01)	0.56
Mod/severe CP	4.2	3.9	1.0 (0.54, 1.83)	0.99
Blindness	1.1	1.2	0.9 (0.28, 2.9)	0.86
Deafness	2.5	2.3	1.16 (0.54, 2.49)	0.70

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# Bayley III cognitive composite scores among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
<b>Bayley III</b>				
Cognitive composite<70	7.2	7.6	0.91(0.58, 1.43)	0.69
Cognitive composite<85	22.3	26.2	0.85(0.68, 1.07)	0.16
Adjusted means	92.2 $\pm$ 0.8	90.5 $\pm$ 0.7	0.70(-1.2, 2.5)	0.48
Cognitive composite				
Median cognitive composite scores	90 (85, 100)	90 (80, 100)		



# Neurological Findings among survivors at 18-22 months corrected age

Outcome (%)	85-89%		91-95%		Adjusted RR	P-value
	N=479	N=511				
Abnormal Neuro exam	22.5	22.3	1.02(0.82,1.28)	0.84		
Any CP	9	8.0	1.12(0.76,1.66)	0.57		
Mild CP vs. none	5	4.3	1.16(0.66,2.02)	0.61		
Mod CP vs. none	2.5	2.1	1.19(0.52,2.72)	0.68		
Severe CP vs. none	2	2.1	0.95(0.39,2.27)	0.90		

CONRAD RESEARCH NETWORK



# Eye findings among survivors at 18-22 m

Outcome (%)	85-89%		91-95%		Adjusted RR	P-value
	N=479	N=511				
Eye surgery	6.5	13.2	0.53(0.35,0.78)	0.002		
Strabismus	9.6	8	1.2(0.8,1.8)	0.38		
Nystagmus	4.6	2.5	1.81(0.89,3.69)	0.10		
Tracks 180 degrees	97.1	97.2	1.0 (0.98,1.02)	0.93		
Corrective lenses vs. normal	4.5	4.1	1.15(0.63,2.10)	0.65		
Blind some function vs. normal	0.7	0.4	1.57(0.27,8.96)	0.61		
Blind no function vs. normal	0.4	0.8	0.54(0.1,2.96)	0.48		
Other vision abnormality vs. normal	1.3	2.5	0.55(0.21,1.46)	0.23		



# Conclusions

There were no significant differences in the pre-specified composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age

Mortality remained higher in the lower target oxygenation group at 18 to 22 months corrected age (22.1% vs. 18.2%,  $P=0.046$ )

NDI was not significant between lower or higher target oxygenation groups.



# Conclusions

Although severe ROP was associated with higher oxygenation target levels, blindness and other eye findings at follow up was not significantly different between survivors at 18 to 22 months



# Neonatal Research Network Centers (2004-2009)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama at Birmingham
- University of California – San Diego
- University of Iowa
- University of Miami
- University of New Mexico
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center
- University of Utah
- Wake Forest University
- Wayne State University
- Yale University

NEONATAL RESEARCH NETWORK



# Thanks

RESEARCH NETWORK





**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer.Stephanie@nih.gov)  
**Subject:** FW: PAS abstract deadline for presentations for NICHD CLEARANCE  
**Date:** Friday, April 06, 2012 2:41:00 PM  
**Attachments:** [SPR2012\\_growth\\_secondary\\_for\\_final\\_NRN\\_review0.pptx](#)

---

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](mailto:higginsr@mail.nih.gov)

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

From: Navarrete, Cristina [<mailto:CNavarrete@med.miami.edu>]  
Sent: Friday, April 06, 2012 1:59 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: PAS abstract deadline for presentations for NICHD CLEARANCE

Hi Dr. Higgins,

This is the latest version (modified after taking into consideration the subcommittee's suggestions). The slides seem a lot but upon practice, I can deliver it within 10min.

Thanks,  
Cristina

---

From: Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
Sent: Friday, March 23, 2012 4:55 PM  
To: 'Beau Batton'; 'Erika Fernandez'; [edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu); 'Susan Hintz'; 'James Wynn, M.D.'; 'Pappas, Athina'; Navarrete, Cristina; 'Kennedy, Kathleen A'; 'Betty Vohr'; 'Natarajan, Girija'; 'Andrea Duncan'; 'Shankaran, Seetha'; [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); 'Michael Cotten [[cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)]'; 'John Kelleher, M.D.'; 'Vaucher, Yvonne'; 'Myriam Peralta, M.D.'  
Cc: 'Michele Walsh'; 'Kristi Watterberg'; 'Krisa Van Meurs'; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); 'Shankaran, Seetha'; Duara, Shahnaz; 'D'Angio, Carl'; 'Wally Carlo, M.D.'; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Archer, Stephanie (NIH/NICHD) [E]; 'Abhik Das ([adas@rti.org](mailto:adas@rti.org))'  
Subject: RE: PAS abstract deadline for presentations for NICHD CLEARANCE

Hi

Just a reminder that presentations are due April 6 for NICHD clearance.

Please insure that all co-authors/subcommittee members have given their input prior to final submission for clearance.

Also- for each presentation, we want to tailor the last slide to acknowledge the NRN sites for which data was used in the individual study.

Stephanie can help you with this so please ask her for assistance.

Thanks for all the effort!!

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852

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301-496-5575

301-496-3790 (FAX)

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

Sent: Friday, March 09, 2012 10:08 AM

To: 'Beau Batton'; 'Erika Fernandez'; 'edward-bell@uiowa.edu'; 'Susan Hintz'; 'James Wynn, M.D.'; 'Pappas, Athina'; 'Navarrete, Cristina'; 'Kennedy, Kathleen A'; 'Betty Vohr'; 'Natarajan, Girija'; 'Andrea Duncan'; 'Shankaran, Seetha'; 'dale\_phelps@urmc.rochester.edu'; 'Michael Cotten [cotte010@mc.duke.edu]'; 'John Kelleher, M.D.'; 'Vaucher, Yvonne'; 'Myriam Peralta, M.D.'

Cc: 'Michele Walsh'; 'Kristi Watterberg'; 'Krisa Van Meurs'; 'goldb008@mc.duke.edu'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'D'Angio, Carl'; 'Wally Carlo, M.D.'; 'nfiner@ucsd.edu'; Archer, Stephanie (NIH/NICHD) [E]; 'Abhik Das (adas@rti.org)'

Subject: RE: PAS abstract deadline for presentations for NICHD CLEARANCE

Importance: High

Hi

Just a reminder that presentations are due April 6 for NICHD clearance.

Please insure that all co-authors/subcommittee members have given their input prior to final submission for clearance.

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Stephanie can help you with this so please ask her for assistance.

Thanks for all the effort!!

Rose

Rosemary D. Higgins, MD

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301-496-5575

301-496-3790 (FAX)

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

Sent: Monday, February 13, 2012 4:00 PM

To: 'Beau Batton'; 'Erika Fernandez'; 'edward-bell@uiowa.edu'; 'Susan Hintz'; 'James Wynn, M.D.'; 'Pappas, Athina'; 'Navarrete, Cristina'; 'Kennedy, Kathleen A'; 'Betty Vohr'; 'Natarajan, Girija'; 'Andrea Duncan'; 'Shankaran, Seetha'; 'dale\_phelps@urmc.rochester.edu'; 'Michael Cotten [cotte010@mc.duke.edu]'; 'John Kelleher, M.D.'; 'Vaucher, Yvonne'; 'Myriam Peralta, M.D.'

Cc: 'Michele Walsh'; 'Kristi Watterberg'; 'Krisa Van Meurs'; 'goldb008@mc.duke.edu'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'D'Angio, Carl'; 'Wally Carlo, M.D.'; 'nfiner@ucsd.edu'; Archer, Stephanie (NIH/NICHD) [E]; 'Abhik Das (adas@rti.org)'

**Subject: PAS abstract deadline for presentations for NICHD CLEARANCE**

**Importance: High**

Hi,

Congratulations to all of you on your PAS presentations. Please note, we need the final presentations by APRIL 6 for NICHD Clearance.

Stephanie Archer will provide you with the appropriate templates. Let me know if there are any questions or issues with meeting the deadline for clearance.

Thanks

Rose

Rosemary D. Higgins, MD

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## Open Call for Proposals Rapid Response Grant

Cristina A. Navarin, PI, M.D., M.P.H., A. Wrager, Ph.D., S. Shalita, D.D.S., D.M.D., on behalf of the NICHD Neonatal Research Network, University of Miami, Miami, FL, RTI International, Durham, NC, NICHD, Rockville, MD



This presentation will not involve discussion of  
unapproved or off-label experimental or investigational  
use of a drug.

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- there is no information on the relationship of growth and differences in oxygen saturation from birth to

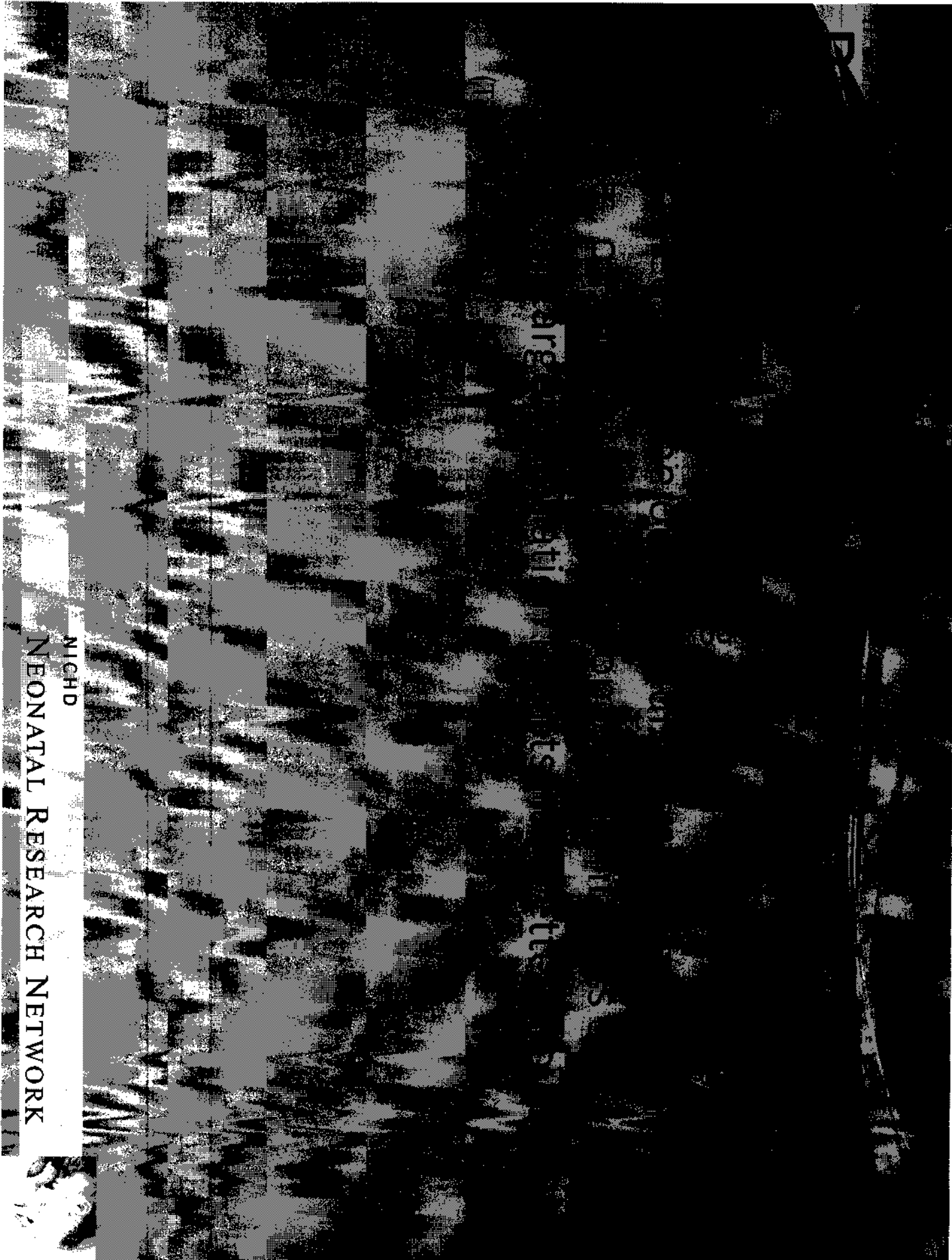
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saturation changes were made at 3 weeks (1991) when were still O<sub>2</sub> dependent. (Askie 2003)

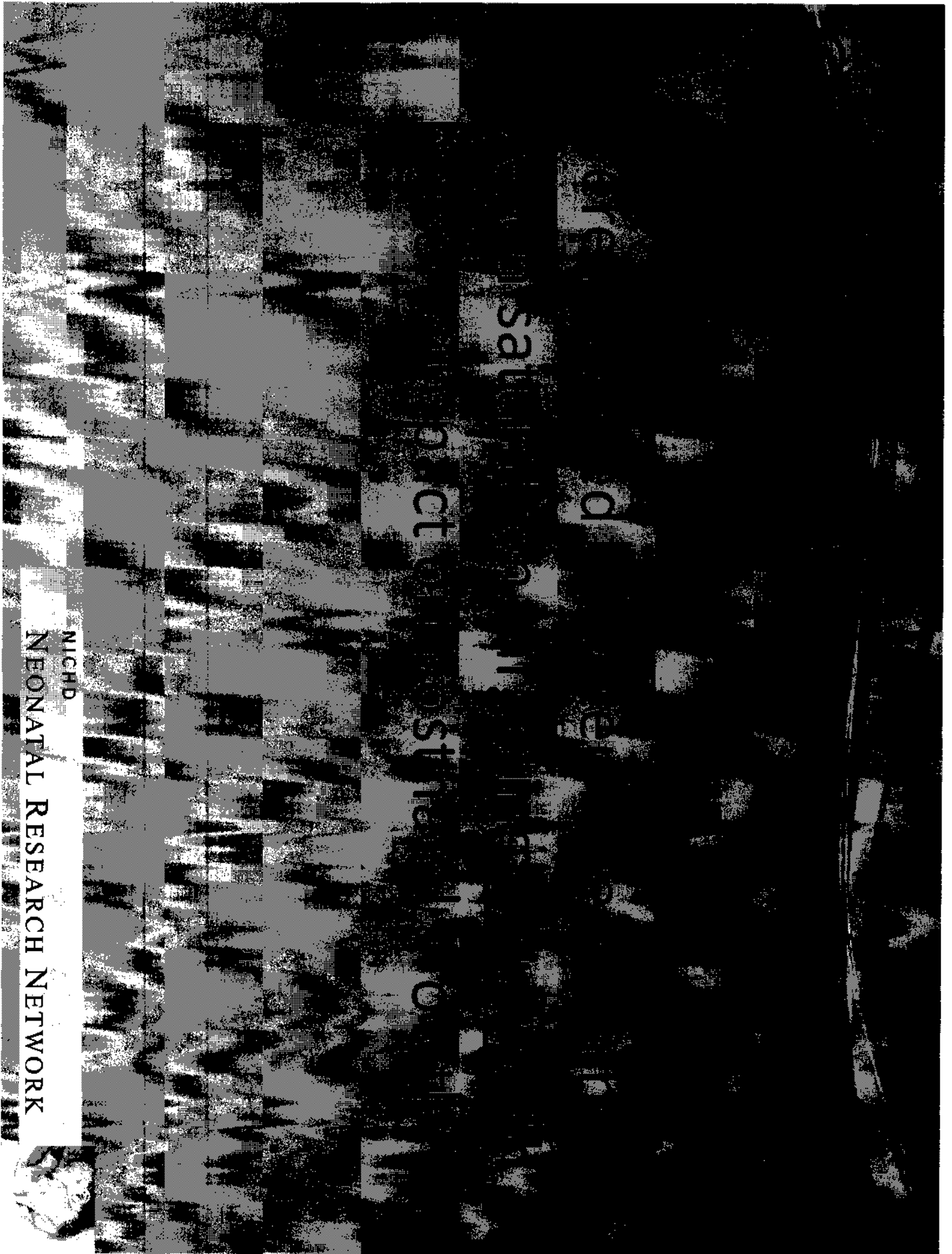
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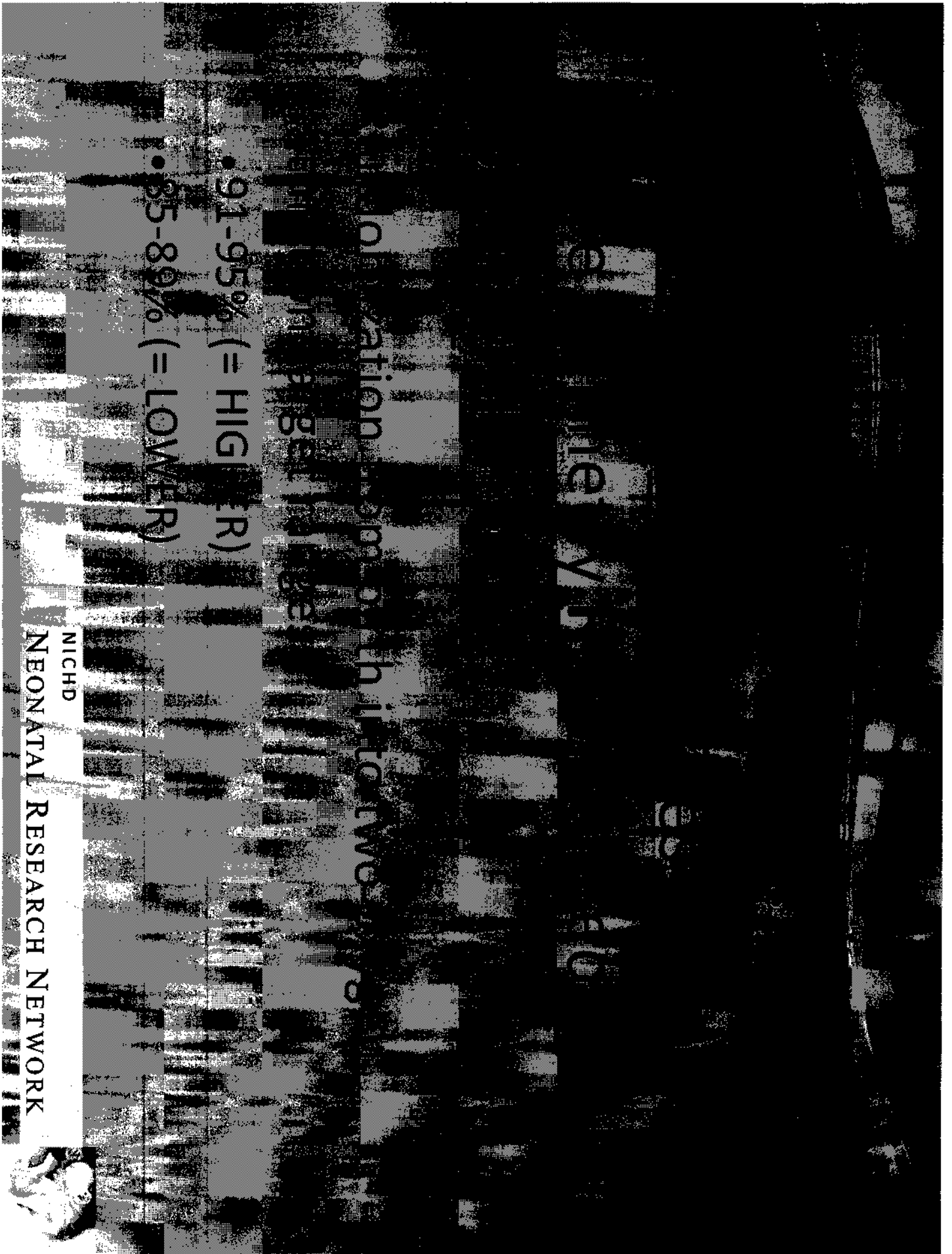
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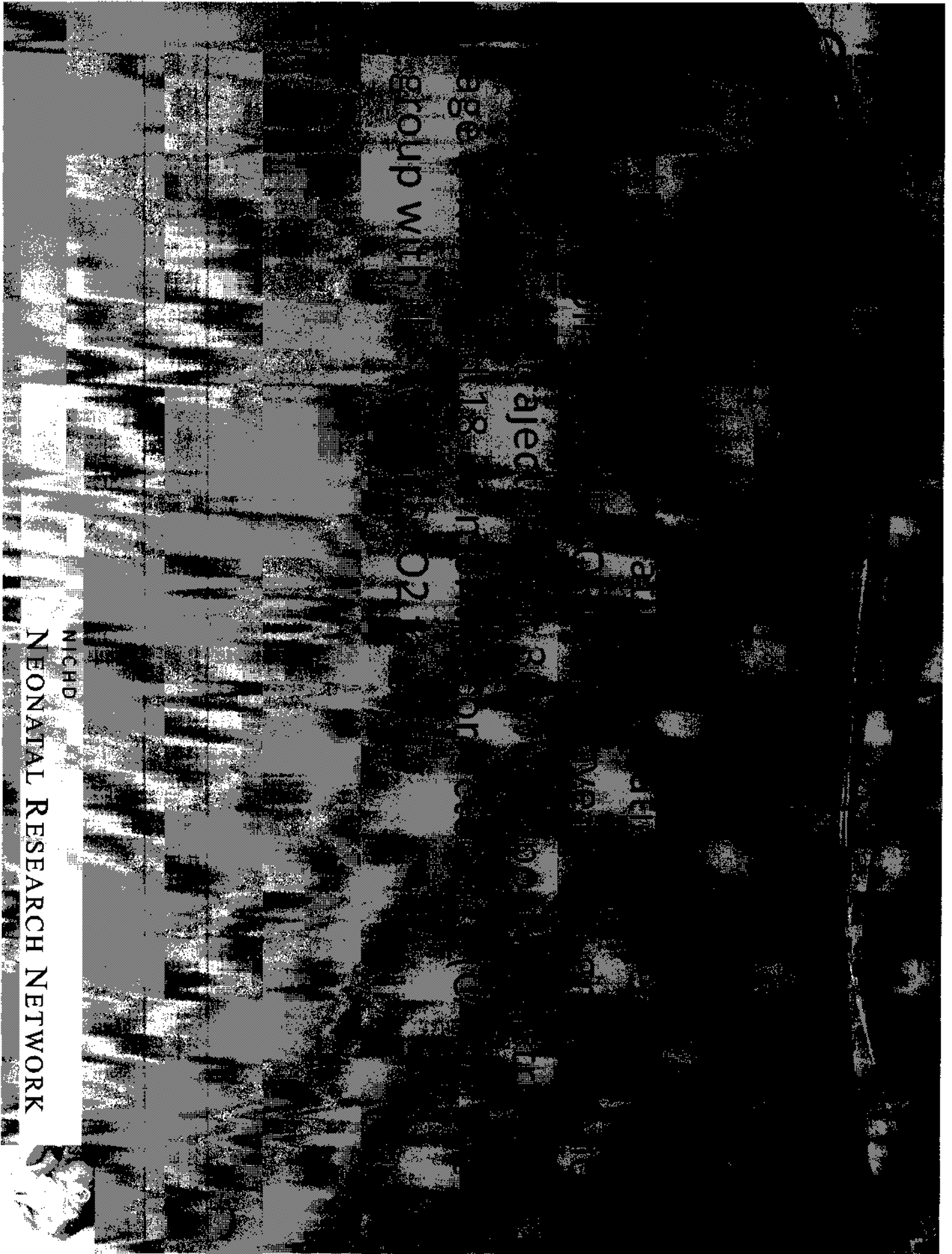
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- 91-95% (= HIGHER)
- 85-89% (= LOWER)

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...s made...  
...significantly altered pulse oximetry  
...Displayed saturation levels of 88 to 91% for both targets of  
...oxygen saturation

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ice B  
over in a uterine Growth Curves  
• 18-24 Month growth WHO 2006 Growth Curves

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adjusted for covariates, multiple birth clustering and SUPPORT stratification variables of GA group and center

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1316 underwent randomization in SUPPORT

506 not randomized to growth secondary study

810 with data available for growth analysis

402 were assigned to target saturation of 85-89%

333 survived to 36 weeks

296 returned at 18-22m

408 were assigned to target saturation of 91-95%

348 survived to 36 weeks

313 returned at 18-22m

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Characteristic	Lower Oxygen Saturation (n=402)	Higher Oxygen Saturation (n=408)
----------------	---------------------------------	----------------------------------

Gestational age, weeks *	26.2 ± 1.1	26.2 ± 1.1
% Male	53	58
Birth weight, g	839 ± 186	840 ± 191
Birth weight < 10th %ile	10.0	13.0
HC at birth, cm	23.5 ± 1.8	23.6 ± 1.9
HC at birth < 10th %ile	10.4	13.3
Length at birth, cm	33.4 ± 2.9	33.3 ± 2.9
Length at birth <10th %ile	12.6	14.3

means ± SD, p < 0.05 for all comparisons

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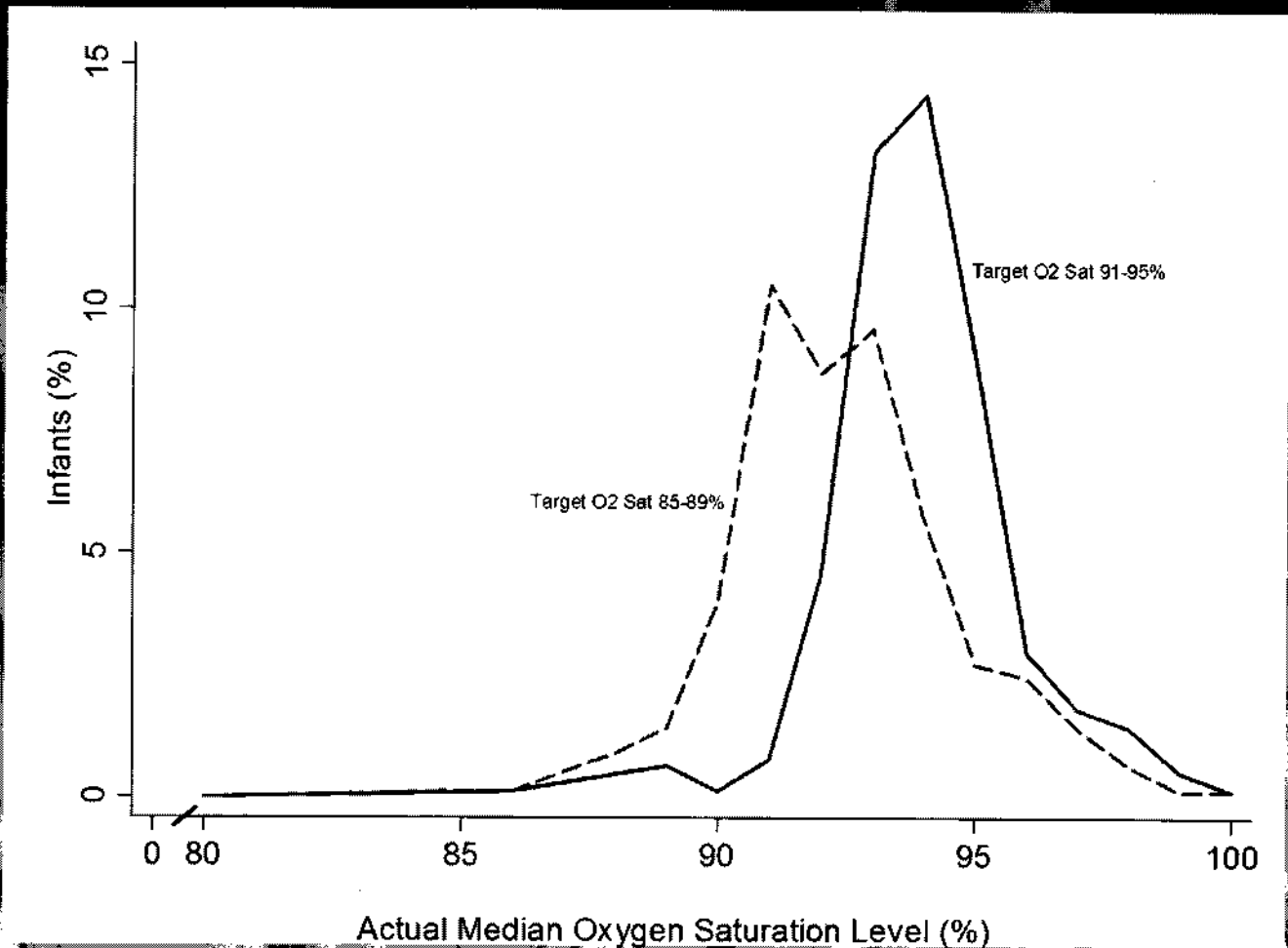
Characteristic	Lower Oxygen Saturation (n=402)	Higher Oxygen Saturation (n=408)	p-value <sup>1</sup>
% Death by 36 weeks PMA	17.2	14.7	0.32
Median days on supplemental O <sub>2</sub> (IQR)	47 (20-80)	60 (30-90)	<0.01*
Median SpO <sub>2</sub> while on supplemental O <sub>2</sub> (IQR)	92 (91-94)	94 (93-95)	<0.0001*

Note: Excludes cases of ICD, post-natal steroid use, NEC, IVH/PVL, PDA, and bronchopulmonary dysplasia (BPD).  
<sup>1</sup>Adjusted for sex, gestational age, and ROP.

<sup>1</sup>Adjusted for covariates; unadjusted rank-sum test for median days on supplemental O<sub>2</sub> and SpO<sub>2</sub> while on supplemental O<sub>2</sub>.  
 \*p<0.05

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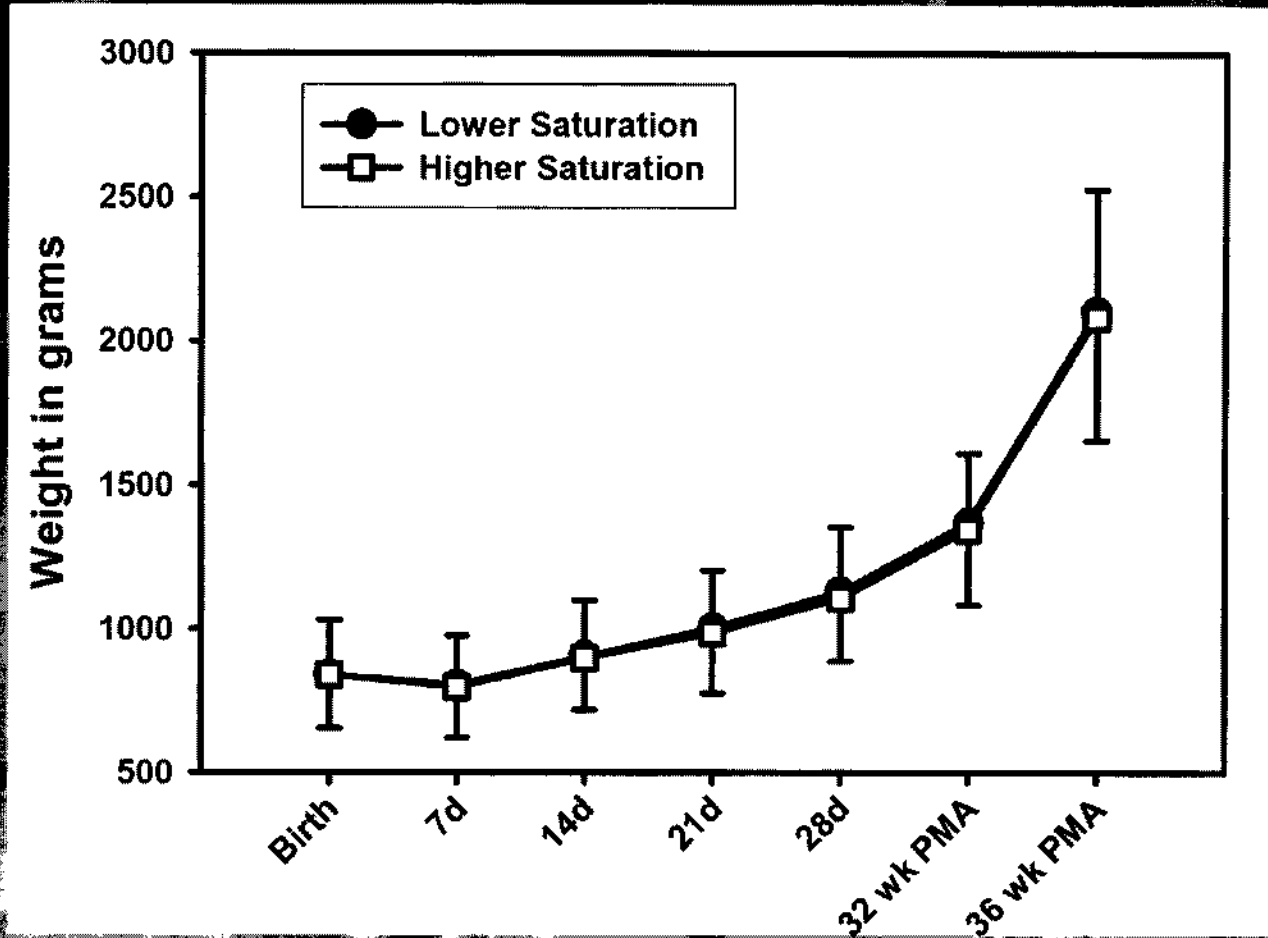
Total Energy Intake (parenteral + enteral) (kcal/kg/d)*	Lower O <sub>2</sub> Saturation (n=402)	Higher O <sub>2</sub> Saturation (n=408)	p-value**
Day 7	84 ± 25	82 ± 22	0.24
Day 14	92 ± 26	90 ± 25	0.57
Day 21	94 ± 38	93 ± 28	0.60
Day 28	97 ± 30	96 ± 29	0.67
32 weeks PMA	104 ± 30	105 ± 27	0.77
36 wks PMA	111 ± 36	108 ± 33	0.44
Age at first enteral feed, med (IQR)	4 (3-7)	4 (3-7.5)	0.38
Age at full enteral feeds, med (IQR)	23 (16-34)	24 (16-34)	0.76

\*means ± SD, full enteral feeds > 120 ml/kg/d

\*\*adjusted for covariates, unadjusted rank sum test for age at first enteral feed and age at first full enteral feed

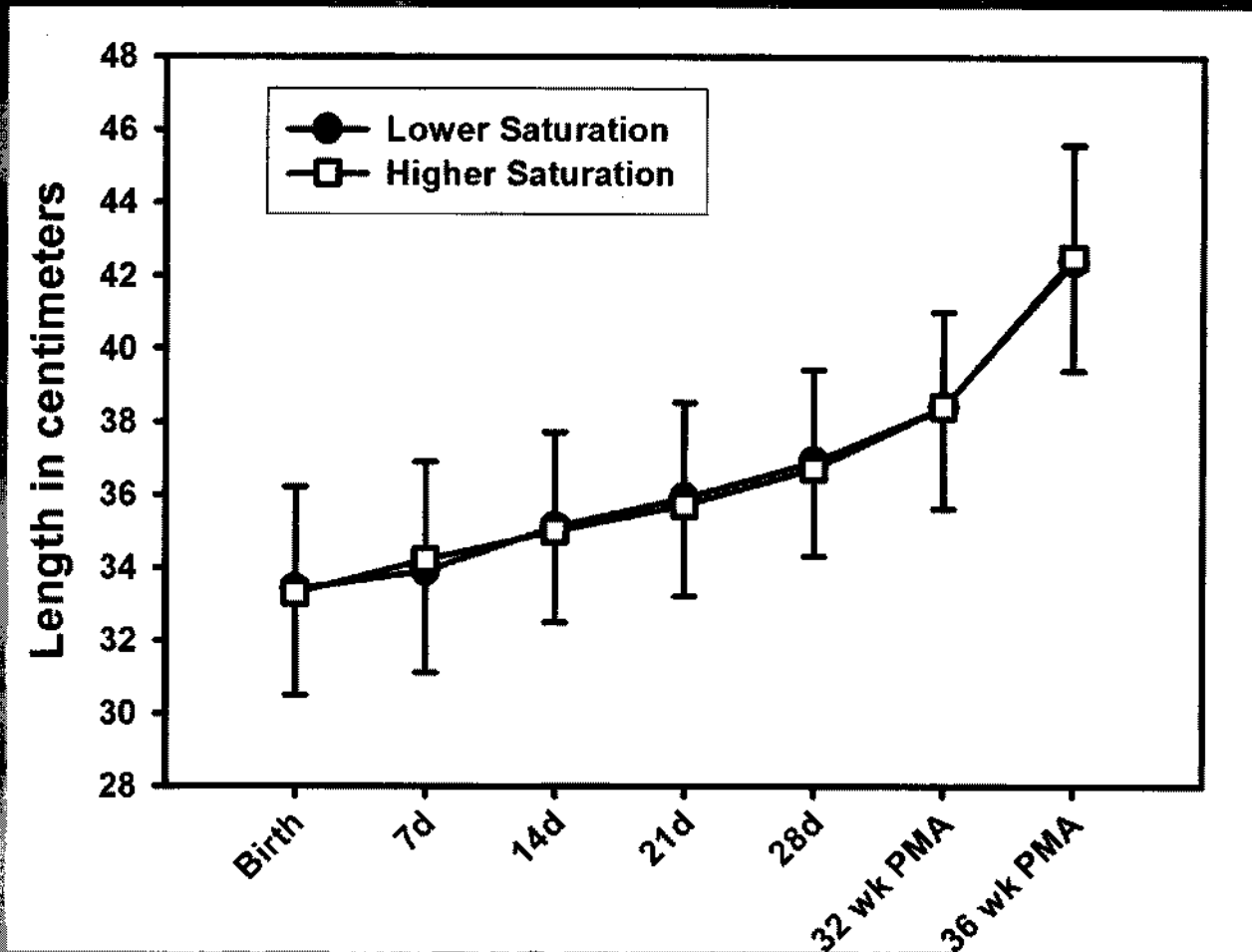
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Mean  $\pm$  SD

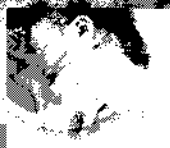
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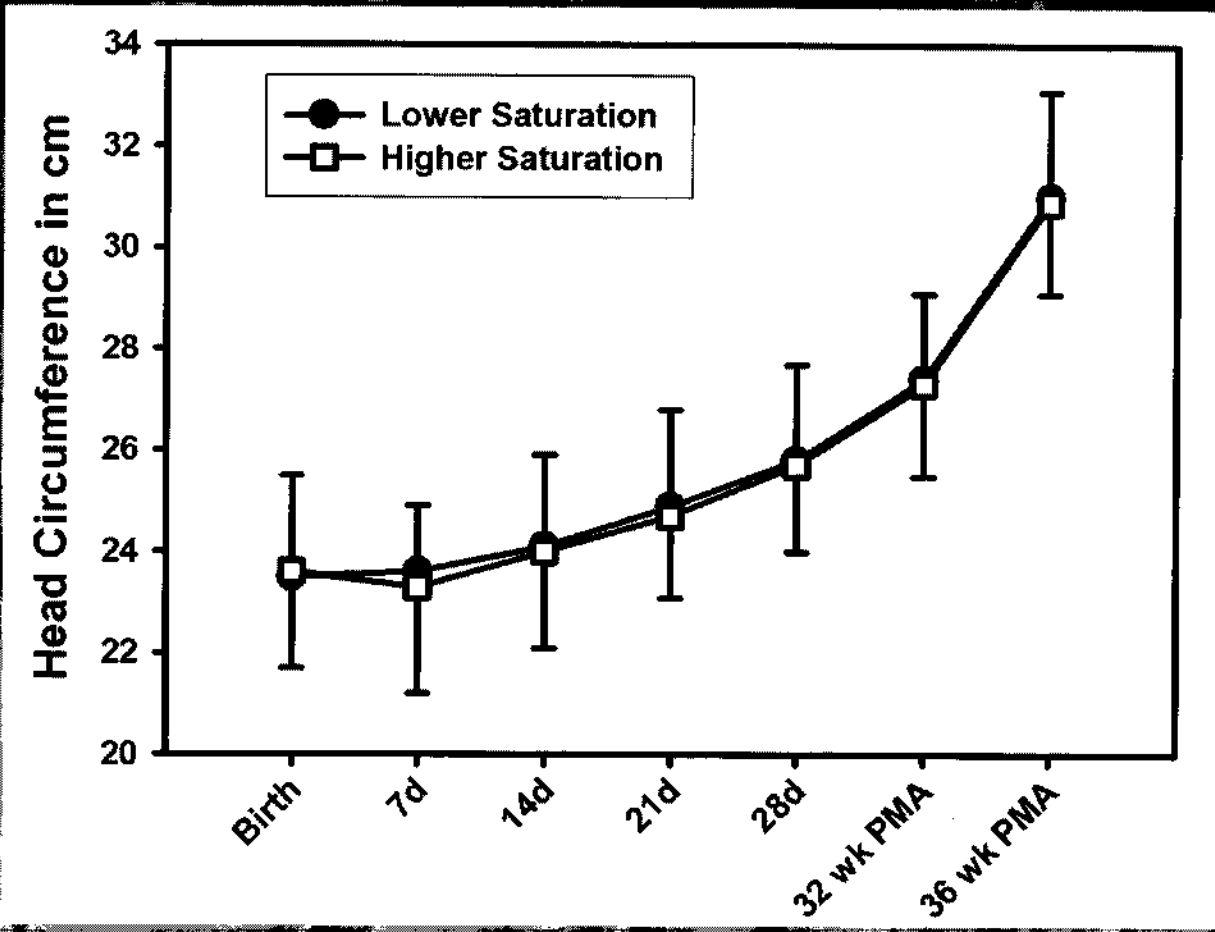


Mean  $\pm$  SD

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Mean ± SD

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<b>Outcome (%)</b>	<b>Lower O<sub>2</sub> Saturation</b>	<b>Higher O<sub>2</sub> Saturation</b>	<b>Relative Risk (95% CI)*</b>	<b>p-value</b>
<b>36 weeks PMA</b>	<b>n=402</b>	<b>n=408</b>		
Death or wt < 10th %ile	56	58	0.95 (0.8-1.1)	0.43
Wt < 10th %ile	47	50	0.93 (0.8-1.1)	0.30
<b>18-22 months CA:</b>	<b>n=384</b>	<b>n=390</b>		
Death or wt < 10th %ile	35	31	1.1 (0.9-1.4)	0.22
Wt < 10th %ile	16	14	1.1 (0.8-1.7)	0.49

\* Full soft regression model, adjusted for covariates

NICHD

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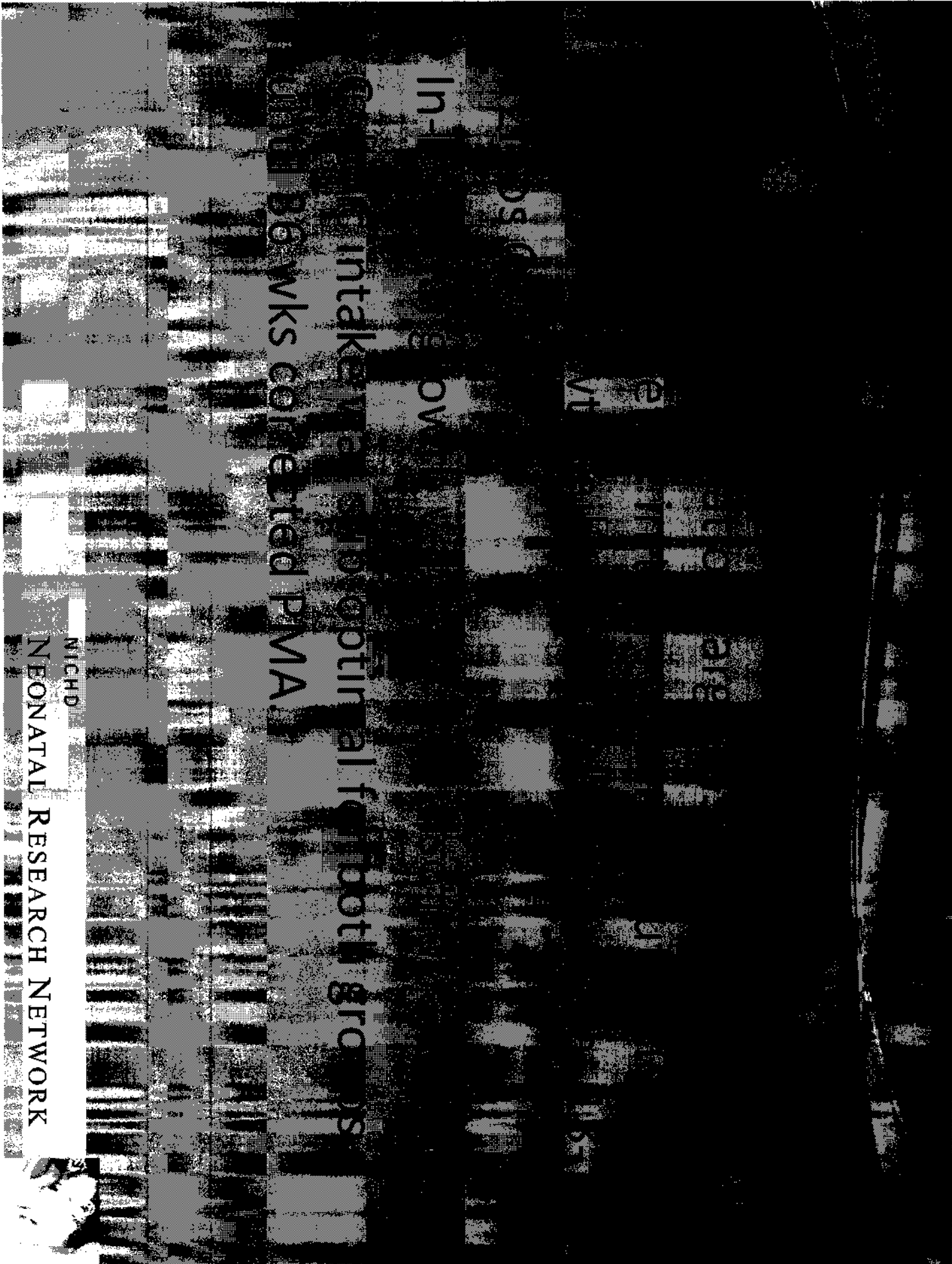


Growth Velocity in-hospital	Lower O <sub>2</sub> Saturation	Higher O <sub>2</sub> Saturation	p-value <sup>†</sup>
All Infants (mean ± SD, n)	13.6 ± 2.4, 260	13.4 ± 2.6, 275	0.69
GA 24-25 weeks	13.9 ± 2.1, 98	13.1 ± 2.8, 110	0.29
GA 26-27 weeks	13.4 ± 2.6, 162	13.6 ± 2.5, 165	0.55

† calculated for the subset of survivors using the exponential method:  $(\text{Growth velocity} = [1000 \times \ln(\text{Weight}_n / \text{Weight}_1)] / (\text{Day}_n - \text{Day}_1))$  adjusted for covariates and compared using linear mixed models.

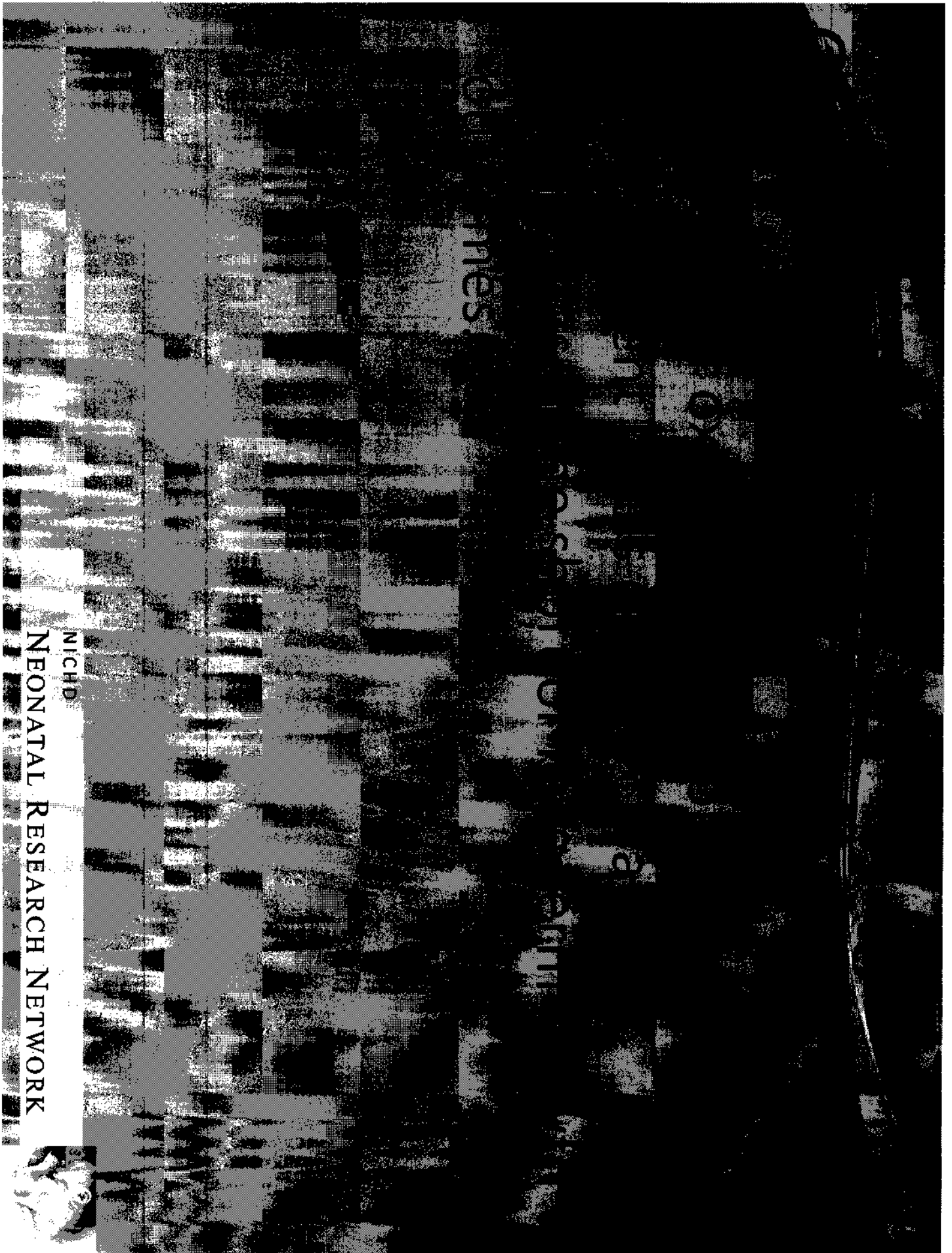
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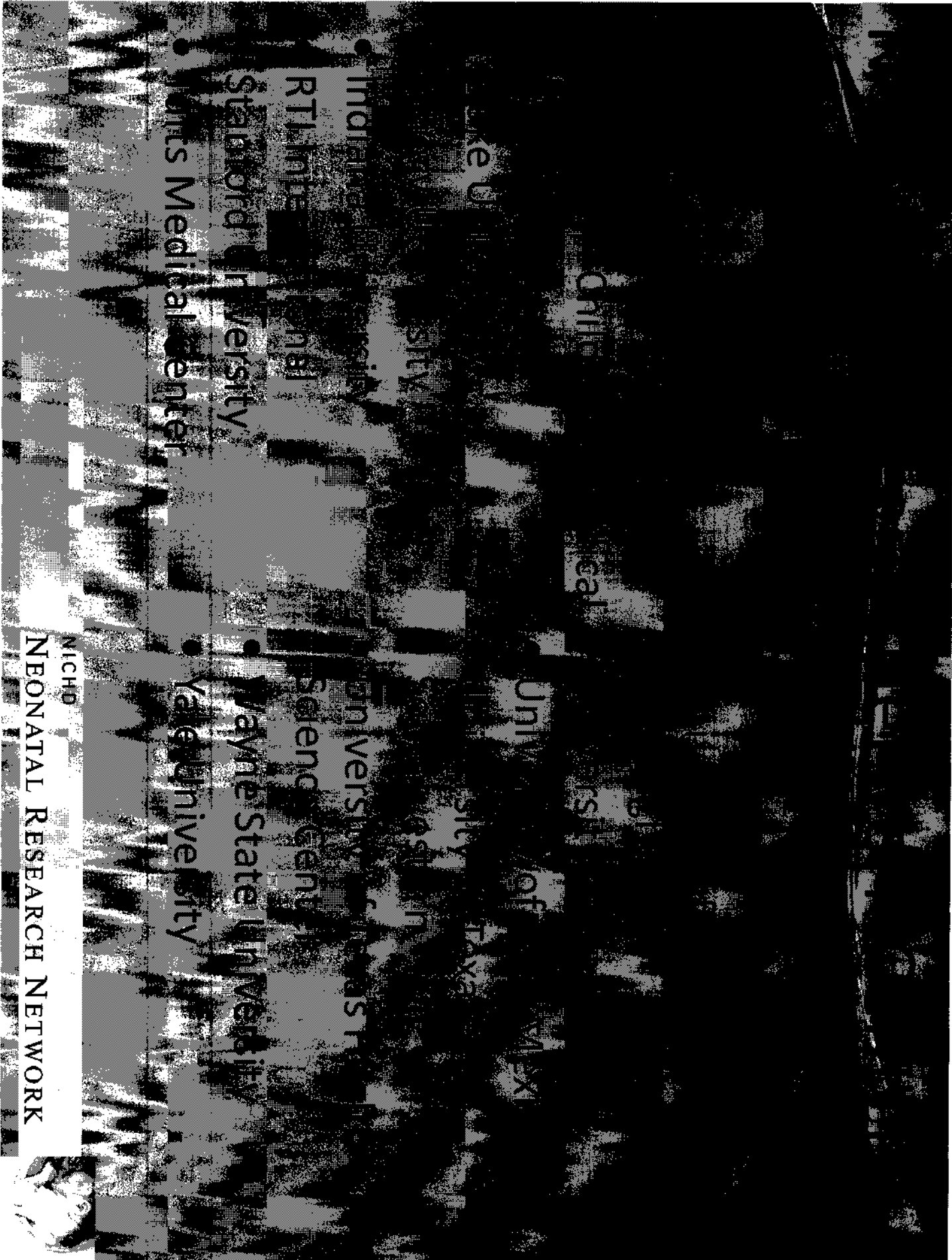


In-...  
... intake... optimal for both growth  
... 26 wks corrected PMA

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- Indiana University
- RTI International
- Stanford University
- Johns Hopkins Medical Center

- University of Massachusetts Lowell
- Science Center
- Wayne State University
- Yale University

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer.Stephanie@NIH/NICHD)  
**Subject:** FW: SCT poster on weighted SUPPORT analysis  
**Date:** Friday, April 06, 2012 10:27:00 AM  
**Attachments:** [Gantz SCT 2012 V7.pptx](#)

---

CAN YOU PUT THIS THROUGH CLEARANCE FOR:

**SCT 2012 33<sup>RD</sup> ANNUAL MEETING**  
MAY 20-23, 2012  
MIAMI, FLORIDA

Society for Clinical trials – Marie has a poster

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](mailto:higginsr@mail.nih.gov)

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Thursday, April 05, 2012 7:45 AM  
**To:** Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Creel, Darryl  
**Subject:** SCT poster on weighted SUPPORT analysis

Wade and Rose,

A draft of the poster of weighted SUPPORT results for the SCT conference is attached. Please let me know if you have any comments or suggestions.

Rose, I am supposed to have the poster to the group at RTI that will produce it by May 1. Given that deadline, when do you need the final version for NICHD clearance?

Thanks,  
Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

# Enrollment Propensity Weighting to Assess the Generalizability of a Randomized Clinical Trial



Marie Gantz<sup>1</sup>, Darryl Creel<sup>1</sup>, Wade Rich<sup>2</sup>, Rosemary Higgins<sup>3</sup> and Abhik Das<sup>1</sup> for the SUPPORT Trial Subcommittee of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network • <sup>1</sup>RTI International, Rockville, MD; <sup>2</sup>University of California, San Diego, CA; <sup>3</sup>NICHD, Rockville, MD

## Abstract

Randomized trials typically enroll a convenience sample of eligible patients without regard to formal probability sampling. However, trial results often substantially change clinical practice for the population at large, without systematic evaluation of the generalizability of results.

The Supportive Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) used a 2x2 factorial design to test different ventilation and oxygenation approaches for respiratory management of extremely premature babies. This influential and largest of its kind trial demonstrated that a less invasive ventilation strategy may be safe to use and indicated increased mortality at lower oxygen saturation.

Because intervention started upon delivery, parental consent was required, restricting the ability to enroll some eligible infants, including those who were born prematurely following the mother's admission. Enrolled babies had significantly higher socioeconomic status and greater exposure to prenatal steroids compared to the non-enrolled, which raised questions about the generalizability of the trial results. We conducted a sensitivity analysis by incorporating enrollment propensity weights so the analysis would better reflect the eligible population.

We used Classification and Regression Trees (CART) to model enrollment based on maternal and infant characteristics of delivery. Using the groups created by the trees, we constructed enrollment propensity weights. These weights were largely similar to the original unweighted analysis.

Although weighting to reflect the characteristics of the target population is common in survey statistics, to our knowledge the approach has not been used to explore the generalizability of results from randomized trials conducted on convenience samples of eligible patients. Where adequate data on the eligible population are available and enrolled individuals are known to differ from those not enrolled, these methods provide a means to assess the sensitivity of trial results to such differences.

## Background

Supportive Positive Airway Pressure and Pulse Oximetry Trial is a Randomized Low Birth Weight Infants (SUPPORT) Clinical Trial. [www.nichd.nih.gov/research/clinicaltrials/clinicaltrials.asp](http://www.nichd.nih.gov/research/clinicaltrials/clinicaltrials.asp)

A randomized controlled trial conducted by the Eunice Kennedy Shriver NICHD Neonatal Research Network (NNRT) in 2002.

2x2 Factorial design

Continuous Positive Airway Pressure (CPAP) vs. early (within 1 hour of birth) intubated ventilation of surfactant followed by conventional mechanical ventilation (Surfactant)

Oxygen saturation (SpO2) target of 85-89% (low) vs. 91-95% (high) with 30 weeks postmenstrual age (PMA)

Inclusion criteria

- Born at 34-36 weeks at 24.00 to 27.67 weeks gestational age (GA)
- Without known major congenital malformations and with full respiratory assessment

Randomization

- Anatomical consent was obtained from parents; if no randomization was performed in the delivery room
- Randomization was stratified by study center and GA group (24.00 - 25.67 weeks and 26.00 - 27.67 weeks)
- Multiple births were randomized together

Primary Outcomes and Analysis

- CPAP vs. Surfactant: Bronchopulmonary dysplasia or death by 36 weeks PMA, using two BPD definitions (BPD1 and BPD2)
- Proportion of infants with BPD (BPD1): Use of supplemental oxygen during challenge at 36 weeks
- Proportion of infants with BPD (BPD2): Use of supplemental oxygen during challenge at 36 weeks
- Low vs. high SpO2: Severe retinopathy of prematurity (ROP) or death before hospital discharge
- Head-to-head analysis with reduced Position Respiration generated estimating equations (REE) model, adjusted for stratification by center and GA group and for interim clustering, published in 2010 (SUPPORT Study Group, 2012)

Infants Enrolled vs. Eligible by Age Group

- Eligible infants were identified in the Census Data base of early low birth weight infants cared for at NNRT centers
- Enrolled infants (n=1,146) differed from those who were eligible but not enrolled (n=3,023) (P<0.001)
- Enrolled infants had higher socioeconomic status (higher education, maternal education, parental occupation) and higher exposure to prenatal steroids (97% vs. 81%) (lower to protect against ROP (Roberts Control 2002))
- Differences were attributed to the prenatal steroid process – women who had pre-eclampsia/diabetes did not have time to be approached for consent or to receive prenatal steroids
- Consensus was used that enrollment bias could have impacted trial results, especially the BPD outcome

## Objective

To conduct a secondary analysis in which the infants enrolled in SUPPORT were weighted to reflect the characteristics of the entire eligible population. We tested the type of weighting or enrollment propensity weighting at large, without systematic evaluation of the generalizability of results.

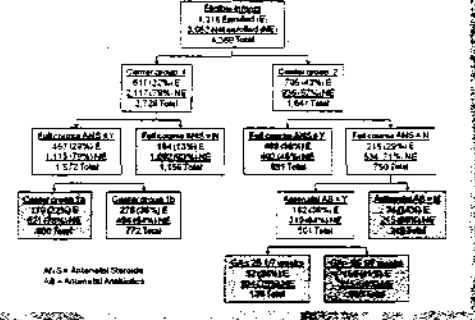
## Methods

- Classification and Regression Tree (CART) methods modeled the propensity for enrollment in SUPPORT
- CART to create the strata based on a series of binary splits that divide characteristics into groups based on values of the independent variables that maximize the within-group homogeneity of the dependent variable
- Predictors were study center, maternal age, maternal marital status, prenatal steroids and cervical, gender, months until birth, weight, GA, race and Apgar scores at 1 and 5 minutes
- CART groups were defined based on groups of infants of each terminal branch of the resulting tree
- SURVEY ADJUSTMENT procedure was used to adjust the enrollment propensity weights
- CARTs for center, gender, race, GA, antenatal steroids, and all course of antenatal steroids were produced in the WEIGHT ADJUSTMENT model
- Propensity weighting values for any antenatal steroids and full course of antenatal steroids were created using SURVEY ADJUSTMENT procedure
- CARTs for center, gender, race, GA, antenatal steroids, and GA were produced for any antenatal steroids and full course of antenatal steroids (using any antenatal steroids were produced for full course of antenatal steroids)
- SURVEY ADJUSTMENT procedure was used to adjust the weighted data
- Model accounted for stratification by center and GA group, and for interim clustering, as in the original analysis
- Model accounted for the stratified weights and outcomes (lower number of events were eligible by SUPPORT) adjustability, reduced the standard error of a beta coefficient estimator

## Results

- CART 10 created the 4,362 eligible infants into 7 groups, ranging in size from 138 to 1,156 infants (Figure 1)
- CART groups were based on if any center full course of antenatal steroids, antenatal steroids, and GA
- The proportion of enrolled infants in each of the 7 CART10 groups ranged from 13% to 56%, demonstrating substantial variation in the likelihood of enrollment, as the enrollment propensity, between the groups

Figure 1. CART 10 Tree



## Results

- SUDAAN's stratification and weighting
- 15 enrolled infants were at study responses for both any antenatal steroids and full course – were missing a response for full course only, values were imputed, included for any antenatal steroids followed by full course
- Adjusted enrollment propensity weights of the 1,518 enrolled infants summed to 4,362, the number of eligible infants. Summed weights for predictors in the weight adjustment model matched the eligible infant count (Table 1)
- The largest difference between the pre- and post-weighting characteristics of the enrolled infants was in antenatal steroid exposure (26 vs. 25% for any steroids; 22 vs. 20% for full course)

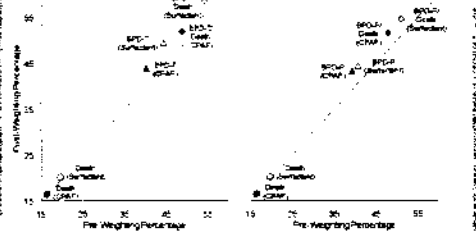
Table 1. Variables Used in Weighting – Pre- and Post-Weighting Means and Percentages

Variable	Pre-Weighting Mean (%)	Post-Weighting Mean (%)	Pre-Weighting Mean (%)	Post-Weighting Mean (%)
Center	11.0	11.0	11.0	11.0
Center group 1	33.0	33.0	33.0	33.0
Center group 2	27.0	27.0	27.0	27.0
Center group 3	31.0	31.0	31.0	31.0
Center group 4	17.0	17.0	17.0	17.0
Center group 5	7.7	7.7	7.7	7.7
Center group 6	8.4	8.4	8.4	8.4
Center group 7	8.2	8.2	8.2	8.2
Gender	50.0	50.0	50.0	50.0
Female	49.0	49.0	49.0	49.0
Male	51.0	51.0	51.0	51.0
Race	75.0	75.0	75.0	75.0
White	74.0	74.0	74.0	74.0
Black	26.0	26.0	26.0	26.0
Hispanic	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0
Maternal age	34.0	34.0	34.0	34.0
Maternal marital status	65.0	65.0	65.0	65.0
Married	35.0	35.0	35.0	35.0
Single	65.0	65.0	65.0	65.0
Other	0.0	0.0	0.0	0.0
Months until birth	9.0	9.0	9.0	9.0
Weight	3.0	3.0	3.0	3.0
GA	26.0	26.0	26.0	26.0
Antenatal steroids	26.0	25.0	26.0	25.0
Any antenatal steroids	26.0	25.0	26.0	25.0
Full course antenatal steroids	22.0	20.0	22.0	20.0
Apgar 1	8.0	8.0	8.0	8.0
Apgar 5	9.0	9.0	9.0	9.0

Comparison of Pre- and Post-Weighting Analysis Results

- The largest difference between pre- and post-weighting results was in the percent of infants with BPD1 or death by 36 weeks PMA for CPAP vs. Surfactant (48 vs. 54% pre-weighting; 37 vs. 50% post-weighting) (Table 2)
- All other BPD and death outcomes increased with the CPAP and Surfactant groups after weighting, relative risks (RR) and 95% confidence intervals (CI) did not change substantially from the original analysis (Table 2)

Figure 2. Percent of Infants with CPAP vs. Surfactant Outcomes Pre- and Post-Weighting



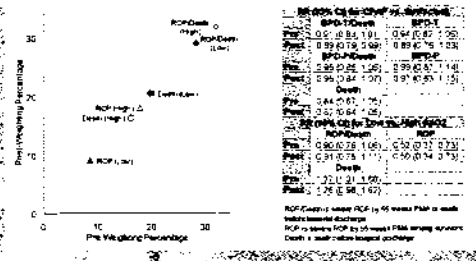
BPD1: Death or Intubated BPD (or at least one) within 36 weeks PMA  
 BPD2: Intubated BPD using surfactant by 36 weeks PMA  
 BPD3: Death or Intubated BPD (or at least one) within 36 weeks PMA using surfactant or death by 36 weeks PMA  
 BPD4: Severe ROP (using surfactant) or death by 36 weeks PMA  
 Death: Respiratory failure or death

## Results

Comparison of Pre- and Post-Weighting Analysis Results

- Results in the Low vs. High SpO2 groups were very similar pre- and post-weighting (percentages of infants with BPD and death outcomes changed by less than one percent, and RRs and CIs were nearly identical to Figure 2, Table 2)

Figure 3. Percent of Infants with Low vs. High SpO2



## Conclusions

- When adequate data on the eligible population are available and enrolled individuals are known to differ from those not enrolled, the propensity weighting methods described here provide a means to assess the sensitivity of the results to such differences
- The sensitivity of the results from the SUPPORT study before and after propensity weighting provides some reassurance that enrollment bias did not necessarily have a substantial impact on the published results of the trial however, the true extent of the enrollment bias remains unknown

## References

Rich W, Allen M, Quilley M, Hsieh E, Hestness A, Higgins R, et al. Post-hoc analysis of the SUPPORT trial: Outcomes with and without antenatal steroids. *Pediatrics*. 2011; 127(4):e102.

Roberts J, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews*. 2002; Issue 3. <http://www.cochrane.org/CD004461/Abstract/CD004461>

SUPPORT Network Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, including Creel D, Rich W, Allen M, Quilley M, Dalziel S, Higgins R, et al. (2010) Low CPAP versus intubation in premature, fragile infants. *New England Journal of Medicine*. 2012; 367: 879.

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, including Creel D, Rich W, Allen M, Quilley M, Dalziel S, Higgins R, et al. (2010) Target ranges of oxygen saturation for premature infants. *New England Journal of Medicine*. 2012; 367: 879.

Creel D, Rich W. The weighted propensity for each eligible procedure. *Proceedings of the Survey Research Methods Section Annual Meeting*. 2012.

## Contact Information

Marie Gantz  
 RTI International, 6110 Executive Boulevard, Suite 202 & 415, Rockville, Maryland 20852-3887  
 Phone: 301-251-0255 • Email: mgantz@rti.org  
 Presenting at Society for Clinical Trials 33rd Annual Meeting, May 20-25, 2012, Miami, Florida  
 Or contact at: marie.gantz@rti.org

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Gantz, Marie"; "Rich, Wade"  
**Cc:** "Das, Abhik"; "Creel, Darryl"  
**Subject:** RE: SCT poster on weighted SUPPORT analysis  
**Date:** Friday, April 06, 2012 10:26:00 AM

---

We will use this version for clearance

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Gantz, Marie [mailto:[mgantz@rti.org](mailto:mgantz@rti.org)]  
**Sent:** Thursday, April 05, 2012 7:45 AM  
**To:** Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Creel, Darryl  
**Subject:** SCT poster on weighted SUPPORT analysis

Wade and Rose,

A draft of the poster of weighted SUPPORT results for the SCT conference is attached. Please let me know if you have any comments or suggestions.

Rose, I am supposed to have the poster to the group at RTI that will produce it by May 1. Given that deadline, when do you need the final version for NICHD clearance?

Thanks,  
Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-354-6255

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper  
**Date:** Friday, April 06, 2012 9:33:00 AM

---

Can you put an \* by Yvonne and Myriam and state that both authors contributed equally to the study and send it to them?

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](mailto:higginsr@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, April 06, 2012 9:08 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Boilerplate | SUPPORT FU Combined paper

What I originally sent.

---

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](mailto:archerst@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wednesday, March 28, 2012 4:16 PM  
**To:** Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)); Neil Finer ([nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)); Myriam Peralta-Carcelen ([MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)); Yvonne Vaucher ([yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu))  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Boilerplate | SUPPORT FU Combined paper

Attached is a combined author list and boilerplate for the new combined SUPPORT FU paper. The only center that had two different authors on each paper was Indiana (highlighted in yellow in the attachment). Need to decide whether to include both of them, or not, and make necessary adjustments to the author list and acknowledgements (at the moment I have them listed in both).



Stephanie

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** "Finer, Neil"  
**Subject:** FW: Boilerplate | SUPPORT FU Combined paper  
**Date:** Friday, April 06, 2012 9:03:00 AM  
**Attachments:** [CombinedCPAPOximeterNEJM\\_VaucherNEJM0040112\\_MG\\_AD\\_WC \(2\\_MP\).docx](#)  
[combined graphic.PPTX](#)

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Rosemary D. Higgins, MD  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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

From: Myriam Peralta, M.D. [<mailto:MPeralta@peds.uab.edu>]  
Sent: Thursday, April 05, 2012 7:45 PM  
To: 'Vaucher, Yvonne'; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

I added more comments, I also added a possible figure for us to use, if we want to combine this. Numbers are not correct yet, I will change this as needed.

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
Sent: Thursday, April 05, 2012 3:23 PM  
To: Wally Carlo, M.D.; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD)  
Cc: Finer, Neil; Myriam Peralta, M.D.  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

PS. Please all work on the same draft which has now been reviewed by Mari, Abhik and Wally. It makes reviewing much easier. Thanks!

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

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
Sent: Thursday, April 05, 2012 1:16 PM  
To: Das, Abhik; Gantz, Marie; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD)  
Cc: Finer, Neil; Myriam Peralta, M.D.  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

I forgot to mention that I worked on Abhik's draft.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
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-----Original Message-----

From: Das, Abhik [mailto:adas@rti.org]  
Sent: Thursday, April 05, 2012 1:59 PM  
To: Gantz, Marie; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD); Wally Carlo, M.D.  
Cc: Finer, Neil; Myriam Peralta, M.D.  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

I have added a few more suggested changes to Marie's revision.

Thanks

Abhik

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

From: Gantz, Marie  
Sent: Thursday, April 05, 2012 11:09 AM  
To: 'Vaucher, Yvonne'; Higgins, Rosemary (NIH/NICHD); wcarlo@peds.uab.edu; Das, Abhik  
Cc: Finer, Neil; mperalta@peds.uab.edu  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

My additions and comments are attached. I am working on the sensitivity analyses and we can discuss them on our call tomorrow.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Tuesday, April 03, 2012 10:20 AM  
To: Higgins, Rosemary (NIH/NICHD); Gantz, Marie; wcarlo@peds.uab.edu; Das, Abhik  
Cc: Vaucher, Yvonne; Finer, Neil  
Subject: FW: Boilerplate | SUPPORT FU Combined paper

Here is my first draft at combining the papers, without Marie's comments, so we still need to shorten some but getting there. I am combining the tables. I included only those outcomes described in the original protocol (i.e. Death and NDI and the individual components.

Yvonne

---

From: Vaucher, Yvonne  
Sent: Monday, April 02, 2012 9:39 PM  
To: Myriam Peralta, M.D.  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

2867 words (excluding abstract and references) so almost there. We need to get down to 2700 so see if you can cut somewhere.

Yvonne

---

From: Myriam Peralta, M.D. [MPeralta@peds.uab.edu]  
Sent: Sunday, April 01, 2012 6:08 PM  
To: Vaucher, Yvonne  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

Yvonne where you able to put some of the paper together, I can work on it this week if you want to send me what you have and I will work on it some, Also I can start on the letter to respond to the reviewers, thanks.

---

From: Vaucher, Yvonne [yvaucher@ucsd.edu]  
Sent: Saturday, March 31, 2012 2:00 PM  
To: Archer, Stephanie (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu); Finer, Neil; Myriam Peralta, M.D.  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | SUPPORT FU Combined paper

All,  
Re boilerplate: We can discuss revised title, authors on Friday.

Yvonne

---

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]  
Sent: Wednesday, March 28, 2012 1:15 PM  
To: Wally Carlo (wacarlo@uab.edu); Finer, Neil; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Vaucher, Yvonne  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Boilerplate | SUPPORT FU Combined paper

Attached is a combined author list and boilerplate for the new combined SUPPORT FU paper. The only center that had two different authors on each paper was Indiana (highlighted in yellow in the attachment). Need to decide whether to include both of them, or not, and make necessary adjustments to the author list and acknowledgements (at the moment I have them listed in both).

Stephanie

**Early CPAP vs. Surfactant and Two different Oxygen Saturation Targets versus Surfactant in Extremely Preterm Infants: Death or and Neurodevelopmental Outcomes Outcome in Early Childhood at 18 to 22 Months**

**Outcome of extremely preterm infants in a trial to receive early CPAP vs. surfactant and two different oxygen saturation targets. (alternative title)**

Yvonne E. Vaucher, MD MPH<sup>1</sup>; Myriam Peralta-Carcelen, MD MPH<sup>2</sup>; Neil N. Finer, MD<sup>1</sup>; Waldemar A. Carlo, MD<sup>2</sup>; Michele C. Walsh, MD MS<sup>3</sup>; Marie G. Gantz, PhD<sup>4</sup>; Abbot R. Lupton, MD<sup>5</sup>; Bradley A. Yoder, MD<sup>6</sup>; Roger G. Faix, MD<sup>6</sup>; Abhik Das, PhD<sup>7</sup>; Kurt Schibler, MD<sup>8</sup>; Wade Rich, RRT<sup>2</sup>; Nancy S. Newman, RN<sup>4</sup>; Betty R. Vohr, MD<sup>5</sup>; Kimberly Yolton, PhD<sup>9</sup>; Roy J. Heyne, MD<sup>9</sup>; Deanne E. Wilson-Costello, MD<sup>4</sup>; Patricia W. Evans, MD<sup>10</sup>; Ricki F. Goldstein, MD<sup>11</sup>; Michael J. Acarregui, MD<sup>12</sup>; Ira Adams-Chapman, MD<sup>13</sup>; Athina Pappas, MD<sup>14</sup>; Susan R. Hintz, MD MS Epi<sup>15</sup>; Anna M. Dusick, MD FAAP<sup>16</sup>; Elisabeth C. McGowan, MD<sup>17</sup>; Richard A. Ehrenkranz, MD<sup>18</sup>; Anna Bodnar, MD<sup>6</sup>; Charles R. Bauer, MD<sup>19</sup>; Janell Fuller, MD<sup>20</sup>; T. Michael O'Shea, MD MPH<sup>21</sup>; Gary J. Myers, MD<sup>22</sup>; Rosemary D. Higgins, MD<sup>23</sup> 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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<sup>22</sup> Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

<sup>23</sup> *Eunice Kennedy Shriver National Institute of Child Health and Human Development*, National Institutes of Health, Bethesda, MD

**Corresponding author and reprints:**

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**Division of Neonatology**

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**200 West Arbor Drive**

**San Diego, CA, 92013**

## ABSTRACT

~~BACKGROUND: The randomized controlled SUPPORT trial used a 2X2 factorial design to randomized trial demonstrated that premature infants, 24 0/7 to 27 6/7 weeks gestation, to treatment with early CPAP vs. early surfactant administration and to treatment with lower (85%-89%) vs. higher (91-95%) oxygen saturation targets. There was no difference in neonatal outcomes between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation targets limits were associated with less a lower rate of severe retinopathy of prematurity but increased mortality. treatment with early CPAP is an alternative to early intubation with surfactant administration, resulting in similar rates of death or BPD in infants born at 24 to 27 weeks gestation. We hypothesized that, compared to early intubation, early CPAP would decrease the composite outcome of death or neurodevelopmental impairment and lower oxygen saturation targeting would each decrease the risk of the composite outcome of death or neurodevelopmental impairment (NDI) at 18-22 months corrected age.~~

~~METHODS: We followed surviving infants, 24 0/7 to 27 6/7 weeks gestation, randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth and conventional ventilation. The primary composite outcome was a composite of death or neurodevelopmental impairment (NDI) at 18-22 months corrected age. Analyses were adjusted for gestational age stratum, center and familial clustering.~~

~~.RESULTS: Death or NDI was determined for 1234/1316 (93.8%) of all infants enrolled in SUPPORT infants; 93.6% (990/1058) of hospital survivors to hospital discharge were evaluated at 18-22 months corrected age. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [27.9% (173/621)] groups (occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (RR 0.93; 95% CI 0.78-1.1, p=0.39)) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)]; oxygen saturation groups (RR risk 1.12; 95% CI 0.94 to 1.32; p=0.21). There Mortality at follow up persisted was increased remained higher in the were no significant differences between treatment arms in death (CPAP 18.4 vs. Surf 21.9%), lower (22.1%) compared to the higher (10.5%) oxygen saturation group (RR 1.25; 95% CI 1 to 1.55, p=0.046).~~

~~NDI (CPAP 10.9 vs. Surfactant 9.1%), or components of NDI including cognitive score < 70 (CPAP 7.2 vs. Surfactant 7.6%), moderate/severe cerebral palsy (CPAP 4.1 vs. Surfactant 4.0%), blindness (CPAP 0.8 vs. Surfactant 1.5%) and hearing impairment (CPAP 3.3 vs. Surfactant 1.5%)~~

~~CONCLUSION: We found no significant differences in the composite outcome of death or NDI at 18-22 months corrected age in between extremely premature infants who were randomized to were randomized to received either early CPAP with a limited ventilation strategy or early intubation with surfactant administration and conventional ventilation or who were assigned to lower compared to higher oxygen saturation target ranges.~~

Comment [AD1]: I would retain this part.

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Comment [MS2]: This should be "randomized to receive" instead of "received" since this is an ITT analysis and we are not looking at what the infants actually received.

**BACKGROUND**

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood. <sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications including intraventricular hemorrhage or periventricular leukomalacia, symptomatic patent ductus arteriosus, necrotizing enterocolitis, sepsis, prolonged ventilation, bronchopulmonary dysplasia and severe retinopathy of prematurity. <sup>4-12</sup> Although surfactant administration decreases both death and bronchopulmonary dysplasia (BPD), randomized controlled trials of various respiratory interventions including high frequency oscillatory ventilation, high frequency jet ventilation, and inhaled nitric oxide have failed to show that any of these treatments consistently decrease mortality and morbidity or improve developmental outcome. <sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks gestation postmenstrual age, air leak, severe intraventricular hemorrhage and other major outcomes. <sup>18</sup>

Although for many preterm infants with infants with respiratory disorders, oxygen supplementation is vital for survival, several studies have shown that oxygen supplementation increases the risk of retinopathy of prematurity, <sup>1</sup> bronchopulmonary dysplasia BPD, <sup>2,3</sup> periventricular leukomalacia, <sup>4</sup> and cerebral palsy. <sup>5</sup> Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials. <sup>6,7</sup>

The recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth is an alternative to surfactant administration after intubation, and results in similar rates of death before or BPD at 36 weeks gestation in extremely premature infants born at from 24 0/7 to 27 6/7 24 through 27 weeks gestation. <sup>18</sup> Compared with randomization to early intratracheal to surfactant administration, randomization to early CPAP resulted in less frequent need for postnatal steroids and shorter duration of mechanical ventilation. Both treatment groups had similar rates of air leak, severe intraventricular hemorrhage and other major outcomes. Mortality was lower in the most immature, 24-25 week gestation, stratum of the CPAP arm. The SUPPORT trial demonstrated no difference in a composite outcome of severe retinopathy of prematurity or death before discharge between a lower-oxygen-saturation target group (85-89%) and a higher-oxygen-saturation target group (91-95%). However, in the lower-oxygen-saturation target group severe retinopathy of prematurity among survivors decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73; p<0.001) but and death before discharge was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60; p=0.04) compared to infants in the higher-oxygen-saturation group target. <sup>6</sup> Similarly, a recent preliminary pooled results meta-analysis that included the SUPPORT trial data and three other subsequently completed multi-center randomized controlled trials (two trials were stopped early) with a total of 3631 infants showed concluded that infants randomized to an oxygen saturation target of 91-95% had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (14.4% vs 17.3% respectively, P=0.015). <sup>7</sup>

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The SUPPORT trial in extremely low birth weight (ELBW) infants was ~~prospectively powered to pre-specified~~ have adequate sample size to ~~the h evaluation of~~ early childhood neurodevelopmental outcomes of among enrolled infants. We hypothesized that ~~compared to randomization to treatment with early surfactant administration after intubation, randomization to early, non-invasive CPAP with a limited ventilation strategy compared to early surfactant administration after intubation, and with a limited ventilation strategy, and that lower compared to higher oxygen saturation limit targets, would each would~~ decrease the rate incidence of a composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age.

**Comment [AD3]:** I think we may have to get away from this, because the protocol is a little fuzzy on this aspect.

## METHODS

### Study Design

1316 extremely preterm infants, (24 weeks 0 days to 27 weeks 6 days through 27 weeks gestation), born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled prior to delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). M- and multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery and a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth and subsequent conventional ventilation<sup>18</sup>. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group) using a specially designed blinded oximeter. Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

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### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months of age, corrected for prematurity (CA), by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>19</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>20</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>21</sup> Moderate to severe cerebral palsy was defined by a GMFCS-  $\geq 2$  plus an abnormal exam as stated above. Hearing loss, defined as the inability to understand directions of the examiner and communicate with or without amplification, and visual impairment, - defined as vision < 20-200), were determined based on examination and parental report.

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq 2$ ), Grades 3-4

intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

#### Outcome

The pre-specified primary outcome at follow up for this trial was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age (CA). This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS  $\geq 2$ , presence of moderate or severe cerebral palsy, permanent hearing or bilateral visual impairment.

#### Statistical Analysis

Aside from the primary outcome of death or NDI, other pre-specified outcomes at 18 to 22 months corrected age were mortality (among the entire trial cohort) or NDI, and NDI, cerebral palsy, and blindness (in at least one eye) among survivors at follow up. Exploratory secondary outcomes at 18 to 22 months corrected age were death and components of NDI (i.e., cognitive composite score < 70, GMFCS  $\geq 2$ , moderate/severe cerebral palsy, bilateral blindness and bilateral hearing impairment).

Comment [AD4]: Wasn't this pre-specified?

The sample size calculations were based on NRN data on infants born in the year 2000, which included the rate of death or neurodevelopmental impairment at 18-22 months CA corrected age. While the sample size for the study was primarily based on the principal hospital outcomes reported earlier (death or BPD for the ventilation intervention, and death or ROP for the oxygenation intervention), the study was designed to have 80% power the final sample size for the study was sufficient to detect a 10% absolute reduction in death or NDI, using a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% and 15% loss to follow up, as well as adjustment for familial clustering. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18</sup> (Marie/Abhik - Do we need a statement here about how the lower incidence of NDI using the Bayley III affected power analysis? Also see comment # 3 from Statistical reviewer #1 re pre-defined treatment effects) Exploratory secondary outcomes at 18 to 22 months corrected age were death and components of NDI (i.e., cognitive composite score < 70, GMFCS  $\geq 2$ , moderate/severe cerebral palsy, bilateral blindness and bilateral hearing impairment). (Marie/Abhik - We need to say something here about interactions between CPAP/SURF and High/Low Sat arms)

Comment [MG5]: Because this is the most conservative outcome rate that could have been used for the power calculations, it does not matter that the initial estimates were based on the Bayley II.

Comment [MG6]: See below.

Data were entered in standard forms and were transmitted to RTI International, the Data Coordinating Center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months CA corrected age could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was

Comment [AD7]: Are we actually presenting any unadjusted t tests? If not, we can take this out.

known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as prespecified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Tests were conducted for the presence of statistical interaction between the two treatment arms interventions. Two-sided p values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. However, given the number of comparisons made, we would expect no more than 4 tests to be significant at the 0.05 level on the basis of chance alone. (Marie/Abhik-Need statement re multiple comparisons)

Sensitivity analyses were conducted to assess the impact of loss to follow up on the primary follow up outcome of death or NDI and the two individual components of the outcome.

Comment [MG8]: Will describe the methods used when I am done with the analysis.

## RESULTS

Of the 1316 infants enrolled in the SUPPORT trial, 250 two hundred fifty eight children were known to have died before 18-22 months (Figure a and b). Sixty eight children of the remaining 1058 children, 68/1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of the 990 children seen for evaluation, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of SUPPORT-enrolled children. The mean corrected age at neurodevelopmental assessment and the follow-up rates were similar for both all treatment arms.

(CPAP 19.9 ± 2.4 months vs. Surf 20.1 ± 2.7 months, unadjusted p=0.31). There was no difference in the follow-up rate between the CPAP and Surfactant arms (93.7 vs. 93.4%) of the trial.

Comment [AD9]: If this is referring to 2 separate CONSORT diagrams, then we should combine them into one.

Comment [m10]: I am sending a possible combination, but not sure it will show all that we will need to show, we could show a separate on the appendix.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%, p=0.01), and more likely to have only public insurance (69 vs. 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups. (Marie/Abhik-Stat Reviewer #2 asked whether sensitivity analyses were performed to determine if the LTFUP group might have changed conclusions)

Comment [AD11]: Shouldn't this comparison be between with 1234 for whom we have outcome and the 82 that we don't?

Comment [MG12]: I am working on the sensitivity analyses.

Follow-up Cohort Characteristics: (Table 1) Almost all mothers (96%) received antenatal steroids. There were more SGA infants children and more infants children with ROP in the higher compared to the lower oxygen saturation group. The difference in SGA was due to the previously published difference in death in the two saturation groups; only one SGA child was lost to follow up. Thirty four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation. Compared to the Surfactant arm, infants children in the CPAP arm with follow up at 18-22 months were significantly more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. Other demographic characteristics and neonatal outcomes were similar in infants in the Surfactant and CPAP arms. Thirty four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation. (MARIE-DO THESE PERCENTAGES HOLD FOR THE FUP COHORT ALSO?)

Comment [MG13]: Can we be sure that they received ventilation, based only on the fact that they received surfactant?

Comment [MG14]: In the FU cohort, 92% were intubated in the DR and 65% received surfactant in the CPAP group.

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Primary neurodevelopmental outcome: (Table 2) The composite outcome of death or NDI at 18-22 months corrected age was not a significantly different between the CPAP and surfactant arms ((27.9 vs. 29.9%, RR 0.93 (95% CI 0.78, 1.1), Table 2 a) adjusted  $p=0.38$  or between the lower and higher oxygen saturation target groups (Table 2 b)). There were no statistically significant differences in the incidence of either death between the death (18.4 vs. 21.9%, RR 0.83 (95% CI 0.67, 1.04) adjusted  $p=0.10$ ) or NDI (10.9 vs. 9.1%, (95% CI 0.79, 1.71, RR 1.16,  $p=0.44$ ) between the CPAP and Surfactant arms. However, mortality was at follow up remained significantly higher in the lower compared to the higher saturation group. Neurodevelopmental impairment among survivors examined at the 18 to 22 month corrected age visit was similar between the early CPAP and Surfactant arms and between lower and the higher oxygen saturation target groups. There was no evidence of any statistical interaction between treatment arms the two interventions was not significant for either the primary outcome of death or NDI, or its components – death, or NDI among survivors (all  $p$  values  $> 0.7$ ).

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Components of NDI among survivors at follow up: (Table 2 a and b) The incidences of cognitive impairment (BSID-III cognitive composite score  $< 70$  (7.2% vs. 7.6%), gross motor function level  $\geq 2$  (5.1 vs. 4.8%), moderate/severe cerebral palsy (4.1 vs. 4.0%), and blindness (0.8 vs. 1.5%) among survivors were similar not different in between the the CPAP and vs. Surfactant treatment arms or between the groups lower vs. higher saturation groups. There was a higher incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant treatment arm but the difference was not statistically significant, (3.3 vs. 1.5%, adjusted  $p=0.06$ ). Overall, 24 infants had hearing loss, 13 of whom had bilateral hearing aids. There were no significant differences in composite outcomes of death or individual NDI components between the CPAP and Surfactant arms (Table 3). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen target group compared to the lower oxygen target group; the rates of bilateral blindness or blindness of at least one eye (were not significantly different at the 18 to 22 month corrected age visit. (Table 3).

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Other neurodevelopmental outcomes: Mean BSID-III composite cognitive scores were similar in both CPAP and Surfactant arms (adjusted means  $\pm$  standard error  $91.3 \pm 0.7$  vs.  $90.4 \pm 0.8$ ). Sixty percent of all children seen at 18-22 months corrected age (CPAP 59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e. BSID-III cognitive composite score  $\geq 85$ ) evaluations.

#### Comparisons of outcome between gestational age strata: (Tables 2 and 3)

The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.5%, adjusted  $p=0.02$ , RR 0.74 (95% CI 0.57, 0.96)), but not in the higher gestational age stratum (12.3 vs. 11.8%). There were no significant differences in the composite outcome of death or NDI at 18-22 months corrected age between the CPAP and surfactant within either of the two gestational age strata (40.1 vs. 44.5% for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation). The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.5%, adjusted  $p=0.02$ , RR 0.74 (95% CI 0.57, 0.96)), but not in the higher gestational age stratum (12.3 vs. 11.8%). Neither were there significant differences between the CPAP and Surfactant arms in the incidence of NDI alone within either of the two gestational age strata (18.1 vs. 12.5, adjusted  $p=0.22$  for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, adjusted  $p=0.81$  for 26 0/7-27 6/7 weeks gestation). Within each gestational age stratum the mean BSID-III composite cognitive scores were similar in both treatment groups (CPAP  $89.2 \pm 1.1$  vs. Surfactant  $88.1 \pm 1.2$  for 24 0/7-25 6/7 weeks gestation; CPAP  $93.4 \pm 0.9$  vs. Surfactant  $92.6 \pm 0.9$  for 26 0/7 to 27 6/7 weeks gestation, adjusted mean  $\pm$  standard error).

Although neurodevelopmental outcomes were similar between treatment arms within each gestational age stratum, children in the lower gestational age stratum were at higher risk of adverse outcome. Compared to those in the 26 0/7-27 6/7 stratum, children in the 24 0/7 to 25 6/7 week gestational age stratum were more likely to have NDI (15.5% vs. 6.7%,  $p<0.0001$ ), to have a cognitive score  $< 70$  (10.7% vs. 5.4%,  $p<0.0001$ ), to have a GMFCS  $\geq 2$  (7% vs. 3.7%,  $p=0.023$ ), to have moderate to severe cerebral palsy (5.9% vs. 2.9%,  $p=0.02$ ), and to be hearing impaired (3.8% vs. 1.6%,  $p=0.035$ ).

#### DISCUSSION:

We report the neurodevelopmental outcome in early childhood at 18-22 months corrected age for extremely premature children, 24-27 weeks gestation, enrolled in the SUPPORT trial. To our knowledge this is the first large, multicenter, RCT published to date comparing neurodevelopmental impairment as a pre-specified outcome between early CPAP vs. early intubation with surfactant administration and between lower vs. higher oxygen saturation limits in extremely premature infants as immature as 24 weeks gestation. although the outcomes of other similarly designed trials will be reported.<sup>7,15</sup> ~~There This trial demonstrated~~ was no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those ~~extremely premature~~ infants randomized to treatment with early CPAP vs. ~~those randomized to treatment with~~ early intubation and surfactant administration or between those randomized to the lower ~~and vs.~~ higher oxygen saturation limit target groups. Neither were there significant differences between among survivors in ~~any of the the CPAP and Surfactant arm~~ treatment arms in NDI or its components of severe cognitive impairment (cognitive score  $< 70$ ), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFCS  $\geq 2$ ), hearing impairment, and bilateral blindness.

The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. Whereas the present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, previous studies used the Bayley, 2<sup>nd</sup> edition. Changes in test design, composition and scoring most likely explain the lower incidence of NDI reported here - as there is no reason to believe that cognitive function in this high risk group has changed substantially in a short period of time.

Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome.<sup>4,8-10</sup> ~~Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge at 36 weeks postmenstrual age.~~

The results of recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>2</sup> In the SUPPORT trial death prior to discharge was increased among neonates randomized to lower-oxygen-saturation target. The distribution of major causes of death prior to discharge has been published previously and there were no significant differences between groups.<sup>6</sup> The difference in mortality persisted at 18 to 22 months corrected age as noted above. Causes of death after discharge are not available for this study. A recent pooled analysis included studies that were completed with different oximeter calibration algorithms.<sup>16</sup> The SUPPORT study was included in the old algorithm arm and the investigators in the pooled analysis did not adjust for clustering for multiple births. Results of additional randomized trials which include pre-specified outcome at two years follow up which will not be available until 2014.<sup>7,15</sup>

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Comment [AD15]: You can reference a number of papers that have come out on this topic, reporting that Bayley III achieves higher scores than Bayley II.

Should we also say that our conclusions remain unchanged even if we use a different Bayley III cutoff? I think Marie has looked at this.

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We previously reported that the lower-oxygen saturation target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors.<sup>6</sup> It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment.<sup>17,18</sup> Although our study was not designed to collect detailed data on eye disorders or visual function at 18 to 22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher in the group with a higher oxygen saturation target and was likely related to a higher incidence of severe retinopathy of prematurity in this group and to the criteria used to define severe retinopathy of prematurity.<sup>6</sup> Specific visual outcomes of eye function after the presence of retinopathy of prematurity were not included in the outcome data collected in this trial. However, there were no differences in other reported visual outcomes, including nystagmus, strabismus or use of corrective lenses.

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or in mean composite cognitive BSID-III scores.

As reported in previous studies, the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were less likely to be normal and were at higher risk for severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment.<sup>22-24</sup>

Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome.<sup>48-49</sup> Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, the very high percentage of participants who were followed and evaluated in early childhood, and the comprehensive and standardized neurodevelopmental evaluation performed on survivors. One third of infants in the CPAP arm were intubated in the delivery room and two thirds ultimately received surfactant treatment and limited ventilation for clinical indications which may have almost certainly blunted any difference in neurodevelopmental outcomes between the two groups. In addition, an adverse effect on neurodevelopmental outcome associated with the increased incidence of NEC in the CPAP arm may have counterbalanced adverse outcomes associated with the longer duration of ventilation and the increased need for supplemental oxygen and post-natal steroids in the surfactant treatment arm. The generalizability of this study may be limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status and receipt of antenatal steroids than the entire eligible cohort.<sup>25</sup> ENREF 35

In summary, we found no significant differences in the composite outcome of death or NDI, or in any of the individual components of NDI among survivors ~~at 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration or followed by conventional ventilation.~~ to lower or higher target saturation limits. The increased death rate at discharge previously reported in the lower target oxygen saturation group was still present at 18 to 22 months corrected age. Although higher rates of retinopathy of prematurity were associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months. On the basis of these findings it appears that early CPAP is an alternative to early intubation and surfactant administration even in extremely premature infants and that higher saturation limits are associated with similar neurodevelopmental outcome in early childhood and less death.

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In this study early CPAP, an alternative respiratory management strategy for the extremely premature infant, did not decrease the composite risk of death or neurodevelopmental impairment in early childhood.

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

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

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Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

*Eunice Kennedy Shriver National Institute of Child Health and Human Development* – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MSED; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Rene Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN;

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.



University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augustino; Julie Babish Johnson, MSW; Erica Burnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons,

PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

Table 1: Demographic and neonatal characteristics of trial and follow-up cohorts

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata

Table 3: Death and components of NDI for entire cohort and by gestational age strata

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Bayley. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
20. Amiel-Tison C GJ. Neurological Development from Birth to Six Years. Baltimore: The Johns Hopkins University Press; 1998.
21. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.

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22. Raz S, Debastos AK, Newman JB, Batton D. Extreme prematurity and neuropsychological outcome in the preschool years. *J Int Neuropsychol Soc* 2010;16:169-79.
23. Leversen KT, Sommerfelt K, Ronnestad A, et al. Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm. *Pediatrics* 2011;127:e630-8.
24. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity--moving beyond gestational age. *N Engl J Med* 2008;358:1672-81.
25. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.



**Table 1: Demographics and Characteristics of Trial Cohort and Follow-up (FUP) Cohorts**

	<u>Follow up Cohort</u>	
	CPAP	Surfactant
	N=511	N=479
Birth weight (grams, Mean ± SD)	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)
<b>Race</b>		
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)
Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)

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With both biological parents†-no./total no.(%)	348/510(68.2)	329/479(68.7)
Maternal education < 12 <sup>th</sup> grade-no./total no.(%)	128/506(25.3)	116/469(24.7)
Income < \$30,000/year†-no./total no.(%)	260/493(52.7)	251/461(54.4)
English as primary language at FUP -no./total no.(%)	426/510(83.5)	403/478(84.3)
Severe ROP in survivors to discharge-no./total no.(%)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia in survivors to 36 weeks	193/511(37.8)	187/479(39)
Gestational age-no./total no.(%)		
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)
NEC-stage ≥2 -no./total no.(%)	56/511(11)	30/479(6.3)**
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)
Postnatal steroids-no./total no.(%)	34/508(6.7)	55/476(11.6)**
Died before discharge no./total no.(%)		

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\*\*p<0.02, \*\*\*p<0.001



**Table 2: Death and NDI for entire cohort and gestational age strata\***

<b>a. CPAP vs. Surfactant (All)</b>	CPAP	Surfactant	RR	p
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

<b>b. <u>24 0/7-25 6/7 weeks Gestational Age</u></b>	<b>CPAP</b>	<b>Surfactant</b>	<b>RR</b>	<b>p</b>
Death or NDI-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

<b>c. <u>26 0/7-27 6/7 weeks Gestational Age</u></b>	<b>CPAP</b>	<b>Surfactant</b>	<b>RR</b>	<b>p</b>
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

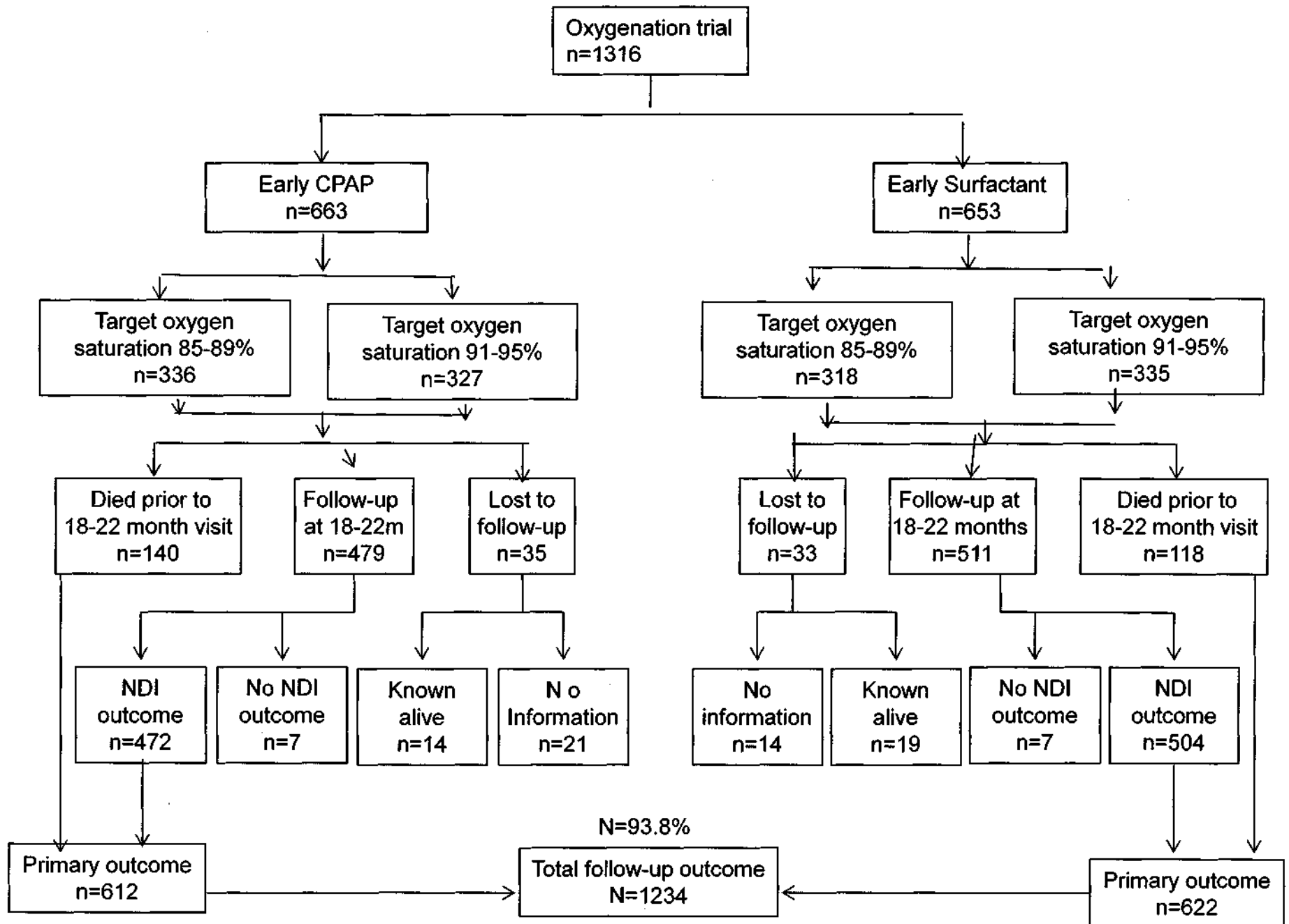
\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Table 3: Death and Components of NDI for entire cohort and gestational age strata\***

<b>a. <u>CPAP vs. Surfactant (All)</u></b>	<b>CPAP</b>	<b>Surfactant</b>	<b>RR</b>	<b>p</b>
Death or cognitive composite<70-no./total no.(%)	154/620(24.8)	176/612(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level $\geq 2$ -no./total no.(%)	144/629(22.9)	163/619(26.3)	0.87(0.72,1.05)	0.16
Death or moderate/severe CP-no./total no.(%)	139/629(22.1)	159/619(25.7)	0.86(0.71,1.05)	0.14
Death or blind in both eyes-no./total no.(%)	122/629(19.4)	147/619(23.7)	0.82(0.67,1.02)	0.07
Death or hearing impairment-no./total no.(%)	135/629(21.5)	147/619(23.7)	0.9(0.74,1.11)	0.33
 <b>b. <u>24 0/7-25 6/7 weeks Gestational Age</u></b>				
Death or cognitive composite<70-no./total no.(%)	96/271(35.4)	113/264(42.8)	0.83(0.67,1.02)	0.08
Death or GMF level $\geq 2$ -no./total no.(%)	90/274(32.8)	106/269(39.4)	0.84(0.67,1.04)	0.12
Death or moderate/severe CP-no./total no.(%)	87/274(31.8)	105/269(39)	0.82(0.65,1.02)	0.08
Death or blind in both eyes-no./total no.(%)	75/274(27.4)	99/269(36.8)	0.75(0.58,0.96)	0.03
Death or hearing impairment-no./total no.(%)	84/274(30.7)	100/269(37.2)	0.83(0.65,1.05)	0.12

<b>c. <u>26 0/7-27 6/7 weeks Gestational Age</u></b>	<b>CPAP</b>	<b>Surfactant</b>	<b>RR</b>	<b>p</b>
Death or cognitive composite<70-no./total no.(%)	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.67
Death or GMF level $\geq 2$ -no./total no.(%)	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.74
Death or moderate/severe CP-no./total no.(%)	52/355(14.6)	54/350(15.4)	0.96(0.68,1.36)	0.82
Death or blind in both eyes-no./total no.(%)	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.89
Death or hearing impairment-no./total no.(%)	51/355(14.4)	47/350(13.4)	1.07(0.74,1.55)	0.71

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering



**From:** [Finer, Neil](#)  
**To:** [Gabrio, Jenna](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine - 12-01618 - Call Scheduled for 4/6, F, 9:00 AM US ET  
**Date:** Friday, April 06, 2012 8:06:36 AM

---

Hi Jenna  
This number does not work from Europe  
Do you have a number that does?  
Thanks  
Neil

---

**From:** [Gabrio, Jenna \[mailto:jgabrio@rti.org\]](mailto:jgabrio@rti.org)  
**Sent:** Friday, April 06, 2012 5:03 AM  
**To:** Myriam Peralta, M.D.; Gantz, Marie; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Das, Abhik  
**Cc:** Wally Carlo, M.D.; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine - 12-01618 - Call Scheduled for 4/6, F, 9:00 AM US ET

A friendly reminder for today's call.

---

**From:** [Gabrio, Jenna](#)  
**Sent:** Friday, March 30, 2012 3:11 PM  
**To:** 'Myriam Peralta, M.D.'; Gantz, Marie; 'Finer, Neil'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Vaucher, Yvonne'; Das, Abhik  
**Cc:** 'Wally Carlo, M.D.'; 'Archer, Stephanie (NIH/NICHD) [E]'  
**Subject:** RE: New England Journal of Medicine - 12-01618 - Call Scheduled for 4/6, F, 9:00 AM US ET

Dear all,

Thank you for your quick responses and flexibility. The call to discuss revisions for the oximeter paper has been scheduled for:

**Friday, 4/6  
9:00am US ET**

Dial:  
**Within the USA**

(b)(6)

or

**Outside the USA**

(b)(6)

**Then enter Participant Passcode:**

(b)(6)

Thanks,  
Jenna

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

From: Myriam Peralta, M.D. [<mailto:MPeralta@peds.uab.edu>]  
Sent: Thursday, March 29, 2012 3:21 PM  
To: Gantz, Marie; Finer, Neil; Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Das, Abhik  
Cc: Wally Carlo, M.D.; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine - 12-01618 - Availability Request

On april 6 I am available between 12pm and 2pm central time.  
On april 9 I can be available any time, april 10 and 11 only in the morning  
and not on april 12.

Thanks

---

From: Gantz, Marie [[mgantz@rti.org](mailto:mgantz@rti.org)]  
Sent: Thursday, March 29, 2012 11:20 AM  
To: Finer, Neil; Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Das, Abhik  
Cc: Wally Carlo, M.D.; Myriam Peralta, M.D.; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine - 12-01618 - Availability Request

I am available on the 6th before 1:00 PM EST. Jenna, I filled out the poll.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]  
Sent: Thursday, March 29, 2012 9:21 AM  
To: Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Vaucher, Yvonne; Das, Abhik  
Cc: [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [mperalta@peds.uab.edu](mailto:mperalta@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine - 12-01618 - Availability Request

I will be in Europe for these dates  
I could do the 6th if it is early in the morning here Neil

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

From: Gabrio, Jenna [<mailto:jgabrio@rti.org>]  
Sent: Thursday, March 29, 2012 5:09 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Vaucher, Yvonne; Das, Abhik  
Cc: Finer, Neil; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [mperalta@peds.uab.edu](mailto:mperalta@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]



Subject: RE: New England Journal of Medicine - 12-01618 - Availability Request

Hi all,

Please provide your availability for this call for the following dates on this Doodle poll (<http://www.doodle.com/tggb53ywrdyvt9ch>):

4/6, F

4/9, M

4/10, Tu

4/11, W

4/12, Th

Thanks,  
Jenna

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

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Thursday, March 29, 2012 2:00 AM  
To: Gantz, Marie; 'yvaucher@ucsd.edu'; Das, Abhik; Gabrio, Jenna  
Cc: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; 'mperalta@peds.uab.edu'  
Subject: Re: New England Journal of Medicine - 12-01618

Please set up a call with all on the email - perhaps Friday april 6?

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

From: Gantz, Marie [<mailto:mgantz@rti.org>]  
Sent: Wednesday, March 28, 2012 04:21 PM  
To: Vaucher, Yvonne <[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)>; Das, Abhik <[adas@rti.org](mailto:adas@rti.org)>  
Cc: Finer, Neil <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; wcarlo@peds.uab.edu <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)>; Myriam Peralta, M.D. <[MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)>; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine - 12-01618

Are we planning to get this small group together to discuss specific responses to the NEJM reviewer comments? I think that would be useful.

On the issue of adjusting for SGA, I don't think the suggestion makes sense, because the imbalance in SGA at follow up was a result of the imbalance in death rates between the oximeter groups. Thus, if we really want to know if there is a trade-off between death and NDI in the oximeter groups, we should not adjust for differences in covariates that result from differences between the treatments. My preference is to respond to the reviewer with our reasons for not adjusting (note that the statistician was not the one who suggested it).

We can clarify our power calculations in the paper. That's not a problem.

I am currently working on an approach to the sensitivity analyses for loss to

follow up.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

From: Vaucher, Yvonne [<mailto:yvaucher@ucsd.edu>]  
Sent: Wednesday, March 28, 2012 4:03 PM  
To: Gantz, Marie; Das, Abhik  
Cc: Finer, Neil; Vaucher, Yvonne  
Subject: FW: New England Journal of Medicine - 12-01618

Marie and Abhik,

Here are the comments for the oximeter paper. Most of the statistical comments overlap (i.e. possible interaction between interventions) but one is specific for this paper (i.e., question of need for adjustment for excess SGA in high sat group) I thought we were explicit in the paper about power calculations specifically for NDI based on previous NRM data but the question is raised about power calculations using pre-defined treatment effects by reviewers. Didn't we do this in the protocol (pg 24, N2) although the power was based on the Bayley II estimate of NDI which was substantially higher? Anyway, I guess we need a clearer statement in the paper.

Yvonne

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

From: [onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com)  
[<mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com>] On Behalf Of  
[editorial@nejm.org](mailto:editorial@nejm.org)  
Sent: Thursday, February 09, 2012 3:24 PM  
To: [mperalta@peds.uab.edu](mailto:mperalta@peds.uab.edu); Vaucher, Yvonne; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Finer, Neil;  
[mgantz@rti.org](mailto:mgantz@rti.org); [mcw3@po.cwrui.edu](mailto:mcw3@po.cwrui.edu); [alaptook@wihri.org](mailto:alaptook@wihri.org);  
[Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu); [roger.faix@hsc.utah.edu](mailto:roger.faix@hsc.utah.edu); [adas@rti.org](mailto:adas@rti.org);  
[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); Rich, Wade; [Nancy.Newman@UHhospitals.org](mailto:Nancy.Newman@UHhospitals.org);  
[BVohr@wihri.org](mailto:BVohr@wihri.org); [kimberly.volton@cchmc.org](mailto:kimberly.volton@cchmc.org); [roy.heyne@utsouthwestern.edu](mailto:roy.heyne@utsouthwestern.edu);  
[drfjcmd@aol.com](mailto:drfjcmd@aol.com); [Patricia.W.Evans@uth.tmc.edu](mailto:Patricia.W.Evans@uth.tmc.edu); [goldso05@mc.duke.edu](mailto:goldso05@mc.duke.edu);  
[michael.acarregui@providence.org](mailto:michael.acarregui@providence.org); [iadamsc@emory.edu](mailto:iadamsc@emory.edu); [apappas@med.wayne.edu](mailto:apappas@med.wayne.edu);  
[schintz@stanford.edu](mailto:schintz@stanford.edu); [bpointindex@iupui.edu](mailto:bpointindex@iupui.edu); [emcgowan@tuftsmedicalcenter.org](mailto:emcgowan@tuftsmedicalcenter.org);  
[richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [annabodnar.ab@gmail.com](mailto:annabodnar.ab@gmail.com);  
[cbauer@peds.med.miami.edu](mailto:cbauer@peds.med.miami.edu); [jafuller@salud.unm.edu](mailto:jafuller@salud.unm.edu); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu);  
[gary\\_myers@urmc.rochester.edu](mailto:gary_myers@urmc.rochester.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov); [pandrhiggins@aol.com](mailto:pandrhiggins@aol.com)  
Subject: New England Journal of Medicine - 12-01618

Dear Dr. Peralta Carcelen and co-authors,

Thank you for submitting your manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets" to the New England Journal of Medicine.

Your manuscript has been forwarded to members of our editorial staff, who will make an initial evaluation and decide whether it merits further consideration. You will be notified of the decision as soon as possible.

Your manuscript ID is 12-01618.

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://mc05.manuscriptcentral.com/nejm> and edit your user information as appropriate. You may also view the status of your manuscript at any time by checking For Authors section of the site.

We are undertaking evaluation of your manuscript with the understanding that neither the substance of the article nor the figures or tables have been published or will be submitted for publication elsewhere during the period of review.

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Please call us at 617-734-9800 if you have any questions.

Sincerely,

Jeffrey M. Drazen, M.D.  
Editor-in-Chief  
New England Journal of Medicine  
Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

**From:** Kennedy, Kathleen A  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Wrage, Lisa Ann (wrage@rti.org); dale\_phetps@urmc.rochester.edu; Einer, Neil; Carlo, Wally (wcarlo@peds.uab.edu); Faix, Roger; Laptook, Abbot; Walsh, Michele; Brad Yoder (Bradley.Yoder@hsc.utah.edu); Das, Abhik; Gantz, Marie; "Rich, Wade"  
**Subject:** Poster for SUPPORT Secondary Study  
**Date:** Thursday, April 05, 2012 5:17:40 PM  
**Attachments:** NRN SUPPORT ROP Observational Study (Final).pptx

---

Here's a "final" version for NICHD clearance.

Thanks for all the input.

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



NICHD  
NEONATAL RESEARCH NETWORK



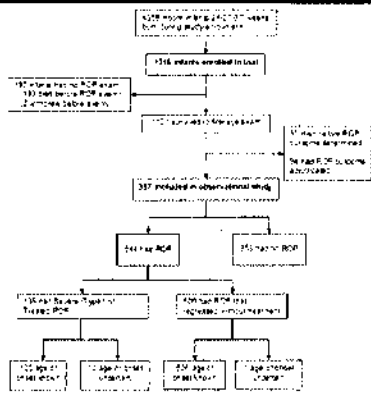
# Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants

Kathleen A Kennedy MD MPH, Lisa A Wraga MPH, Dale Phelps MD, Rosemary Higgins MD and the SUPPORT Subcommittee of the NICHD Neonatal Research Network

Timely detection of treatable ROP is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997; screening should begin by 31 wks postmenstrual age (PMA) or 4 wks after birth, if later and continue until vessels have reached the ora serrata, vessels have reached zone III if no prior ROP and after 35 wks, 45 wks PMA for infants without prethreshold ROP, or regression of ROP. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I; or stage 2-3 with plus disease in zone II) is now recommended.

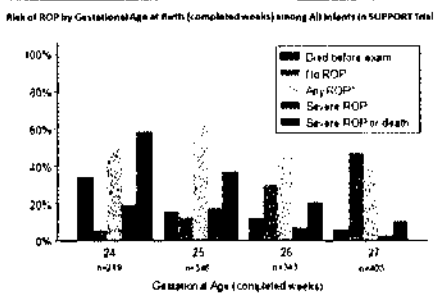
To evaluate the 2006 ROP screening guidelines for 24-27 wk GA infants born 2005-2009

Descriptive natural history study using outcome data from the NICHD Network SUPPORT trial. In this trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial trial. Inborn infants 24<sup>0/7</sup> to 27<sup>6/7</sup> wks GA with consent prior to delivery were eligible. Examinations followed current screening recommendations. Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA. For this observational study, age of onset is defined as age of detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 wks (1 wk if the previous exam had ROP in zone I) were defined as having an uncertain age of onset.



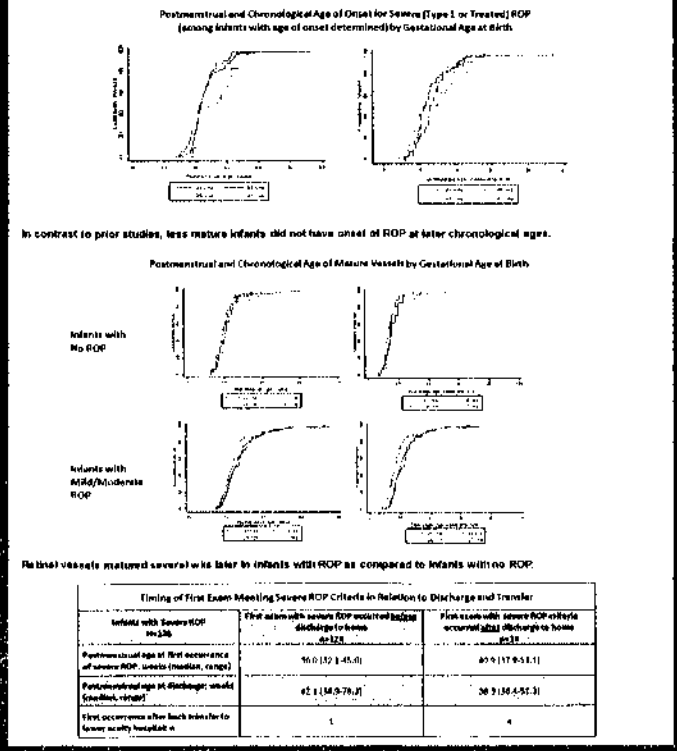
597/1091 (55%) of survivors had a definitive ROP outcome. 128/138 (92%) with severe ROP had sufficient data (no missing or delayed exams) to determine the age of onset of ROP.

Characteristic	Infants Included in SUPPORT Trial		Infants Included in Observational Study (Reached Final ROP Outcome)		
	n	%	All ROP Outcomes	No ROP	Severe (Type 1 or Treated) ROP
Gestational Age (Mean [SD])	26.2 (1.1)	26.6 (1.1)	26.8 (0.9)	26.8 (1.0)	26.5 (0.9)
Birth Weight (Mean [SD])	830 (103)	849 (100)	943 (113)	798 (119)	708 (144)
Survival to Discharge (%)	89	92	95	94	70
Survival to Discharge with Severe ROP (%)	49	51	55	51	42
Survival to Discharge with No Severe ROP (%)	40	41	40	43	28
Survival to Discharge with Death (%)	40	41	40	43	28
Survival to Discharge with Death or Severe ROP (%)	80	82	95	94	70
Survival to Discharge with Death or Severe ROP or Death (%)	129	131	140	137	108
Survival to Discharge with Death or Severe ROP or Death or Death (%)	129	131	140	137	108



As expected, infants with severe ROP were less mature and lower birth weight than infants without ROP.

ROP Type	Postmenstrual Age (weeks)										Chronological Age (weeks)									
	n	m%	1%	5%	25%	50%	75%	95%	99%	100%	m%	1%	5%	25%	50%	75%	95%	99%	100%	
Any ROP	642	29.3	30.8	31.8	33.1	34.1	35.1	36.4	37.4	38.1	46.7	4.0	4.8	5.4	6.7	8.0	9.4	11.9	15.3	19.7
Type 1 ROP	158	29.3	31.7	33.1	34.3	34.1	35.1	36.4	37.4	38.1	46.7	4.4	4.6	6.3	6.7	10.8	12.0	15.0	21.0	27.7
Severe (Type 1/Treated) ROP	128	32.1	32.7	33.9	35.1	35.4	36.6	38.0	38.0	38.1	46.7	6.4	7.1	8.4	8.6	13.0	14.1	17.0	18.0	20.4



In these 997 infants, we did not observe treatable ROP before 32 wks PMA; only 1 infant developed severe ROP after 45 wks PMA. Our contemporary data support continued use of the 2006 ROP screening guidelines. Some infants who are stable enough for back transfer or discharge home are still at risk to develop treatable ROP. A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug. Acknowledgments: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in the study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California - San Diego; University of Iowa; University of Michigan; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

**From:** Kennedy, Kathleen A  
**To:** [Finer, Neil](mailto:Finer_Neil); [Carlo, Wally \(wcarlo@peds.uab.edu\)](mailto:wcarlo@peds.uab.edu); [Faix, Roger](mailto:Faix_Roger); [Laptook, Abbot](mailto:Laptook_Abbot); [Walsh, Michele](mailto:Walsh_Michele); [Brad Yoder \(Bradley.Yoder@hsc.utah.edu\)](mailto:Brad_Yoder); [Das, Abhik](mailto:Das_Abhik); [Gantz, Marie](mailto:Gantz_Marie); [Rich, Wade](mailto:Rich_Wade)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins_Rosemary); [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer_Stephanie); [Wrage, Lisa Ann \(wrage@rti.org\)](mailto:Wrage_LisaAnn); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)  
**Subject:** RE: Poster for SUPPORT Secondary Study  
**Date:** Wednesday, April 04, 2012 9:55:47 AM

---

There's a table on the poster that shows that the "14" were discharged at an earlier PMA and had severe ROP diagnosed at a later PMA as compared to babies who had severe ROP detected before discharge. We have another table in the manuscript draft (no room for it on the poster) that compares the ROP exams prior to discharge for babies who did and did not develop treatable ROP after discharge. They look different but don't discriminate well.

I suspect that we will find the same thing (they look a little different but you can't discriminate the subgroup of babies who are really high risk) if we compare them for GA at birth, BW, days on oxygen, PDA, early onset sepsis, late onset sepsis, Candida sepsis, IVH, NEC. We haven't done this yet but I'm hoping Lisa can do it after we send to poster off to the NIH and we can get back to working on the manuscript (hopefully before the PAS meeting.)

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

---

**From:** [Finer, Neil \[mailto:nfiner@ucsd.edu\]](mailto:Finer_Neil)  
**Sent:** Wednesday, April 04, 2012 5:15 AM  
**To:** [Kennedy, Kathleen A](mailto:Kennedy_KathleenA); [Carlo, Wally \(wcarlo@peds.uab.edu\)](mailto:wcarlo@peds.uab.edu); [Faix, Roger](mailto:Faix_Roger); [Laptook, Abbot](mailto:Laptook_Abbot); [Walsh, Michele](mailto:Walsh_Michele); [Brad Yoder \(Bradley.Yoder@hsc.utah.edu\)](mailto:Brad_Yoder); [Das, Abhik](mailto:Das_Abhik); [Gantz, Marie](mailto:Gantz_Marie); [Rich, Wade](mailto:Rich_Wade)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\)](mailto:Higgins_Rosemary); [Archer, Stephanie](mailto:Archer_Stephanie); [Wrage, Lisa Ann \(wrage@rti.org\)](mailto:Wrage_LisaAnn); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)  
**Subject:** RE: Poster for SUPPORT Secondary Study

Thanks Kathleen  
Have you looked at the 14 infants with late severe disease?  
The poster looks fine to me  
Thanks  
Neil

---

**From:** [Kennedy, Kathleen A \[mailto:Kathleen.A.Kennedy@uth.tmc.edu\]](mailto:Kennedy_KathleenA)  
**Sent:** Tuesday, April 03, 2012 8:19 AM  
**To:** [Finer, Neil](mailto:Finer_Neil); [Carlo, Wally \(wcarlo@peds.uab.edu\)](mailto:wcarlo@peds.uab.edu); [Faix, Roger](mailto:Faix_Roger); [Laptook, Abbot](mailto:Laptook_Abbot); [Walsh, Michele](mailto:Walsh_Michele); [Brad Yoder \(Bradley.Yoder@hsc.utah.edu\)](mailto:Brad_Yoder); [Das, Abhik](mailto:Das_Abhik); [Gantz, Marie](mailto:Gantz_Marie); [Rich, Wade](mailto:Rich_Wade)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\)](mailto:Higgins_Rosemary); [Archer, Stephanie](mailto:Archer_Stephanie); [Wrage, Lisa Ann \(wrage@rti.org\)](mailto:Wrage_LisaAnn); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)  
**Subject:** Poster for SUPPORT Secondary Study

I've made some revisions based on the comments I've received. I'm still hoping to get revised

graphs with somewhat thicker lines and better separation of the plots, but I'm sending this out for your final review because we need to send it to Rose for NIH clearance **by Apr 6**. If you additional suggestions, please send them to me before **Thurs Apr 5**. Thanks.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

**From:** Finer, Neil  
**To:** Navarrete, Cristina; Higgins, Rosemary (NIH/NICHD) [E]; WCarlo@peds.uab.edu; Rich, Wade; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; Brenda Poindexter (bpoindex@iupui.edu); 'kurt.schibler@cchmc.org'; mcw3@cwru.edu; 'Roger Faix'; 'Bradley Yoder'; Das, Abhik; 'Gantz, Marie'; 'Nancy Newman'; Wrage, Lisa Ann  
**Cc:** Duara, Shahnaz  
**Subject:** RE: Request Review of Presentation of Growth Outcomes SUPPORT  
**Date:** Wednesday, April 04, 2012 6:15:28 AM

---

Thanks Cristina  
This looks fine to me  
Neil

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

**From:** Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]  
**Sent:** Tuesday, April 03, 2012 7:25 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; WCarlo@peds.uab.edu; Rich, Wade; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; Brenda Poindexter [bpoindex@iupui.edu]; 'kurt.schibler@cchmc.org'; mcw3@cwru.edu; 'Roger Faix'; 'Bradley Yoder'; Das, Abhik; 'Gantz, Marie'; 'Nancy Newman'; Wrage, Lisa Ann  
**Cc:** Duara, Shahnaz  
**Subject:** Request Review of Presentation of Growth Outcomes SUPPORT

Good Morning!  
I have attached a copy of the presentation. I'll appreciate your comments/critique.  
Thanks,  
Cristina

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Wednesday, October 05, 2011 2:13 PM  
**To:** nfiner@ucsd.edu; WCarlo@peds.uab.edu; Navarrete, Cristina; Duara, Shahnaz; 'Rich, Wade'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; Brenda Poindexter [bpoindex@iupui.edu]; 'kurt.schibler@cchmc.org'; mcw3@cwru.edu; 'Roger Faix'; 'Bradley Yoder'; Das, Abhik; 'Gantz, Marie'; 'Nancy Newman'; Wrage, Lisa Ann  
**Subject:** Abstract\_Growth\_Outcomes\_SUPPORT1

Hi,  
Here is the SUPPORT GROWTH OUTCOMES draft abstract. Please send comments back to Shahnaz and Tina.

Thanks  
Rose



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: our phone call  
**Date:** Tuesday, April 03, 2012 11:14:47 AM

---

No  
Neil is efficient

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, April 03, 2012 10:59 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: our phone call

Do you think the SUPPORT NEJM call on Friday at 9:00 is likely to go longer than an hour?

---

**From:** Truog, William (MD) [mailto:wtruog@cmh.edu]  
**Sent:** Tuesday, April 03, 2012 10:57 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Kilbride, Howard (MD); Gauldin, Cheri,; 'kzaterka@rti.org'; 'adas@rti.org'; 'mcunningham@rti.org'  
**Subject:** RE: our phone call

Can we do 9 or 10 our time (11 or 12 Eastern?)  
We have a Department meeting from 0730 to about 0900 central that morning.  
Bill T.

---

**From:** Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]  
**Sent:** Tuesday, April 03, 2012 9:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Truog, William (MD)  
**Cc:** Kilbride, Howard (MD); Gauldin, Cheri,; 'kzaterka@rti.org'; 'adas@rti.org'; 'mcunningham@rti.org'  
**Subject:** RE: our phone call

Please send me your availability for a teleconference on Friday, April 6<sup>th</sup> from 10 AM-5PM Eastern time.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 03, 2012 10:48 AM  
**To:** 'wtruog@cmh.edu'  
**Cc:** 'hkilbride@cmh.edu'; 'cagauldin@cmh.edu'; 'kzaterka@rti.org'; Archer, Stephanie (NIH/NICHD) [E]; 'adas@rti.org'; 'mcunningham@rti.org'  
**Subject:** Re: our phone call

Bill

I am (b)(6) with no cell phone, so can discuss on Friday. Stephanie can get your availability. For centers with multiple hospitals, we require IRB approval from each hospital for gdb. Although you receive the records at Children's Mercy, the information's primary. In the site visit report we state:

Discussion continues regarding the use of CMH IRB as the IRB of record for outreach centers should the addition of these centers be approved as NRN sites of Mercy Children's.

If Children's Mercy is the IRB of record, we need some documentation from each referral hospital

that this arrangement has been made and is acknowledge by each of the individual centers. Further, each infant included will need to have the referral center have a site indication to have the birth hospital included in the database. So if there are 3-4 hospitals where the virtual inborns are from, we will have additional sites for your center.

Thanks

Rose

---

**From:** Truog, William (MD) [mailto:wtruog@cmh.edu]  
**Sent:** Tuesday, April 03, 2012 10:08 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Kilbride, Howard (MD) <hkilbride@cmh.edu>; Truog, William (MD) <wtruog@cmh.edu>; Gauldin, Cheri, <cagauldin@cmh.edu>  
**Subject:** our phone call

Hi Rose,

Howard and I were hoping to reach you to see if we can get on the same page about the virtual inborn population.

As far as we can tell, nothing happens at those institutions that has any bearing on any kind of data collection for the GDB and so it was our understanding that when the CMH IRB approved our amendment, we were good to go. In some ways it would be as if these infants were delivered in our emergency room (happens sometimes). We are not sure what question we would even ask of the IRB Chairs at these other Hospitals. Nothing of a research or data repository data collection happens there—it's all routine patient care and gathering up information to allow uneventful movement of the patient into another part of our virtual Center.

Bill T..

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**From:** Kennedy, Kathleen A  
**To:** [Finer, Nell](#); [Carlo, Wally \(wcarlo@peds.uab.edu\)](#); [Falx, Roger](#); [Laptook, Abbot](#); [Walsh, Michele](#); [Brad Yoder \(Bradley.Yoder@hsc.utah.edu\)](#); [Das, Abhik](#); [Gantz, Marie](#); "Rich, Wade"  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Wrage, Lisa Ann \(wrage@rti.org\)](#); [dale\\_phelps@urmc.rochester.edu](#)  
**Subject:** Poster for SUPPORT Secondary Study  
**Date:** Tuesday, April 03, 2012 11:22:34 AM  
**Attachments:** [NRN SUPPORT RQP Observational Study \(resized\).pptx](#)

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I've made some revisions based on the comments I've received. I'm still hoping to get revised graphs with somewhat thicker lines and better separation of the plots, but I'm sending this out for your final review because we need to send it to Rose for NIH clearance **by Apr 6**. If you additional suggestions, please send them to me before **Thurs Apr 5**. Thanks.

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



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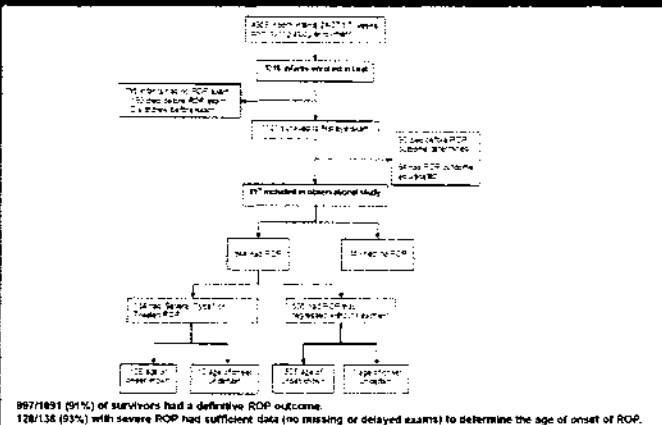
# Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants

Kathleen A Kennedy MD MPH, Lisa A Wrage MPH, Dale Phelps MD, Rosemary Higgins MD and the SUPPORT Subcommittee of the NICHD Neonatal Research Network

Timely detection of treatable ROP is important for optimal outcomes. The current (2006) screening guidelines are based on infants born in 1986-1997: screening should begin by 31 wks postmenstrual age (PMA) or 4 wks after birth, if later and continue until vessels have reached the ora serrata, vessels have reached zone III if no prior ROP and after 35 wks PMA for infants without prethreshold ROP, or regression of ROP. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I; or stage 2-3 with plus disease in zone II) is now recommended.

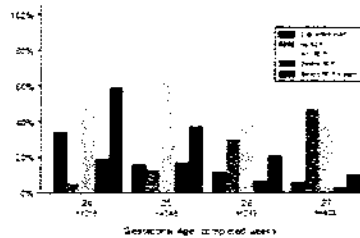
To evaluate the 2006 ROP screening guidelines for 24-27 wk GA infants born 2005-2009

Descriptive natural history study using outcome data from the NICHD Network SUPPORT trial. In this trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial trial. Inborn infants 24 1/2 to 27 1/2 wks GA with consent prior to delivery were eligible. Examinations followed current screening recommendations. Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA. For this observational study, age of onset is defined as age of detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 wks (1 wk if the previous exam had ROP in zone I) were defined as having an uncertain age of onset.



	Infants Enrolled to SUPPORT Trial	Infants included in Observational Study (Observed Post ROP Outcomes)			
		All ROP Outcomes	Any ROP	Any Severe (Type 1 or Treatment) ROP	Severe (Type 1 or Treatment) ROP
<b>n</b>	3316	997	505	344	136
Postmenstrual Age (Weeks PMA)	26.2 (1.3)	26.3 (1.3)	25.8 (1.9)	26.0 (1.0)	25.5 (2.0)
Birth Weight (Mean SD)	4.0 (25.1)	3.6 (13.0)	3.5 (17.3)	7.0 (1.9)	7.0 (1.0)
<b>Survivability (n %)</b>					
Non-Respirator-Weaned	498 (57.2)	274 (67.5)	153 (43.5)	221 (96.9)	42 (30.4)
Respirator-Weaned	272 (120.2)	388 (99.3)	156 (75.6)	215 (94.2)	13 (44.2)
Other	259 (109.2)	335 (194.2)	59 (49.6)	123 (103.8)	26 (20.2)
	47 (15.9)	35 (13.5)	6 (11.7)	29 (16.5)	7 (5.1)
Males (n %)	712 (54.1)	320 (55.1)	195 (55.2)	334 (55.9)	74 (54.5)
Admission Weight (kg)	1,285 (95.2)	555 (95.4)	340 (96.3)	313 (95.5)	125 (97.4)
Multiple Births (n %)	217 (15.4)	25 (10.4)	31 (12.0)	12 (12.5)	4 (7.1)

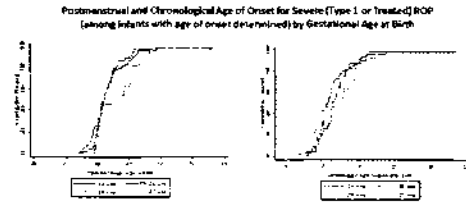
Risk of ROP by Gestational Age at Birth (completed weeks) among All Infants in SUPPORT Trial



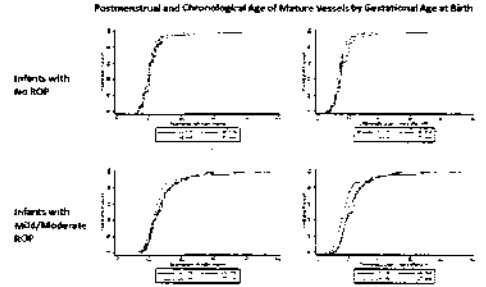
As expected, infants with severe ROP were less mature and lower birth weight than infants without ROP.

ROP type	Postmenstrual Age (weeks)										Chronological Age (weeks)									
	26	26.5	27	27.5	28	28.5	29	29.5	30	30.5	26	27	28	29	30	31	32	33	34	35
<b>Any ROP</b>	542	79	30	31.4	33.9	35.1	37.9	41.0	45.7	51.0	57.4	64.7	73.0	82.4	92.8	104.2	117.5	132.7	149.8	168.9
<b>Type II ROP*</b>	154	25.3	28.7	31.1	34.3	37.1	40.4	45.4	51.9	59.8	69.0	79.6	91.7	105.5	121.2	138.9	158.7	180.6	205.5	234.4
<b>Severe (Type I or Treatment) ROP</b>	128	12.1	12.7	13.9	15.1	16.4	18.6	21.1	25.0	31.1	38.4	47.4	58.3	72.1	88.6	107.9	130.0	155.7	185.0	218.1

\*Age of onset is defined as the age at which the earliest onset of ROP was first observed unless following the most appropriate protocol. \*Type II ROP is defined as Stage 1-3 with 0 or 1 plus sign or Stage 2-3 with 0 or 1 plus sign after exclusion of plus disease in the fellow eye. ROP with regression and Type I with retrolental fibroplasia were excluded.



In contrast to prior studies, less mature infants did not have onset of ROP at later chronological ages.



Retinal vessels matured several weeks later in infants with ROP as compared to infants with no ROP.

Infants with Severe ROP (n=138)	First exam with severe ROP criteria at discharge or home visit	First exam with severe ROP criteria at discharge or home visit
Postmenstrual age at first occurrence of severe ROP: weeks (mean, range)	36.3 (33.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (range)	42.9 (34.9-74.3)	38.3 (26.4-51.3)
First exam since a Ret back transfer to lower acuity hospital: n	2	4

In these 997 infants, we did not observe treatable ROP before 32 wks PMA; only 1 infant developed severe ROP after 45 wks PMA. Our contemporary data support continued use of the 2006 ROP screening guidelines. Some infants who are stable enough for back transfer or discharge home are still at risk to develop treatable ROP. A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. This paper does not involve discussion of unapproved or off-label, experimental or investigational use of a drug. Acknowledgments: The National Institutes of Health and the Swiss Research Foundation provided support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University, Case Western Reserve University, Cincinnati Children's Hospital Medical Center, Duke University, Emory University, Indiana University, RT International, Stanford University, Tufts Medical Center, University of Alabama at Birmingham, University of California - San Diego, University of Iowa, University of Iowa, University of Michigan, University of New Mexico, University of Rochester, University of Southwestern Medical Center, University of Texas Health Science Center at Houston, Wake Forest University, Wake State University, Yale University.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: Request Review of Presentation of Growth Outcomes SUPPORT  
**Date:** Tuesday, April 03, 2012 10:26:23 AM  
**Attachments:** SPR2012\_growth\_secondary\_for\_NRN\_review.pptx

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

**From:** Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]  
**Sent:** Tuesday, April 03, 2012 10:25 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; WCarlo@peds.uab.edu <WCarlo@peds.uab.edu>; 'Rich, Wade' <wrich@ucsd.edu>; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)' <richard.ehrenkranz@yale.edu>; Brenda Poindexter [bpoindex@iupui.edu] <bpoindex@iupui.edu>; 'kurt.schibler@cchmc.org' <kurt.schibler@cchmc.org>; mcw3@cwru.edu <mcw3@cwru.edu>; 'Roger Faix' <Roger.Faix@hsc.utah.edu>; 'Bradley Yoder' <Bradley.Yoder@hsc.utah.edu>; Das, Abhik <adas@rti.org>; 'Gantz, Marie' <mgantz@rti.org>; 'Nancy Newman' <nxs5@cwru.edu>; Wrage, Lisa Ann <wrage@rti.org>  
**Cc:** Duara, Shahnaz <SDuara@med.miami.edu>  
**Subject:** Request Review of Presentation of Growth Outcomes SUPPORT

Good Morning!

I have attached a copy of the presentation. I'll appreciate your comments/critique.

Thanks,

Cristina

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Wednesday, October 05, 2011 2:13 PM  
**To:** nfiner@ucsd.edu; WCarlo@peds.uab.edu; Navarrete, Cristina; Duara, Shahnaz; 'Rich, Wade'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; Brenda Poindexter [bpoindex@iupui.edu]; 'kurt.schibler@cchmc.org'; mcw3@cwru.edu; 'Roger Faix'; 'Bradley Yoder'; Das, Abhik; 'Gantz, Marie'; 'Nancy Newman'; Wrage, Lisa Ann  
**Subject:** Abstract\_Growth\_Outcomes\_SUPPORT1

Hi,

Here is the SUPPORT GROWTH OUTCOMES draft abstract. Please send comments back to Shahnaz and Tina.

Thanks

Rose



# NICHD NEONATAL RESEARCH NETWORK

## THE NICHD CONGRESSional CONFERENCE ON NEONATAL RESEARCH

The following are the speakers at the conference:

- Dr. James M. Anderson, University of Michigan, Ann Arbor, MI
- Dr. Stephen D. Durrant, University of North Carolina, Chapel Hill, NC
- Dr. Robert M. Anderson, University of North Carolina, Chapel Hill, NC
- Dr. Robert M. Anderson, University of North Carolina, Chapel Hill, NC
- Dr. Robert M. Anderson, University of North Carolina, Chapel Hill, NC



...will not involve discussion of  
unapproved or off-label experimental or investigational  
use of a drug.

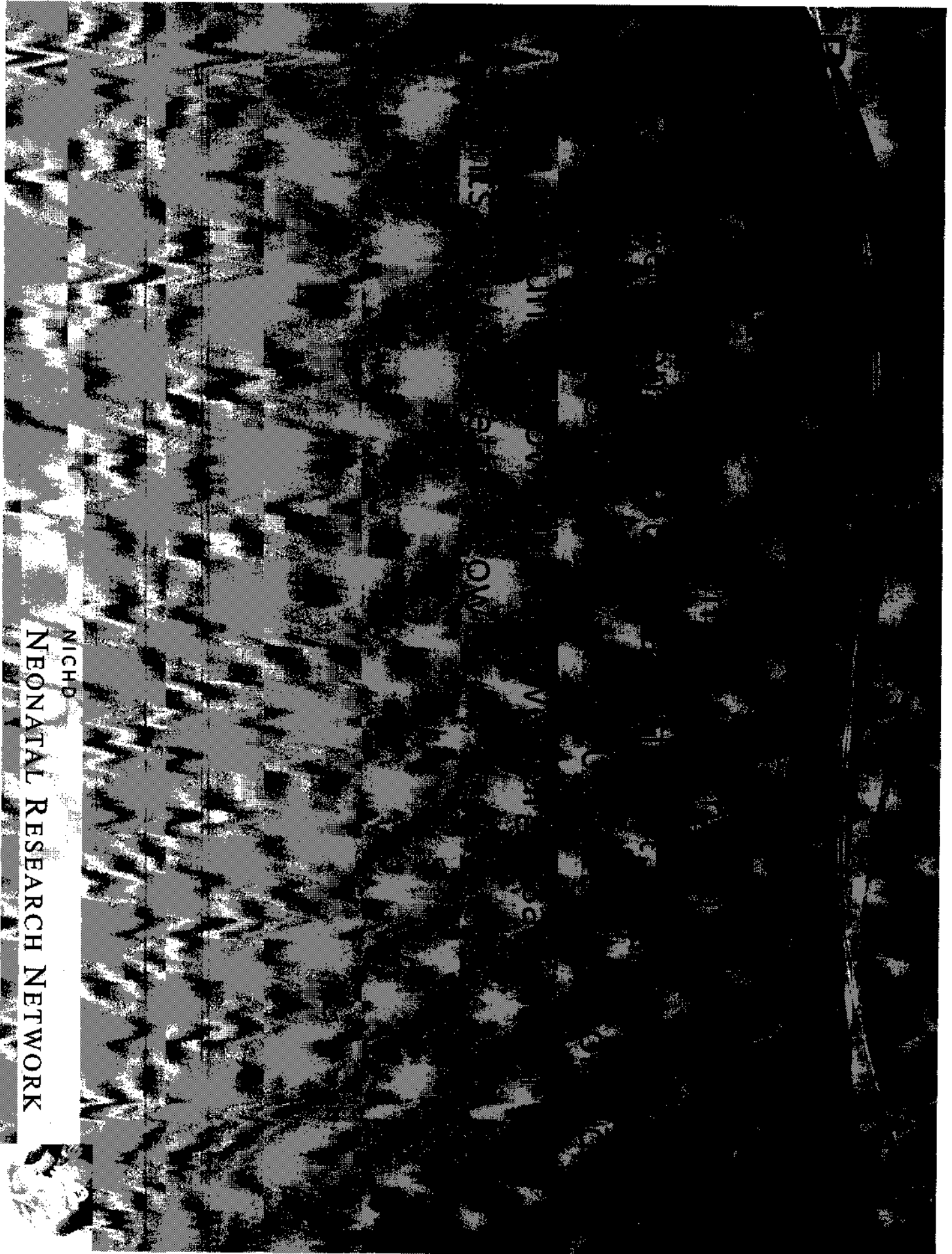
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...of the ...  
...inconsistency in the relationship between  
oxygenation and postnatal growth.  
There is no information on the relationship of growth  
to differences in target oxygen saturation from birth.



NO...ANCE...BROW...A 2...RE...WHI...  
ORGANIZATION...GET SATISFACTION...91...  
95-98...WAS MADE AT 32 WEEKS PMA...THEY WERE STILL...  
DEPENDENT. (ASKED NEJM 2003;34:959-969)

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# Opp

(59)

- Redirection from diaphragm to two target (a)
- Conventional oxygen saturation of 91-95% (=HIGH)
- Low oxygen conventional oxygen saturation of 85-89% (=LOW)

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80% with the lowest 500 ZIP codes

enroll

10%

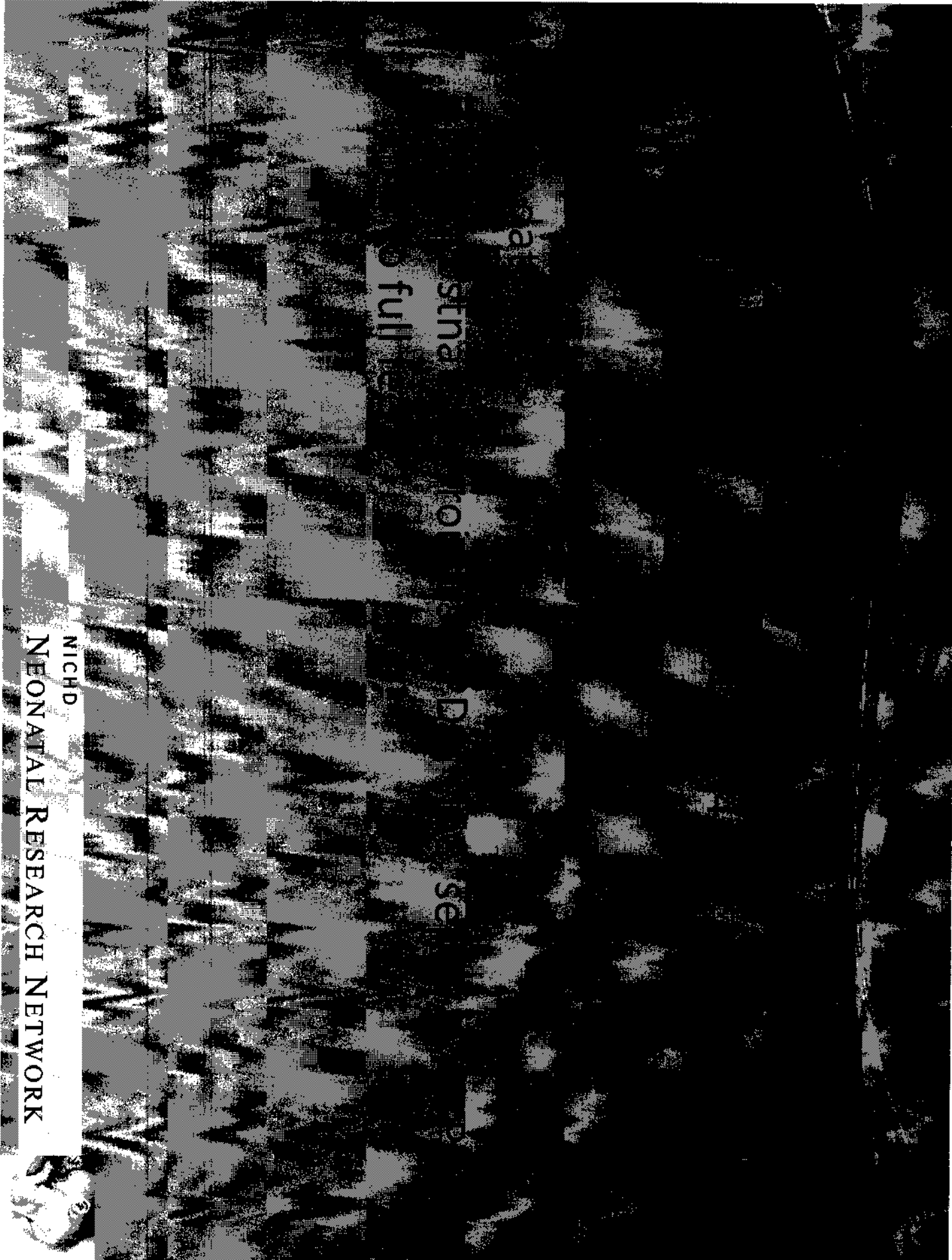
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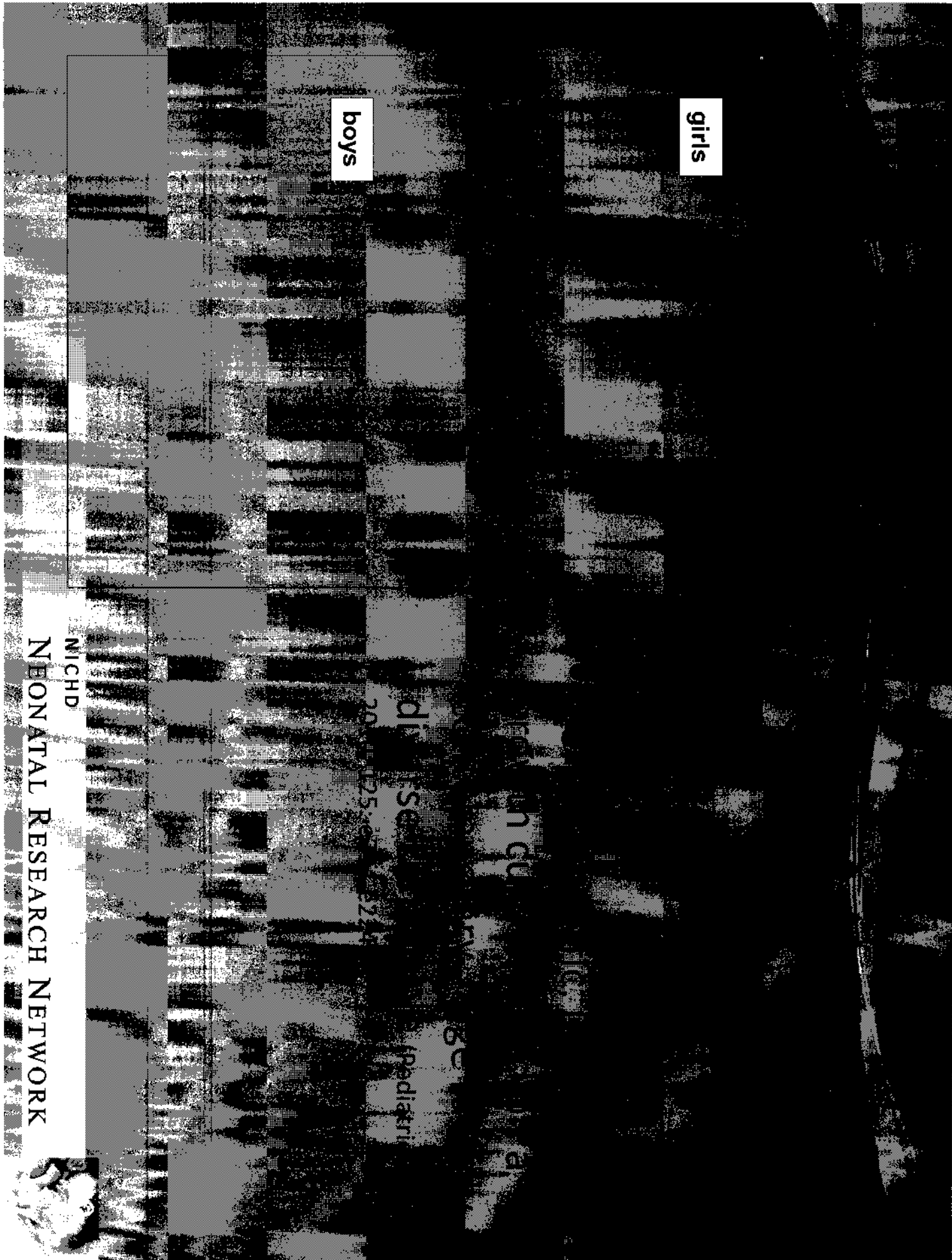
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Office of the Surgeon General  
Department of Health and Human Services  
Office of Pediatric Nursing, 25: 62  
18-22 month growth: WHO 2006 Growth Table

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boys

girls

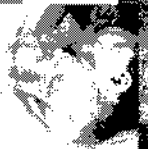
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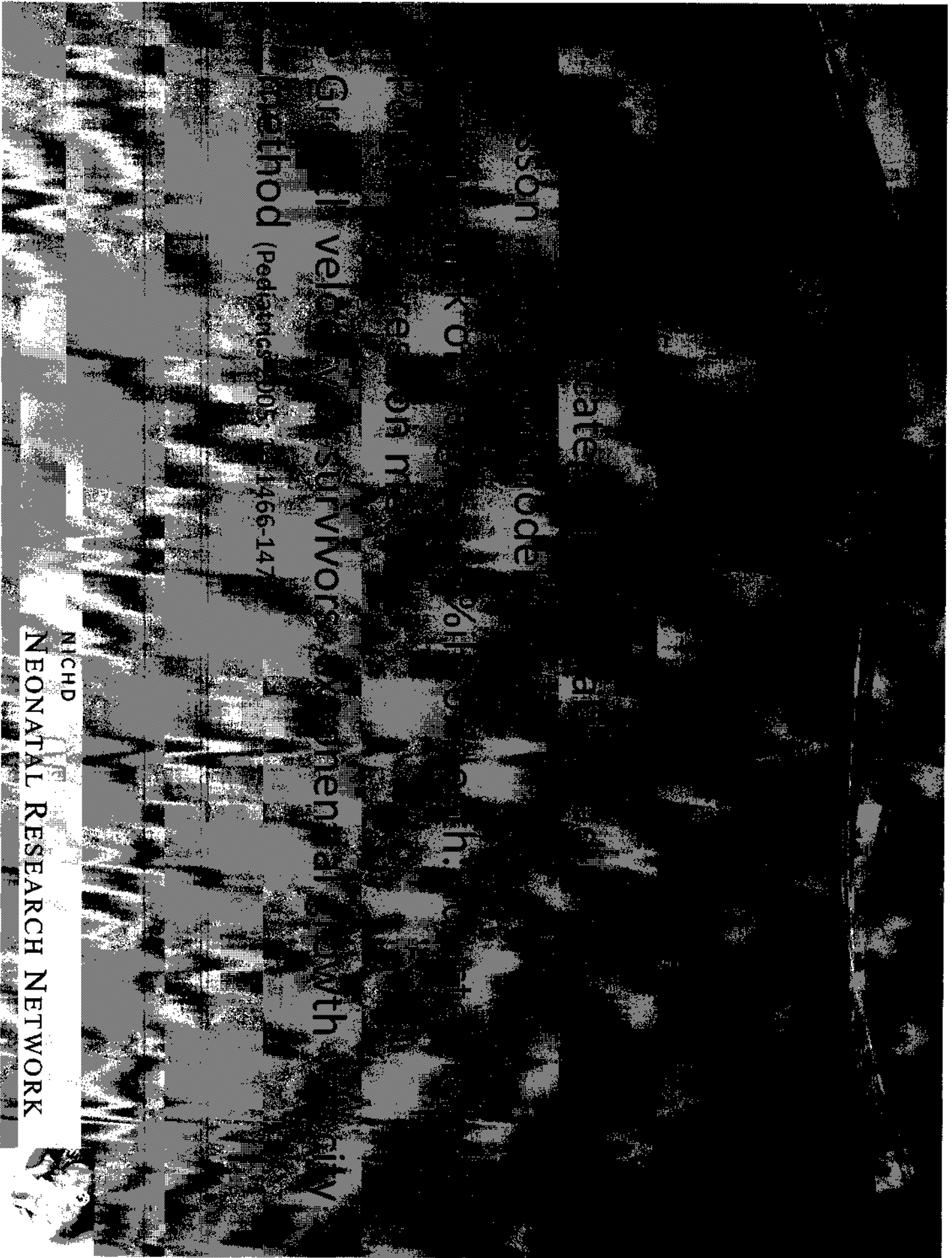


# 2006 WHO weight-for-age gender specific growth standards

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Method (Pediatrics) 2005; 116:1466-1471

Growth velocity of survivors of neonatal encephalopathy

University

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1316 underwent randomization in SUPPORT

506 randomized before  
secondary study started

810 with data available for growth analysis

402 were assigned to  
target saturation of 85-89%

333 survived to 36 weeks

296 returned at 18-22m

408 were assigned to  
target saturation of 91-95%

348 survived to 36 weeks

313 returned at 18-22m

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Characteristic	Low Saturation (n=402)	High Saturation (n=408)
----------------	---------------------------	----------------------------

Gestational age, weeks *	26.2 ± 1.1	26.2 ± 1.1
Male (%)	53	58
Birth weight, g	839 ± 186	840 ± 191
Birth weight < 10th %ile	10.0	13.0
HC at birth, cm	23.5 ± 1.8	23.6 ± 1.9
HC at birth < 10th %ile	10.4	13.3
Length at birth, cm	33.4 ± 2.9	33.3 ± 2.9
Length at birth < 10th %ile	12.6	14.3

\*plus-minus values are means ± SD

no difference in ethnicity, antenatal steroids, mode of delivery, APGAR score, maternal education

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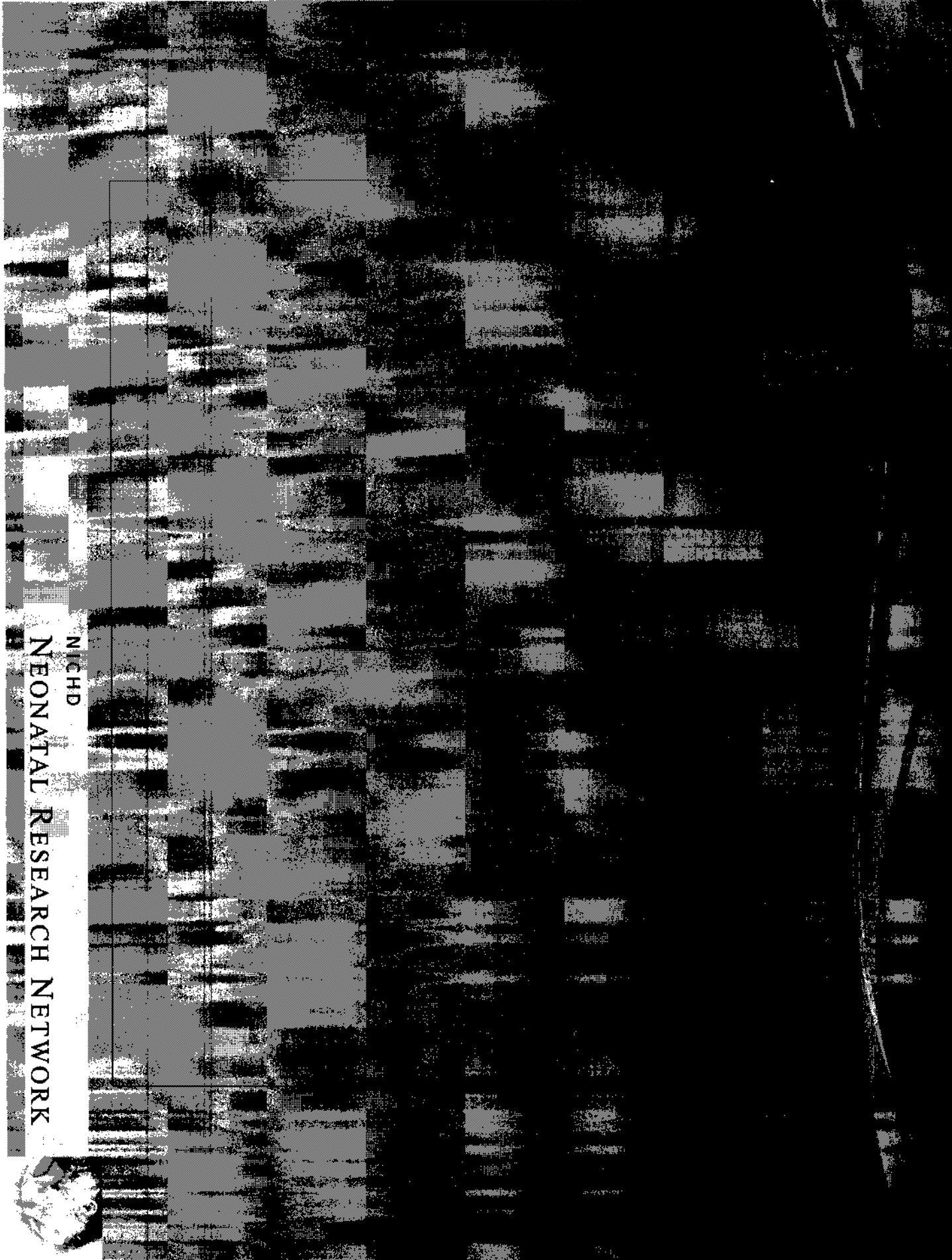
Characteristic	Low Saturation (n=402)	High Saturation (n=408)	p-value <sup>1</sup>
% Death by 36 weeks PMA	17.2	14.7	0.32
% BPD, oxygen at 36 weeks PMA	39.6	45.4	0.10
% BPD, moderate	20.3	23.4	0.27
% BPD, severe	19.1	21.3	0.54
% Postnatal steroids for BPD	8.4	9.8	0.46
Median days on ventilator (IQR)	9(2-33)	14 (2-36)	0.17
Median days on supplemental O <sub>2</sub> (IQR)	47 (20-80)	60 (30-90)	0.0094**
Median SpO <sub>2</sub> while on supplemental O <sub>2</sub> (IQR)	92 (91-94)	94 (93-95)	<.0001**

<sup>1</sup>adjusted for multiple birth clustering using PREGMIXT stratification variables GA, group, and center, using linear mixed models for continuous variables and robust Poisson regression for categorical variables; unadjusted rank sum tests for days on ventilator and supplemental O<sub>2</sub>

p<0.05

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Characteristic (%)	Low Saturation (n=402)	High Saturation (n=408)	p-value*
NEC (Bell Stage $\geq 2$ )	12.9	11.9	0.63
PDA	45.6	49.6	0.29
Late-onset Sepsis	36.3	34.4	0.70
IVH (Grade 3 or 4)	14.8	15.2	0.84
PVL	4.1	5.0	0.59

adjusted for age, sex, gestational age, and SUPPOD stratification variables from a single center using logistic regression.

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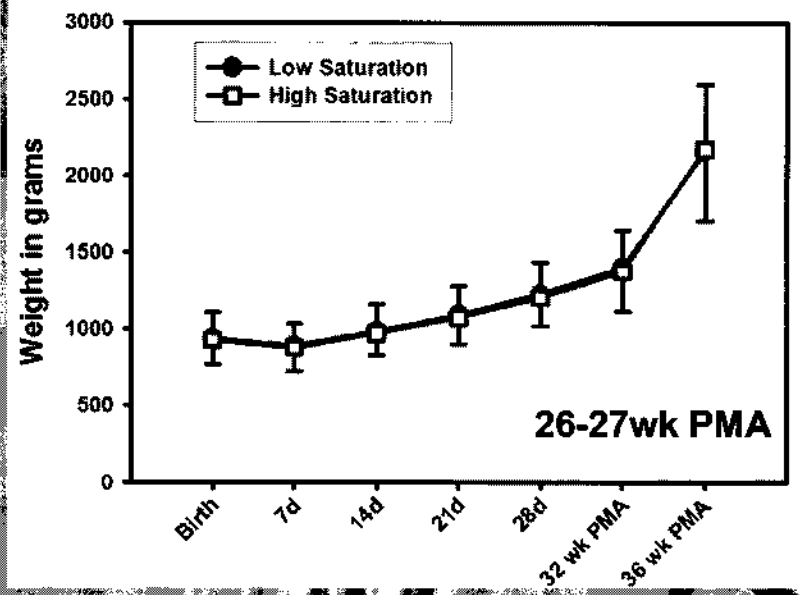
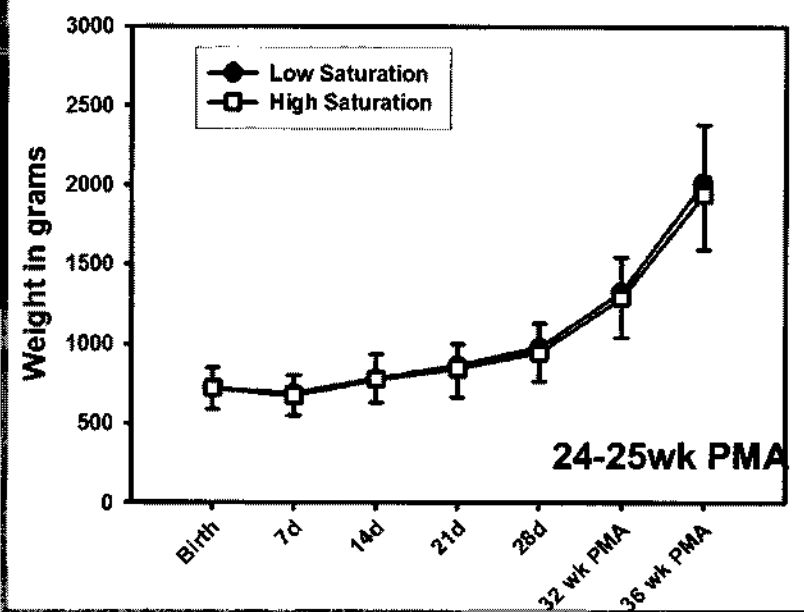
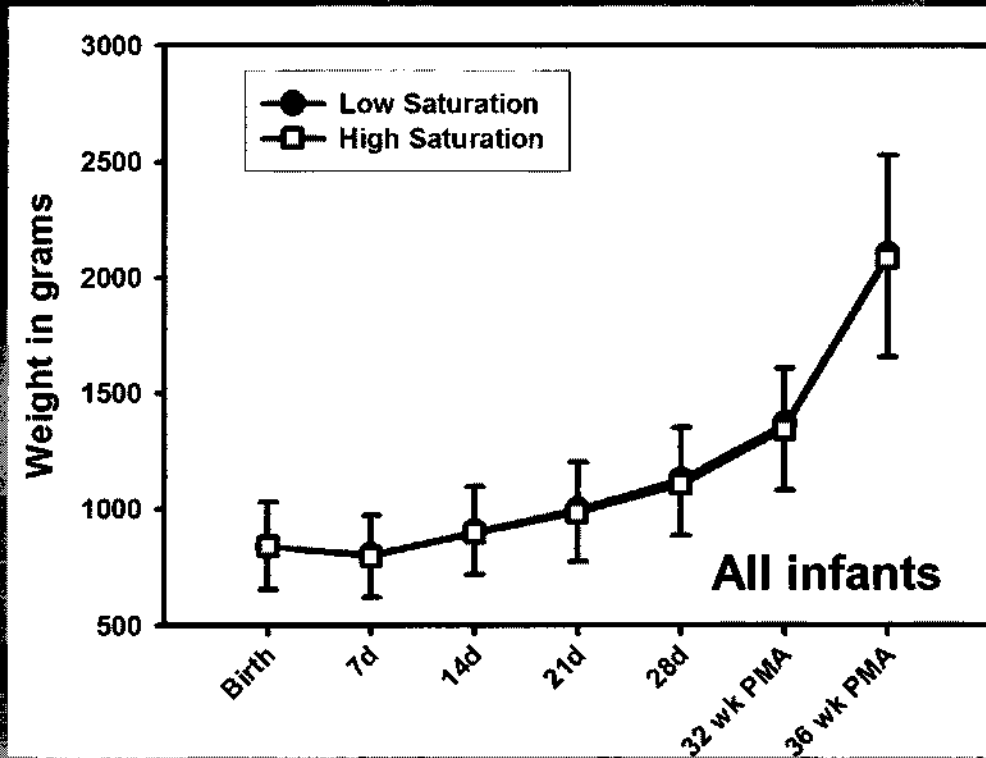


Total Energy Intake (parenteral + enteral) (kcal/kg/d)**	Low Saturation (n=402)	High Saturation (n=408)	p-value
Day 7	84 ± 25	82 ± 22	0.24
Day 14	92 ± 26	90 ± 25	0.57
Day 21	94 ± 38	93 ± 28	0.60
Day 28	97 ± 30	96 ± 29	0.67
32 weeks PMA	104 ± 30	105 ± 27	0.77
36 wks PMA	111 ± 36	108 ± 33	0.44
Age at first enteral feed, med (IQR)	4 (3-7)	4 (3-7.5)	0.38
Age at full enteral feeds, med (IQR)	23 (16-34)	24 (16-34)	0.76

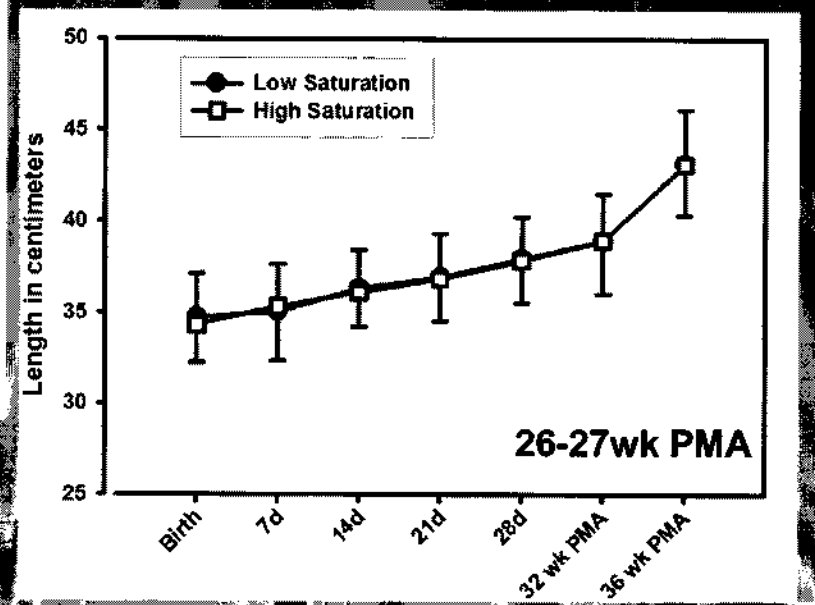
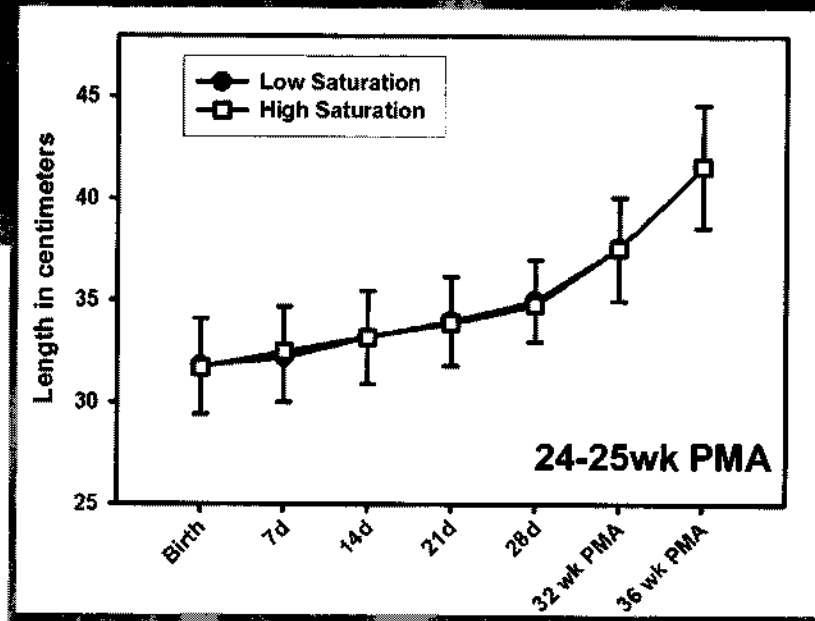
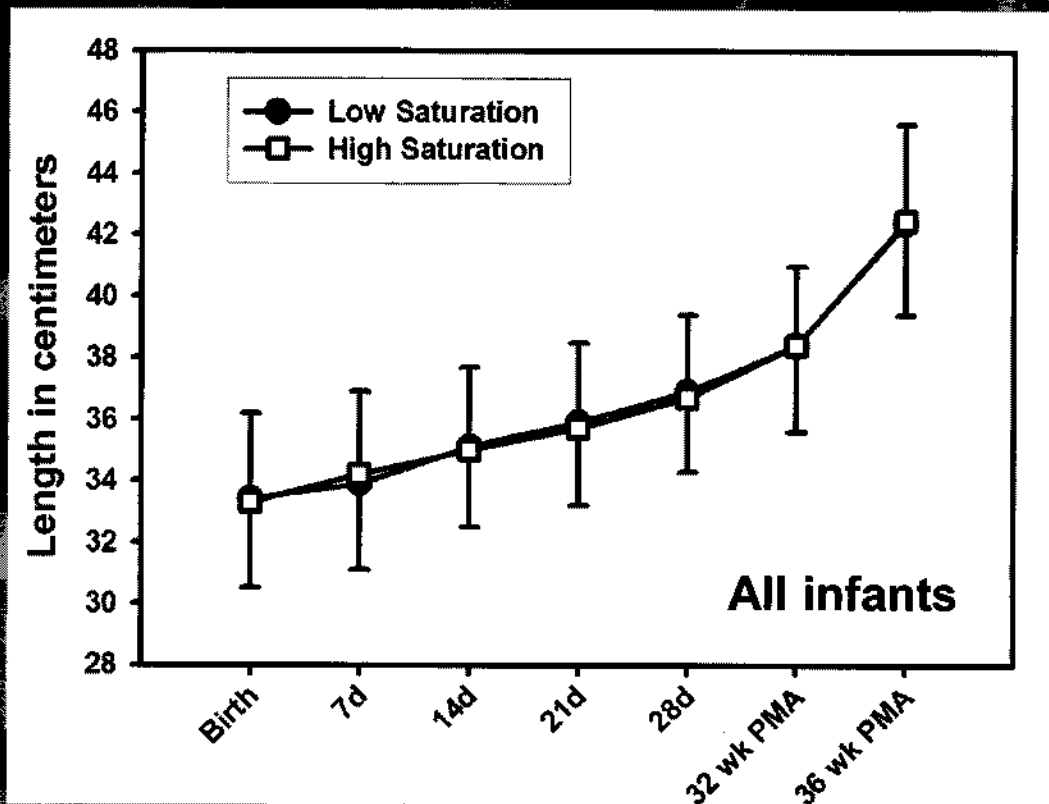
US minus values are means ± SD, full enteral feeds > 120 kcal/kg/d  
 linear mixed model, unadjusted rank-sum test for age at first enteral feed and age at first full enteral feeds

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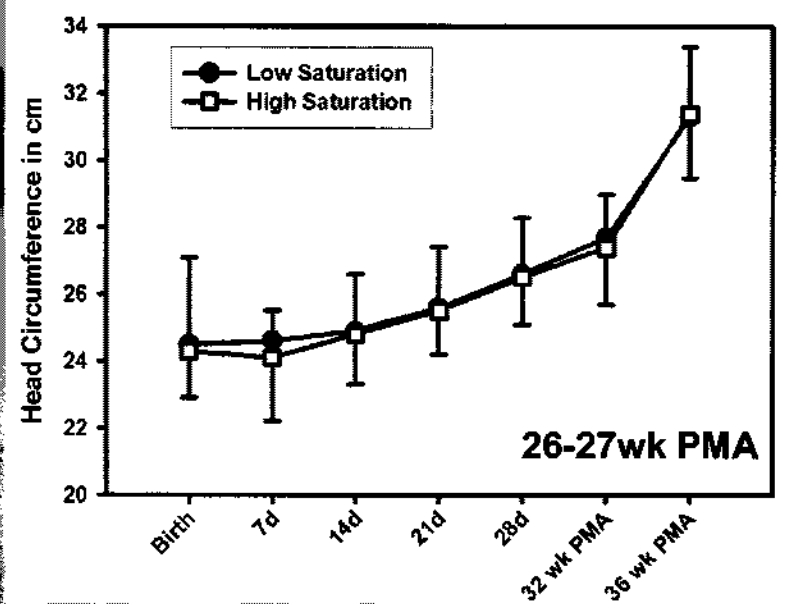
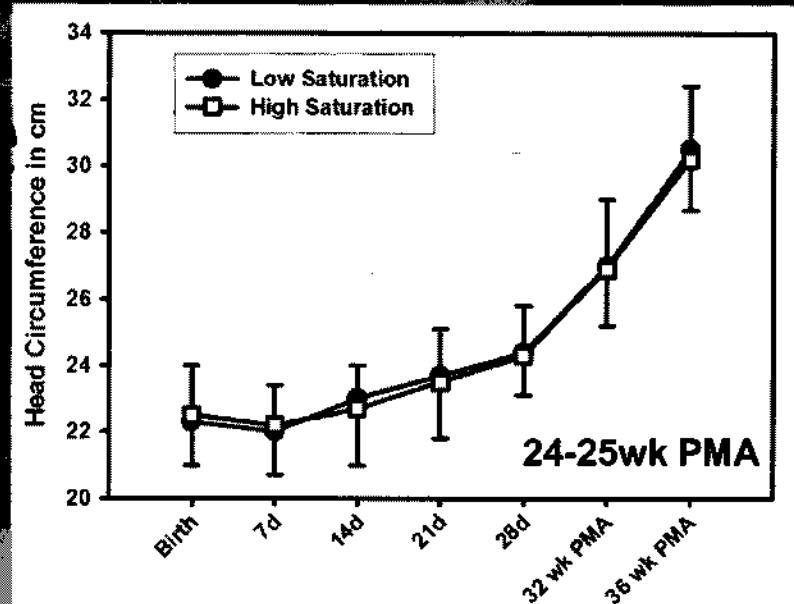
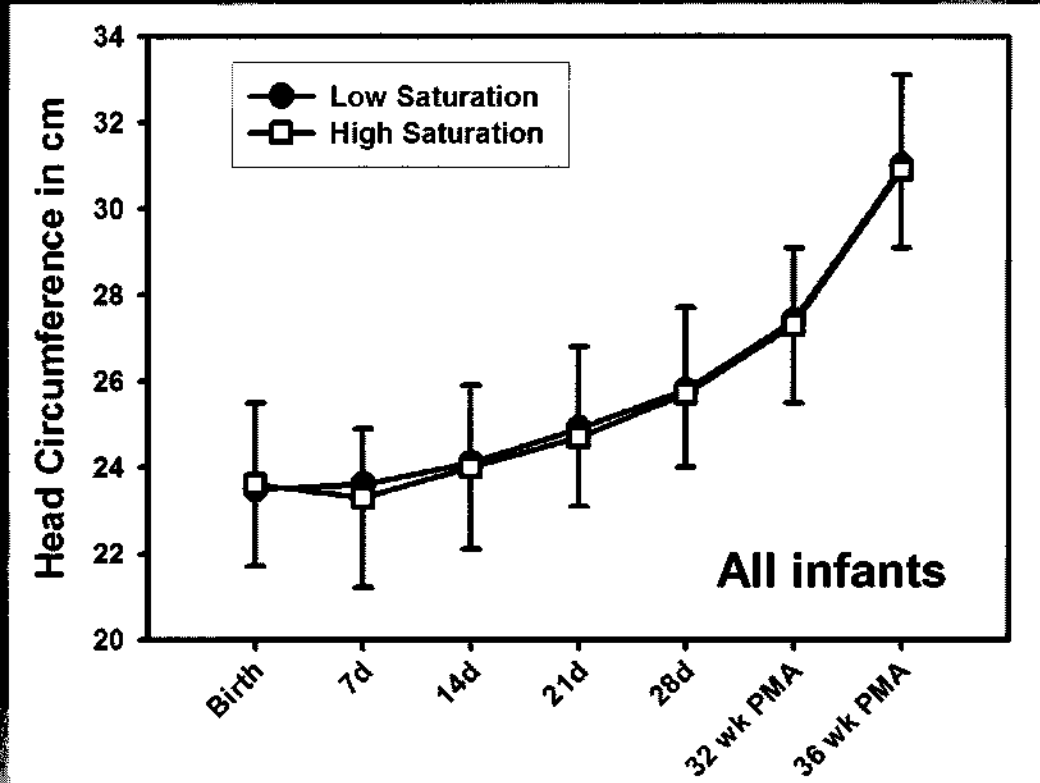


Mean  $\pm$  SD, no difference



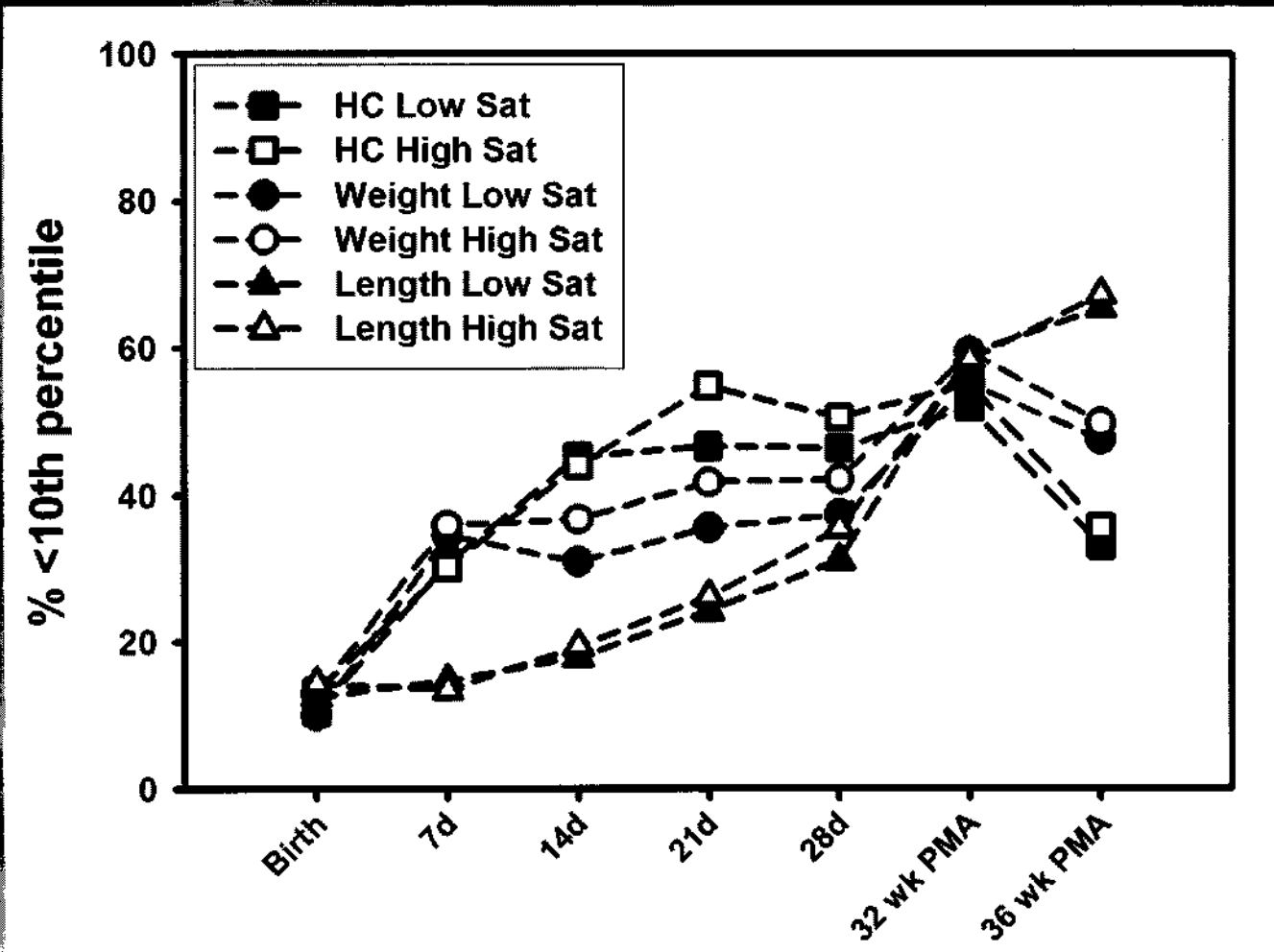
Mean ± SD, no difference





Mean  $\pm$  SD, \*No difference





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**Outcome (%)**

**Low  
Saturation  
N=402**

**High  
Saturation  
N=408**

**Relative Risk  
(95% CI)\***

**p-value**

36 weeks PMA				
Death or wt < 10th %ile	56	58	0.95 (0.8-1.1)	0.43
Wt < 10th %ile	47	50	0.93 (0.8-1.1)	0.30
18-22 months FU:				
Death or wt < 10th %ile	35	31	1.1 (0.9-1.4)	0.22
Wt < 10th %ile	16	14	1.1 (0.8-1.7)	0.49

\*Robust Poisson regression model; adjusted for multiple birth clustering, SUPPORT stratification variable, center, and gestational age group

No difference when analyzing according to AGA or SGA status nor by gestational age stratification (24-25 weeks and 26-27 weeks).

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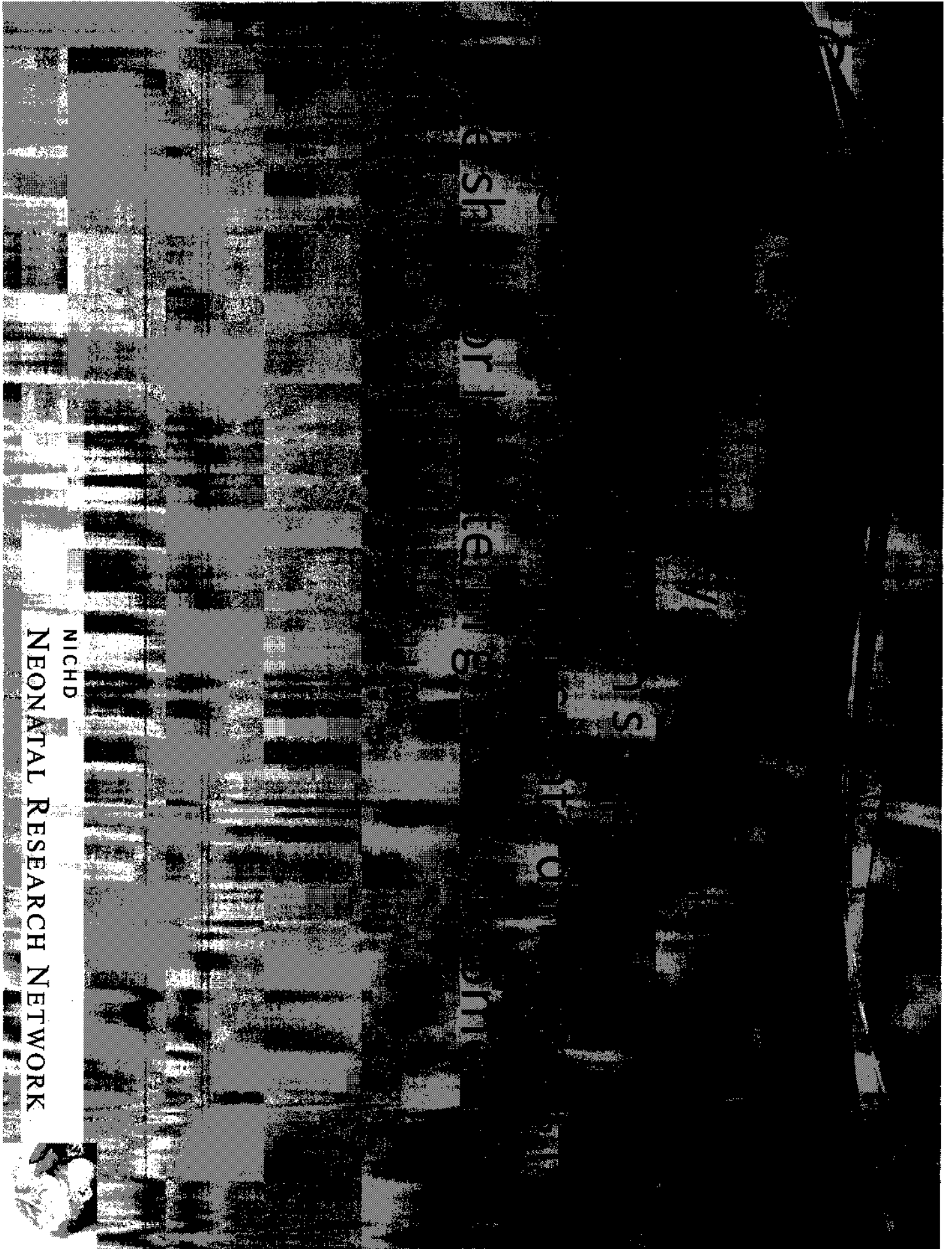
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<b>GV in-hospital</b>	<b>Low Sat</b>	<b>High Sat</b>	<b>p-value<sup>†</sup></b>
All Infants (mean $\pm$ SD, n)	13.6 $\pm$ 2.4, 260	13.4 $\pm$ 2.6, 275	0.69
GA 24-25 weeks	13.9 $\pm$ 2.1, 98	13.1 $\pm$ 2.8, 110	0.29
GA 26-27 weeks	13.4 $\pm$ 2.6, 162	13.6 $\pm$ 2.5, 165	0.55

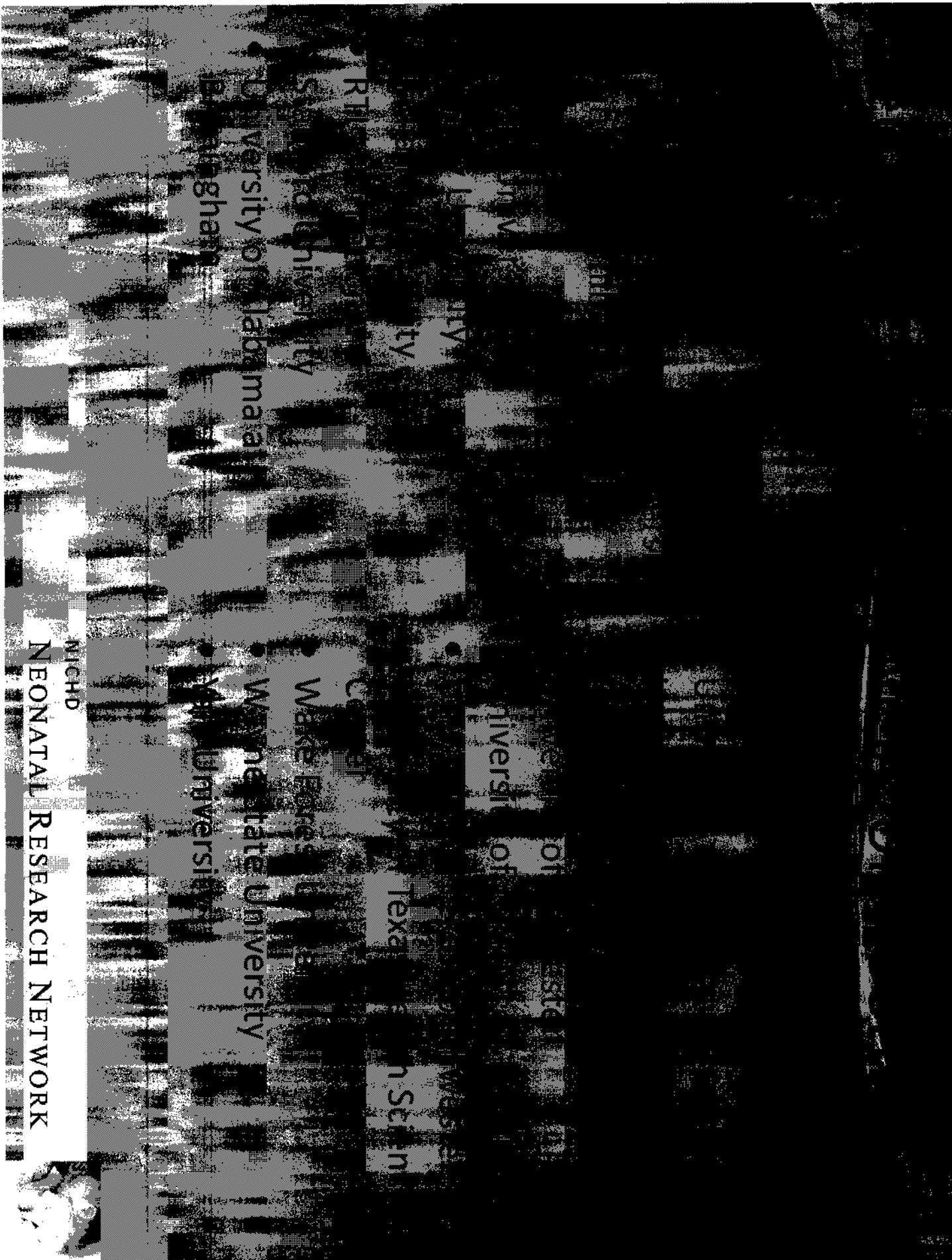
...calculated for the survivors to 36 weeks of age. ...the ...  
...growth velocity ...  
...birth clusters and ... variables. A group ...  
...enter for GA subgroups using linear mixed models.



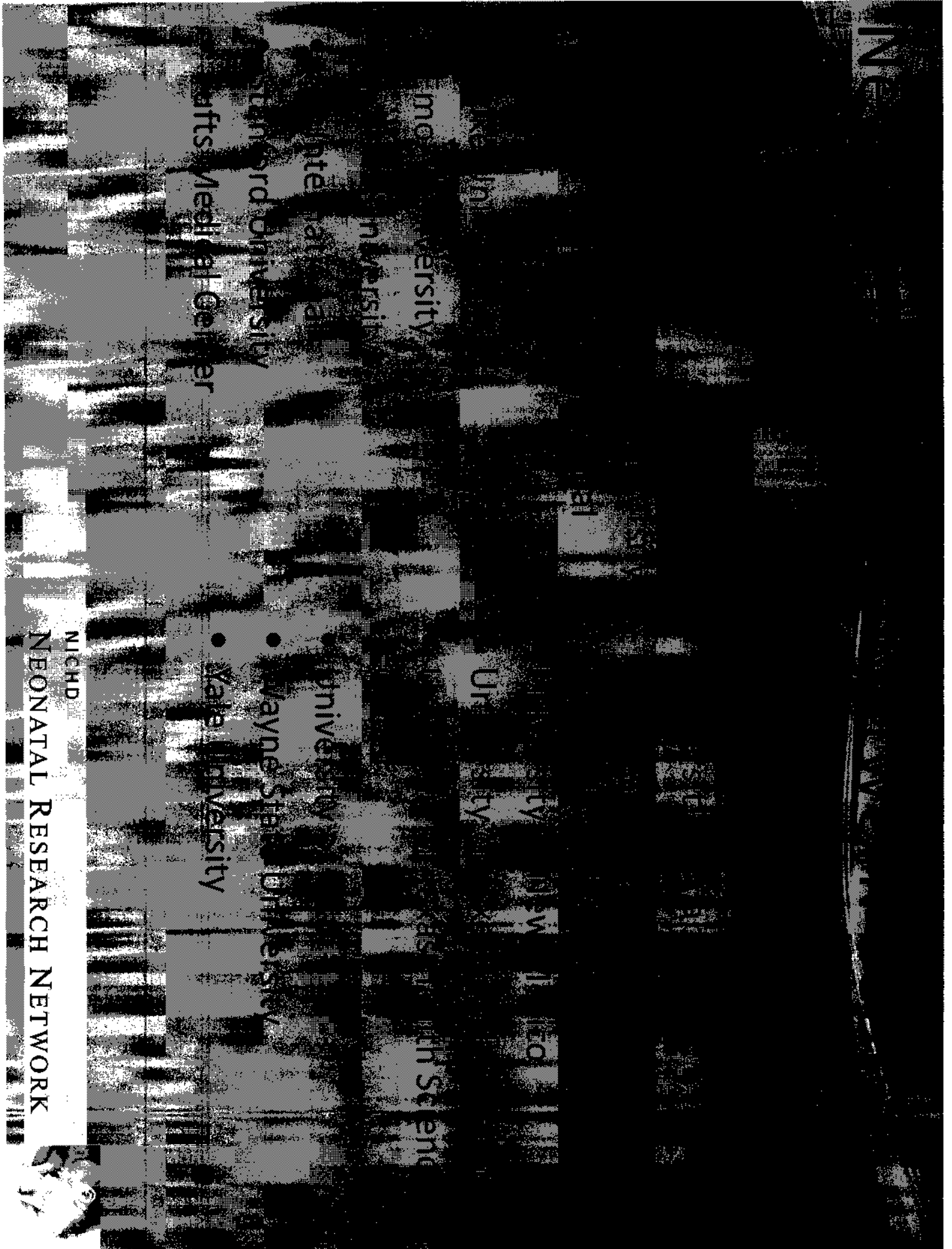




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Harvard Medical Center  
Harvard University

- Wayne State University
- Yale University

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- National Children's Hospital
- Ohio State University
- International
- Stanford University

- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center
- Wayne State University

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**From:** [Vaucher, Yvonne](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Gantz, Marie](#); [wcarlo@peds.uab.edu](#); [Das, Abhik](#)  
**Cc:** [Vaucher, Yvonne](#); [Finer, Neil](#)  
**Subject:** FW: Boilerplate | SUPPORT FU Combined paper  
**Date:** Tuesday, April 03, 2012 10:24:00 AM  
**Attachments:** [CombinedCPAPOximeterNEJM\\_VaucherNEJM0040112.docx](#)

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Here is my first draft at combining the papers, without Marie's comments, so we still need to shorten some but getting there. I am combining the tables. I included only those outcomes described in the original protocol (i.e. Death and NDI and the individual components.

Yvonne

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**From:** Vaucher, Yvonne  
**Sent:** Monday, April 02, 2012 9:39 PM  
**To:** Myriam Peralta, M.D.  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

2867 words (excluding abstract and references) so almost there. We need to get down to 2700 so see if you can cut somewhere.

Yvonne

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**From:** Myriam Peralta, M.D. [[MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)]  
**Sent:** Sunday, April 01, 2012 6:08 PM  
**To:** Vaucher, Yvonne  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

Yvonne where you able to put some of the paper together, I can work on it this week if you want to send me what you have and I will work on it some,  
Also I can start on the letter to respond to the reviewers, thanks.

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**From:** Vaucher, Yvonne [[yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu)]  
**Sent:** Saturday, March 31, 2012 2:00 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]; [Wally Carlo \(wcarlo@uab.edu\)](#); [Finer, Neil](#); [Myriam Peralta, M.D.](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Boilerplate | SUPPORT FU Combined paper

All,  
Re boilerplate: We can discuss revised title, authors on Friday.

Yvonne

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**From:** Archer, Stephanie (NIH/NICHD) [E] [[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)]  
**Sent:** Wednesday, March 28, 2012 1:15 PM  
**To:** [Wally Carlo \(wcarlo@uab.edu\)](#); [Finer, Neil](#); [Myriam Peralta-Carcelen \(MPeralta@peds.uab.edu\)](#); [Vaucher, Yvonne](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Boilerplate | SUPPORT FU Combined paper

Attached is a combined author list and boilerplate for the new combined SUPPORT FU paper. The only center that had two different authors on each paper was Indiana (highlighted in yellow in the attachment). Need to decide whether to include both of them, or not, and make necessary adjustments to the author list and acknowledgements

(at the moment I have them listed in both).

Stephanie

**Early CPAP vs. Surfactant and Oxygen Saturation targets versus Surfactant in Extremely Preterm Infants: ~~Death and Neurodevelopmental Outcomes~~ Outcome in Early Childhood at 18 to 22 Months**

Yvonne E. Vaucher, MD MPH<sup>1</sup>; Myriam Peralta-Carcelen, MD MPH<sup>2</sup>; Neil N. Finer, MD<sup>3</sup>; Waldemar A. Carlo, MD<sup>4</sup>; Michele C. Walsh, MD MS<sup>5</sup>; Marie G. Gantz, PhD<sup>6</sup>; Abbot R. Laptook, MD<sup>7</sup>; Bradley A. Yoder, MD<sup>8</sup>; Roger G. Faix, MD<sup>9</sup>; Abhik Das, PhD<sup>10</sup>; Kurt Schibler, MD<sup>11</sup>; Wade Rich, RRT<sup>12</sup>; Nancy S. Newman, RN<sup>13</sup>; Betty R. Vohr, MD<sup>14</sup>; Kimberly Yolton, PhD<sup>15</sup>; Roy J. Heyne, MD<sup>16</sup>; Deanne E. Wilson-Costello, MD<sup>17</sup>; Patricia W. Evans, MD<sup>18</sup>; Ricki F. Goldstein, MD<sup>19</sup>; Michael J. Acarregui, MD<sup>20</sup>; Ira Adams-Chapman, MD<sup>21</sup>; Athina Pappas, MD<sup>22</sup>; Susan R. Hintz, MD MS Epi<sup>23</sup>; Anna M. Dusick, MD FAAP<sup>16</sup>; Elisabeth C. McGowan, MD<sup>17</sup>; Richard A. Ehrenkrantz, MD<sup>18</sup>; Anna Bodnar, MD<sup>6</sup>; Charles R. Bauer, MD<sup>19</sup>; Janell Fuller, MD<sup>20</sup>; T. Michael O'Shea, MD MPH<sup>21</sup>; Gary J. Myers, MD<sup>22</sup>; Rosemary D. Higgins, MD<sup>23</sup> 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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## ABSTRACT

**BACKGROUND:** ~~The randomized controlled SUPPORT trial randomized trial demonstrated that premature infants, 24 0/7 to 27 6/7 weeks gestation, to treatment with early CPAP vs. early surfactant administration and to treatment with lower (85%-89%) vs. higher (91-95%) saturation targets. There was no difference in neonatal outcomes between infants receiving early CPAP vs. early surfactant. Lower oxygen saturation limits were associated with less retinopathy of prematurity but increased mortality. treatment with early CPAP is an alternative to early intubation with surfactant administration, resulting in similar rates of death or BRD in infants born at 24 to 27 weeks gestation. We hypothesized~~ The pre-specified hypothesis of this study was that that, compared to early intubation, early CPAP would decrease the composite outcome of death or neurodevelopmental impairment and lower oxygen saturation targeting would each decrease the risk of the composite outcome of death or neurodevelopmental impairment (NDI).

**METHODS:** ~~We followed surviving infants, 24 0/7 to 27 6/7 weeks gestation, randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth and conventional ventilation. The primary composite outcome was death or neurodevelopmental impairment (NDI) at 18-22 months corrected age. Analyses were adjusted for gestational age stratum, center and familial clustering.~~

**RESULTS:** ~~Death or NDI was determined for 1234/1316 (93.8%) of all infants enrolled in SUPPORT infants; 93.6% (990/1058) of hospital survivors to hospital discharge were evaluated at 18-22 months corrected age. The composite outcome of death or NDI was not different in the CPAP [27.9% (173/621)] vs. Surfactant [27.9% (173/621)] groups (occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (RR 0.93, 95% CI 0.78-1.1, p=0.39)) or in the lower [30.2% (185/612)] vs. higher [27.5% (171/622)]; oxygen saturation groups (RR risk 1.12, 95% CI 0.94 to 1.32; p=0.21). There Mortality was increased in the were no significant differences between treatment arms in death (CPAP 18.4 vs. Surf 21.9%) lower (22.1%) compared to the higher (10.5%) oxygen saturation group (RR 1.25; 95% CI, 1 to 1.55, p=0.046).~~

~~NDI (CPAP 10.9 vs. Surfactant 9.1%), or components of NDI including cognitive score < 70 (CPAP 7.2 vs. Surfactant 7.6%), moderate/severe cerebral palsy (CPAP 4.1 vs. Surfactant 4.0%), blindness (CPAP 0.8 vs. Surfactant 1.5%) and hearing impairment (CPAP 3.3 vs. Surfactant 1.5%)~~

**CONCLUSION:** ~~We found no significant differences in the composite outcome of death or NDI at 18-22 months corrected age in between extremely premature infants who were randomized to received either early CPAP with a limited ventilation strategy or early intubation with surfactant administration and conventional ventilation or who were assigned to lower compared to higher oxygen saturation ranges.~~

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## BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications including intraventricular hemorrhage or periventricular leukomalacia, symptomatic patent ductus arteriosus, necrotizing enterocolitis, sepsis, prolonged ventilation, bronchopulmonary dysplasia and severe retinopathy of prematurity.<sup>4-12</sup> Although surfactant administration decreases both death and BPD, randomized controlled trials of various respiratory interventions including high frequency oscillatory ventilation, high frequency jet ventilation, and inhaled nitric oxide have failed to show that any these treatments consistently decrease mortality and morbidity or improve developmental outcome.<sup>13-17</sup> Likewise, the recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely premature infants born from 24 through 27 weeks gestation demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth results in similar rates of death or BPD at 36 weeks gestation, air leak, severe intraventricular hemorrhage and other major outcomes.<sup>18</sup>

Although for preterm infants with infants with respiratory disorders, oxygen supplementation is vital for survival, oxygen supplementation increases the risk of retinopathy of prematurity,<sup>1</sup> bronchopulmonary dysplasia,<sup>2,3</sup> periventricular leukomalacia,<sup>4</sup> and cerebral palsy.<sup>5</sup> Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials.<sup>6,7</sup>

The recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth is an alternative to surfactant administration after intubation, and results in similar rates of death before or BPD at 36 weeks gestation in extremely premature infants born at from 24-0/7 to 27-6/724 through 27 weeks gestation.<sup>18</sup> Compared with randomization to early intratracheal to surfactant administration, randomization to early CPAP resulted in less frequent need for postnatal steroids and shorter duration of mechanical ventilation. Both treatment groups had similar rates of air leak, severe intraventricular hemorrhage and other major outcomes. Mortality was lower in the most immature, 24-25 week gestation, stratum of the CPAP arm. The SUPPORT trial demonstrated no difference in a composite outcome of severe retinopathy of prematurity or death before discharge between a lower-oxygen-saturation target group (85-89%) and a higher-oxygen-saturation target group (91-95%). However, in the lower-oxygen-saturation target group severe retinopathy of prematurity among survivors decreased (8.6% vs. 17.9%; RR 0.52; 95% CI 0.37 to 0.73; p<0.001) and death before discharge was increased (19.9% vs. 16.2%; RR 1.27; 95% CI 1.01 to 1.60; p=0.04) compared to the higher saturation target.<sup>6</sup> Similarly, a recent preliminary pooled results analysis that included the SUPPORT trial data and three other subsequently completed multi-center randomized controlled trials (two trials were stopped early) with a total of 3631 infants showed that infants randomized to an oxygen saturation target of 91-95% had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (14.4% vs 17.3% respectively, P=0.015).<sup>7</sup>

The SUPPORT trial in extremely low birth weight (ELBW) infants was powered to have adequate sample size to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to randomization to treatment with early surfactant administration after intubation, randomization to early, non-invasive CPAP compared to early surfactant administration after intubation, and a limited ventilation

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strategy ~~and that lower compared to higher oxygen saturation limits would each would~~ decrease the rate ~~would~~ incidence of a composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age.

## METHODS

### Study Design

1316 extremely preterm infants, ~~(24 weeks 0 days to 27 weeks 6 days through 27 weeks gestation)~~, born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled prior to delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). ~~M-, and~~ multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery and a limited ventilation strategy as described previously if subsequent intubation was required or intubation with surfactant administration within an hour after birth and subsequent conventional ventilation<sup>18</sup>. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group). Procedures for enrollment, intervention, and data collection have been previously reported.<sup>18</sup> The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

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### Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months of age, corrected for prematurity (CA), by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3<sup>rd</sup> ed. (BSID-III).<sup>19</sup> Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.<sup>20</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).<sup>21</sup> Moderate to severe cerebral palsy was defined by a GMFCS- ~~≥~~ 2 plus an abnormal exam as stated above. Hearing loss, defined as the inability to understand directions of the examiner and communicate with or without amplification, and visual ~~impairment~~ impairment, defined as vision < 20/200, were determined based on examination and parental report.

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage  $\geq$  2), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month

visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

#### Outcome

The ~~pre-specified primary follow-up~~ outcome at follow-up for this trial was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age [CA]. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS  $\geq$  2, ~~presence of moderate~~ or severe cerebral palsy, permanent hearing or bilateral visual impairment ~~t~~.

#### Statistical Analysis

Pre-specified outcomes at 18 to 22 months corrected age were mortality or NDI, NDI, cerebral palsy, blindness in at least one eye. The sample size calculations were based on NRN data on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months ~~CA corrected age~~. Details regarding sample size calculations for the SUPPORT trial have been previously reported.<sup>18</sup>

~~(Marie/Abhik- Do we need a statement here about how the lower incidence of NDI using the Bayley III affected power analysis? Also see comment # 3 from Statistical reviewer #1 re pre-defined treatment effects)~~  
Exploratory secondary outcomes at 18 to 22 months corrected age were death and components of NDI (i.e., cognitive composite score < 70, GMFCS  $\geq$  2, moderate/severe cerebral palsy, bilateral blindness and bilateral hearing impairment). ~~(Marie/Abhik- We need to say something here about interactions between CPAP/SURF and High/Low Sat arms)~~

Data were entered in standard forms and were transmitted to RTI International which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months ~~CA, corrected age could be assigned~~. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as prespecified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Two-sided p values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. ~~(Marie/Abhik-Need statement re multiple comparisons)~~

## RESULTS

~~Of the 1316 infants enrolled in the SUPPORT trial, 250 two hundred fifty eight children were known to have died before 18-22 months (Figure a and b). Sixty eight children of the remaining 1058 children, 68/1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of the 990 children seen for evaluation, NDI was determined for 976 children; 14 children were seen~~

but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of ~~SUPPORT~~ enrolled children. The mean corrected age at neurodevelopmental assessment and the follow-up rates were ~~was~~ similar for both all treatment arms, (CPAP  $19.9 \pm 2.4$  months vs. Surf  $20.1 \pm 2.7$  months, unadjusted  $p=0.31$ ). There ~~was no~~ difference in the follow-up rate between the CPAP and Surfactant arms (93.7 vs. 93.4%) of the trial.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%,  $p=0.01$ ), and more likely to have only public insurance (69 vs. 52%,  $p=0.008$ ). No other demographic variables or neonatal characteristics were significantly different between the groups. (Marie/Abhik-Stat Reviewer #2 asked whether sensitivity analyses were performed to determine if the LTFUP group might have changed conclusions)

Follow-up Cohort Characteristics: (Table 1) Almost all mothers (96%) received antenatal steroids. ~~There were more SGA infants and more infants with ROP in the higher compared to the lower saturation group. Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation.~~ Compared to the Surfactant arm, infants in the CPAP arm with follow-up at 18-22 months were significantly more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids. ~~Other demographic characteristics and neonatal outcomes were similar in infants in the Surfactant and CPAP arms. Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation.~~ (MARIE-DO THESE PERCENTAGES HOLD FOR THE FUP COHORT ALSO?)

Primary neurodevelopmental outcome: (Table 2) The composite outcome of death or NDI at 18-22 months corrected age was not a significantly different between the CPAP and surfactant arms ( $27.9$  vs.  $29.9\%$ , RR  $0.93$  (95% CI  $0.78, 1.1$ ); Table 2 a) adjusted  $p=0.38$  or between the lower and higher oxygen saturation target groups (Table 2 b). There ~~was~~ no statistically significant differences in the incidence of either death between the death ( $18.4$  vs.  $21.9\%$ , RR  $0.83$  (95% CI  $0.67, 1.04$ ) adjusted  $p=0.10$ ) or NDI ( $10.9$  vs.  $9.1\%$ , (95% CI  $0.0.79, 1.71$ , RR  $1.16$ ,  $p=0.44$ ) between the CPAP and Surfactant arms. However, mortality as significantly higher in the lower compared to the higher saturation group. Neurodevelopmental impairment among survivors examined at the 18 to 22 month corrected age visit was similar between the early CPAP and Surfactant arms and between lower and the higher-oxygen-saturation target groups.

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Components of NDI: (Table 2 a and b) The incidences of cognitive impairment (BSID-III cognitive composite score  $< 70$  ( $7.2\%$  vs.  $7.6\%$ ), gross motor function level  $\geq 2$  ( $5.1$  vs.  $4.8\%$ ), moderate/severe cerebral palsy ( $4.1$  vs.  $4.0\%$ ), and blindness ( $0.8$  vs.  $1.5\%$ ) among survivors were similar not different in-between the the CPAP and vs. Surfactant treatment arms or between the groups lower vs. higher saturation groups. There was a higher incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant treatment arm but the difference was not statistically significant ( $2.3$  vs.  $1.5\%$ , adjusted  $p=.06$ ). Overall 24 infants had hearing loss, 13 of whom had bilateral hearing aids. There were no significant differences in composite outcomes of death or individual NDI components between the CPAP and Surfactant arms (Table 3). Although the rates of severe retinopathy of prematurity and eye surgery among survivors to follow-up were increased in the higher oxygen target group compared to the lower oxygen target group; the rate of bilateral blindness or blindness of at least one eye (were not significantly different at the 18 to 22 month corrected age visit. (Table 3).

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Other neurodevelopmental outcomes: Mean BSID-III composite cognitive scores were similar in both CPAP and Surfactant arms (adjusted means  $\pm$  standard error 91.3  $\pm$  0.7 vs. 90.4  $\pm$  0.8). Sixty percent of all children seen at 18-22 months corrected age (CPAP 59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e., BSID-III cognitive composite score  $\geq$  85) evaluations.

Comparisons of outcome between gestational age strata: (Tables 2 and 3)

The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.5%, adjusted p=0.02, RR 0.74 (95%CI 0.57,0.96)), but not in the higher gestational age stratum (12.3 vs. 11.8%). There were no significant differences in the composite outcome of death or NDI at 18-22 months corrected age between the CPAP and surfactant within either of the two gestational age strata (40.1 vs. 44.5% for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 19.7% for 26 0/7 to 27 6/7 weeks gestation). The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.5%, adjusted p=0.02, RR 0.74 (95%CI 0.57,0.96)), but not in the higher gestational age stratum (12.3 vs. 11.8%). Neither were there significant differences between the CPAP and Surfactant arms in the incidence of NDI alone within either of the two gestational age strata (18.1 vs. 12.5, adjusted p=0.22 for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, adjusted p=0.81 for 26 0/7-27 6/7 weeks gestation). Within each gestational age stratum the mean BSID-III composite cognitive scores were similar in both treatment groups (CPAP 89.2  $\pm$  1.1 vs. Surfactant 88.1  $\pm$  1.2 for 24 0/7-25 6/7 weeks gestation; CPAP 93.4  $\pm$  0.9 vs. Surfactant 92.6  $\pm$  0.9 for 26 0/7 to 27 6/7 weeks gestation, adjusted mean  $\pm$  standard error).

Although neurodevelopmental outcomes were similar between treatment arms within each gestational age stratum, children in the lower gestational age stratum were at higher risk of adverse outcome. Compared to those in the 26 0/7-27 6/7 stratum, children in the 24 0/7 to 25 6/7 week gestational age stratum were more likely to have NDI (15.5% vs. 6.7%, p<0.0001), to have a cognitive score < 70 (10.7% vs. 5.4%, p<0.0001), to have a GMFCS  $\geq$  2 (7% vs. 3.7%, p=0.023), to have moderate to severe cerebral palsy (5.9% vs. 2.9%, p=0.02), and to be hearing impaired (3.8% vs. 1.6%, p=0.035).

**DISCUSSION:**

We report the neurodevelopmental outcome in early childhood at 18-22 months corrected age for extremely premature children, 24-27 weeks gestation, enrolled in the SUPPORT trial. To our knowledge this is the first large, multicenter, RCT published to date comparing neurodevelopmental impairment as a pre-specified outcome between early CPAP vs. early intubation with surfactant administration and between lower vs. higher oxygen saturation limits in extremely premature infants as immature as 24 weeks gestation. although the outcomes of other similarly designed trials will be reported.<sup>7,15</sup> ~~There~~ This trial demonstrated ~~was~~ no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those ~~extremely premature~~ infants randomized to treatment with early CPAP vs. ~~those randomized to treatment with~~ early intubation and surfactant administration ~~or between those randomized to the lower and higher saturation limit groups~~. Neither were there significant differences between survivors in ~~any the CPAP and Surfactant arms~~ treatment arms in NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFCS  $\geq$  2), and bilateral blindness.

The incidence of NDI in extremely premature infants in this study is substantially lower than the incidence of NDI previously reported by the NRN. Whereas the present study used the Bayley, 3<sup>rd</sup> edition for cognitive assessment, previous studies used the Bayley, 2<sup>nd</sup> edition. Changes in test design, composition and scoring most likely explain the lower incidence of NDI reported here as there is no reason to believe that cognitive function in this high risk group has changed substantially in a short period of time.

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Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome.<sup>4,8-10</sup> Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge.

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The results of recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants.<sup>7</sup> In the SUPPORT trial death prior to discharge was increased among neonates randomized to lower-oxygen-saturation target. The distribution of major causes of death prior to discharge has been published previously and there were no significant differences between groups.<sup>6</sup> This difference in mortality persisted at 18 to 22 months corrected age as noted above. Causes of death after discharge are not available for this study. A recent pooled analysis included studies that were completed with different oximeter calibration algorithms.<sup>16</sup> The SUPPORT study was included in the old algorithm arm and the investigators in the pooled analysis did not adjust for clustering for multiple births. Results of additional randomized trials which include pre-specified outcome at two years follow up which will not be available until 2014.<sup>7,15</sup>

We previously reported that the lower-oxygen saturation target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors.<sup>6</sup> It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment.<sup>17,18</sup> Although our study was not designed to collect detailed data on eye disorders or visual function at 18 to 22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher in the group with a higher oxygen saturation target and was likely related to a higher incidence of severe retinopathy of prematurity in this group and to the criteria used to define severe retinopathy of prematurity.<sup>6</sup> Specific visual outcomes of eye function after the presence of retinopathy of prematurity were not included in the outcome data collected in this trial. However, there were no differences in other reported visual outcomes, including nystagmus, strabismus or use of corrective lenses.

or in mean composite cognitive BSID-III scores.

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As reported in previous studies, the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were less likely to be normal and were at higher risk for severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment.<sup>22-24</sup>

Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome.<sup>4,8-10</sup> Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge.

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The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, the very high percentage of participants who were followed and evaluated in early childhood, and the comprehensive and standardized neurodevelopmental evaluation performed on survivors. One third of infants in the CPAP arm were intubated in the delivery room and two thirds ultimately received surfactant treatment and limited ventilation for clinical indications which ~~may have almost certainly blunted~~ blunted any difference in neurodevelopmental outcomes between the two groups. In addition, an adverse effect on neurodevelopmental outcome associated with the increased incidence of NEC in the CPAP arm may have counterbalanced adverse outcomes associated with the longer duration of ventilation and the increased need

for supplemental oxygen and post-natal steroids in the surfactant treatment arm. The generalizability of this study may be limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status and receipt of antenatal steroids than the entire eligible cohort.<sup>25</sup>

In summary, we found no significant differences in the composite outcome of death or NDI, or in any of the individual components of NDI among survivors to 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP ~~with a limited ventilation strategy~~ or early intubation with surfactant administration ~~or followed by conventional ventilation~~ to lower or higher target saturation limits. The increased death rate at discharge previously reported in the lower target oxygen saturation group was still present at 18 to 22 months corrected age. Although higher rates of retinopathy of prematurity were associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months. On the basis of these findings it appears that early CPAP is an alternative to early intubation and surfactant administration even in extremely premature infants and that higher saturation limits are associated with similar neurodevelopmental outcome in early childhood and less death.

~~In this study early CPAP, an alternative respiratory management strategy for the extremely premature infant, did not decrease the composite risk of death or neurodevelopmental impairment in early childhood.~~

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Table 1: Demographic and neonatal characteristics of trial and follow-up cohorts

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata

Table 3: Death and components of NDI for entire cohort and by gestational age strata

## References

1. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000;343:378-84.
2. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics* 2005;116:1391-400.
3. Arpino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst* 2010;26:1139-49.
4. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-26.
5. Beaino G, Khoshnood B, Kaminski M, et al. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. *Dev Med Child Neurol* 2010;52:e119-25.
6. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;123:313-8.
7. Farooqi A, Hagglof B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127:e1247-57.
8. Walsh MC, Morris BH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798-804.
9. Neubauer AP, Voss W, Kattner E. Outcome of extremely low birth weight survivors at school age: the influence of perinatal parameters on neurodevelopment. *Eur J Pediatr* 2008;167:87-95.
10. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005;115:673-80.
11. Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 2008;121:73-81.
12. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007;161:583-90.
13. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;38:597-600.
14. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F320-6.
15. Truffert P, Paris-Llado J, Escande B, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119:e860-5.
16. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. *Pediatrics* 2011;127:e414-22.
17. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev* 2010:CD000509.
18. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970-9.
19. Bayley. Bayley Scales of Infant and Toddler Development. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006.
20. Amiel-Tison C GJ. Neurological Development from Birth to Six Years. Baltimore: The Johns Hopkins University Press; 1998.
21. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
22. Raz S, Debastos AK, Newman JB, Batton D. Extreme prematurity and neuropsychological outcome in the preschool years. *J Int Neuropsychol Soc* 2010;16:169-79.

23. Leversen KT, Sommerfelt K, Ronnestad A, et al. Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm. *Pediatrics* 2011;127:e630-8.
24. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity--moving beyond gestational age. *N Engl J Med* 2008;358:1672-81.
25. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics* 2010;126:e215-21.

**Table 1: Demographics and Characteristics of ~~Trial Cohort~~ and Follow-up (FUP) Cohorts**

	<u>Follow-up Cohort</u>	
	CPAP	Surfactant
	N=511	N=479
Birth weight (grams, Mean ± SD)	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1
Small for gestational age (< 10 <sup>th</sup> %)-no./total no.(%)	23/511(4.5)	32/479(6.7)
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)
Race		
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)
Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)

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With both biological parents†-no./total no.(%)	348/510(68.2)	329/479(68.7)
Maternal education < 12 <sup>th</sup> grade-no./total no.(%)	128/506(25.3)	116/469(24.7)
Income < \$30,000/year†-no./total no.(%)	260/493(52.7)	251/461(54.4)
English as primary language at FUP -no./total no.(%)	426/510(83.5)	403/478(84.3)
Severe ROP in survivors to discharge-no./total no.(%)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia in survivors to 36 weeks	193/511(37.8)	187/479(39)
Gestational age-no./total no.(%)		
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)
NEC-stage ≥2 -no./total no.(%)	56/511(11)	30/479(6.3)**
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)
Postnatal steroids-no./total no.(%)	34/508(6.7)	55/476(11.6)**
Died before discharge no./total no.(%)		

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\*\*p<0.02, \*\*\*p<0.001



**Table 2: Death and NDI for entire cohort and gestational age strata\***

<b>a. CPAP vs. Surfactant (All)</b>	CPAP	Surfactant	RR	p
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

<b>b. <u>24 0/7-25 6/7 weeks Gestational Age</u></b>	CPAP	Surfactant	RR	p
Death or NDI-no./total no. (%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no. (%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no. (%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no. (%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no. (%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no. (%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no. (%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no. (%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no. (%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

<b>c. <u>26 0/7-27 6/7 weeks Gestational Age</u></b>	<b>CPAP</b>	<b>Surfactant</b>	<b>RR</b>	<b>p</b>
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

**Table 3: Death and Components of NDI for entire cohort and gestational age strata\***

<b>a. <u>CPAP vs. Surfactant (All)</u></b>	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	154/620(24.8)	176/612(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level $\geq 2$ -no./total no.(%)	144/629(22.9)	163/619(26.3)	0.87(0.72,1.05)	0.16
Death or moderate/severe CP-no./total no.(%)	139/629(22.1)	159/619(25.7)	0.86(0.71,1.05)	0.14
Death or blind in both eyes-no./total no.(%)	122/629(19.4)	147/619(23.7)	0.82(0.67,1.02)	0.07
Death or hearing impairment-no./total no.(%)	135/629(21.5)	147/619(23.7)	0.9(0.74,1.11)	0.33
<b>b. <u>24 0/7-25 6/7 weeks Gestational Age</u></b>				
Death or cognitive composite<70-no./total no.(%)	96/271(35.4)	113/264(42.8)	0.83(0.67,1.02)	0.08
Death or GMF level $\geq 2$ -no./total no.(%)	90/274(32.8)	106/269(39.4)	0.84(0.67,1.04)	0.12
Death or moderate/severe CP-no./total no.(%)	87/274(31.8)	105/269(39)	0.82(0.65,1.02)	0.08
Death or blind in both eyes-no./total no.(%)	75/274(27.4)	99/269(36.8)	0.75(0.58,0.96)	0.03
Death or hearing impairment-no./total no.(%)	84/274(30.7)	100/269(37.2)	0.83(0.65,1.05)	0.12

c. <u>26 0/7-27 6/7 weeks Gestational Age</u>	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.67
Death or GMF level $\geq 2$ -no./total no.(%)	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.74
Death or moderate/severe CP-no./total no.(%)	52/355(14.6)	54/350(15.4)	0.96(0.68,1.36)	0.82
Death or blind in both eyes-no./total no.(%)	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.89
Death or hearing impairment-no./total no.(%)	51/355(14.4)	47/350(13.4)	1.07(0.74,1.55)	0.71

\*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

**From:** Stevens, Timothy  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: 2012 PAS Late Breaking Abstract Notification (#450038)  
**Date:** Sunday, April 01, 2012 7:03:54 PM

---

Hi Rose,

Apparently, the PAS Program Committee decided not to hold a Late Breaker session this year.

I'll get started on the manuscript.

Thanks

Tim

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

**From:** Pediatric Academic Societies - Marathon Multimedia [mailto:support@marathonmultimedia.com]  
**Sent:** Friday, March 30, 2012 3:59 PM  
**To:** Stevens, Timothy  
**Cc:** campaign@marathonmultimedia.com  
**Subject:** 2012 PAS Late Breaking Abstract Notification (#450038)

**RE: Respiratory Outcomes of the NICHD SUPPORT Trial (Abstract #: 450038)**

Dear Dr. Timothy Stevens:

Thank you for submitting your late-breaker abstract entitled, "Respiratory Outcomes of the NICHD SUPPORT Trial," whose first author is Timothy Stevens.

A review panel has elected not to accept your abstract submitted through the late breaker abstract submission process for presentation at the 2012 PAS Annual Meeting in Boston, Massachusetts. The decision process is a difficult one for the Program Committee, but, because none of the abstracts strictly met the late-breaker abstract criteria, the decision was made not to hold a late breaking abstract session this year.

To Access your official letter use the information below to log back into the submission site and print your notification:

Website: [http://www.call4abstracts.com/pas\\_lb](http://www.call4abstracts.com/pas_lb)

Username: (b)(6)

Password: (b)(6)

We still encourage you to attend the 2012 PAS Annual Meeting in Boston and participate in an excellent scientific program. Please visit the meeting web site at [www.pas-meeting.org](http://www.pas-meeting.org) to view the final program, complete meeting registration, and secure housing. You may also contact our office at the number below to receive a meeting packet. Remember, you must register by March 30, 2012, to receive your meeting materials before the meeting.

We hope that you will continue your research efforts. We look forward to seeing an abstract submission from you next November.

Sincerely,

Gail Harrison, MD  
PAS Program Chair

The Pediatric Academic Societies

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**PAS Program Office**

**3400 Research Forest Dr., Ste. B7 - The Woodlands, TX 77381**

**Phone: 281-419-0052**

**Email: [info@pas-meeting.org](mailto:info@pas-meeting.org)**

**URL: [www.pas-meeting.org](http://www.pas-meeting.org)**

**From:** [Kennedy, Kathleen A](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Poster for SUPPORT Secondary Study  
**Date:** Friday, March 30, 2012 7:04:53 AM

---

Thanks. I'll send out another revision to the rest of the subcommittee when Lisa finishes revising the other figures.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Friday, March 30, 2012 2:43 AM  
**To:** Kennedy, Kathleen A; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Poster for SUPPORT Secondary Study

Kathleen  
I am viewing on my BB- they look blue/black and gray and look fine.  
Thanks!  
Rose

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Thursday, March 29, 2012 03:33 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Poster for SUPPORT Secondary Study

Do you like the colors on this figure better? I think it looks good but I was happy with the previous one so I'd thought I'd ask you if this is what you meant by "brighter".

I'm still working on the graphs. I don't like the axes and I think the plots need to be thicker lines.

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:** [Kennedy, Kathleen A](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Poster for SUPPORT Secondary Study  
**Date:** Thursday, March 29, 2012 3:42:48 PM

---

Good pickup. Thanks.

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:** Archer, Stephanie (NIH/NICHD) [E] [<mailto:archerst@mail.nih.gov>]  
**Sent:** Thursday, March 29, 2012 2:38 PM  
**To:** Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Poster for SUPPORT Secondary Study

I think it looks good. In the bar graph, if you can move the footnote up, you could probably enlarge the entire image and use up more of the white space.

On the line graphs, I agree about the axes. It would be good if they have identical axes so that you could easily compare them between the three groupings. Thicker lines would help people from straining their eyes!

---

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](mailto:archerst@mail.nih.gov)

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Thursday, March 29, 2012 3:33 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Poster for SUPPORT Secondary Study

Do you like the colors on this figure better? I think it looks good but I was happy with the previous one so I'd thought I'd ask you if this is what you meant by "brighter".

I'm still working on the graphs. I don't like the axes and I think the plots need to be thicker lines.

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:** [Kennedy, Kathleen A](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Poster for SUPPORT Secondary Study  
**Date:** Thursday, March 29, 2012 3:33:24 PM  
**Attachments:** [NRN SUPPORT ROP Observational Study\\_edhw29Mar12.nptx](#)

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Do you like the colors on this figure better? I think it looks good but I was happy with the previous one so I'd thought I'd ask you if this is what you meant by "brighter".

I'm still working on the graphs. I don't like the axes and I think the plots need to be thicker lines.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
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713 500-6708



NICHD  
NEONATAL RESEARCH NETWORK



# Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants

Kathleen A Kennedy MD MPH, Lisa A Wrage MPH, Dale Phelps MD, Rosemary Higgins MD and the SUPPORT Subcommittee of the NICHD Neonatal Research Network

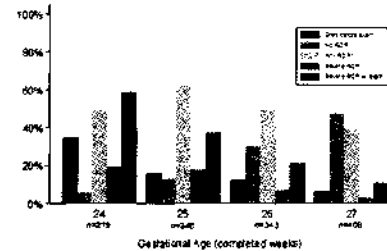
- Timely detection of treatable ROP is important for optimal outcomes.
- The current (2006) screening guidelines are based on infants born in 1986-1997:
  - screening should begin by 31 wks postmenstrual age (PMA)
  - and continue until vessels have reached zone III at 35 wks or, for infants without prethreshold ROP, until 45 wks PMA.
- Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

To validate the 2006 ROP screening guidelines for 24-27 wk GA infants.

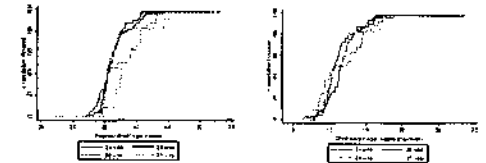
- Descriptive natural history study using outcome data from the NICHD Network SUPPORT trial
- In this trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial trial.
- Inborn infants 24 1/2 to 27 1/2 wks GA with consent prior to delivery were eligible.
- Examinations followed current screening recommendations.
- Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA.
- For this observational study, age of onset is defined as age of detection.
- Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 wks (1 wk if the previous exam had ROP in zone I) were defined as having an uncertain age of onset.

Outcome	By ROP Outcome Category			
	Severe (Type 1 or Treated) ROP			
	All ROP Outcomes	No ROP	Any ROP	Severe (Type 1 or Treated) ROP
Number of Infants	997	311	686	97
Number of Exams	463 (46)	268 (86)	196 (28)	25 (26)
Number of Exams with ROP	349 (75)	133 (49)	216 (31)	25 (26)
Number of Exams with Severe ROP	109 (23)	49 (15)	60 (9)	25 (26)
Number of Exams with Uncertain Age of Onset	109 (23)	49 (15)	60 (9)	25 (26)
Number of Exams with No ROP	114 (23)	219 (70)	106 (15)	0
Number of Exams with Plus Disease	114 (23)	219 (70)	106 (15)	0
Number of Exams with Stage 2-3 ROP	114 (23)	219 (70)	106 (15)	0
Number of Exams with Stage 4 ROP	114 (23)	219 (70)	106 (15)	0
Number of Exams with Stage 5 ROP	114 (23)	219 (70)	106 (15)	0
Number of Exams with Death	114 (23)	219 (70)	106 (15)	0
Number of Exams with Unknown Outcome	114 (23)	219 (70)	106 (15)	0

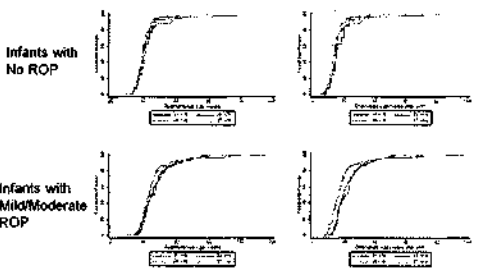
Risk of ROP by Gestational Age at Birth (completed weeks) among All Infants in SUPPORT Trial



Postmenstrual and Chronological Age of Onset for Severe (Type 1 or treated) ROP (among Infants with age of onset determined) by Gestational Age at Birth

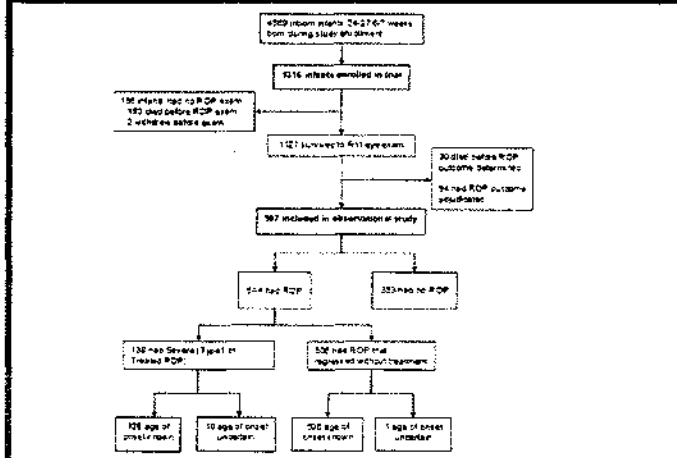


Postmenstrual and Chronological Age of Mature Vessels by Gestational Age at Birth



Outcome	First exam with severe ROP occurred before discharge to home (n=4)	First exam with severe ROP occurred after discharge to home (n=4)
Mean gestational age at first exam with severe ROP	36.0 (34.4-37.6)	40.9 (37.9-43.8)
Mean postmenstrual age at first exam with severe ROP	48.1 (46.9-49.3)	58.3 (56.4-60.2)

- In these 997 infants, we did not observe treatable ROP before 32 wks PMA; only 1 infant developed severe ROP after 45 wks PMA.
- Our data do not support a change in the 2006 guidelines.
- Some infants who are stable enough for back transfer or discharge home are still at risk to develop treatable ROP.
- A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.



ROP type	Postmenstrual Age (weeks)										Chronological Age (weeks)									
	n	min	1%	5%	25%	50%	75%	95%	99%	100%	n	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	64	29.3	30.4	31.4	32.7	33.9	35.1	37.0	41.0	46.7	49.0	49.6	54	52	55.6	59.4	61.9	63.3	67	
Type 1 ROP	158	29.3	30.7	31.1	32.5	34.1	36.4	40.4	45.4	49.0	49.4	49.6	53	53.7	57.8	61.6	65.0	66.0	67	
Severe (Type 1 or Treated) ROP	148	29.1	31.7	33.0	35.1	36.4	38.0	43.3	45.0	53.1	54.4	54.4	58.4	58.8	61.3	63.1	67.0	67.0	68.4	

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug. Acknowledgements: The National Institute of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Johns Hopkins University; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California - San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wrich@ucsd.edu"  
**Subject:** Re:  
**Date:** Thursday, March 29, 2012 2:00:22 AM

---

Full trial please

---

**From:** Rich, Wade [mailto:wrich@ucsd.edu]  
**Sent:** Wednesday, March 28, 2012 05:58 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:**

Hi Rose,

Do you need an enrollment table for the full support trial, or only those subjects who will be seen in the upcoming period. ?

Wade

Wade Rich, BSHS, RRT, CCRC  
UCSD Medical Center  
Division of Neonatology  
402 Dickinson St. Rm 1-140  
San Diego, CA 92103-8774  
Ph. 619-543-5375  
FAX 619-543-3812

**From:** Finer, Neil  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine - 12-01618 - Availability Request  
**Date:** Thursday, March 29, 2012 11:04:31 AM

---

Hi Rose

I am speaking in Philadelphia till Wednesday and then I go to (b)(6)

That is where (b)(6)

I guess we will be in the same time zone so can you do a call there Friday?

We are working on a combined manuscript ( Yvonne and I ) and we will send this as a draft to work on in the next day or so.

Your trip sounds like fun. Safe travels

Neil

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 29, 2012 7:27 AM  
**To:** Finer, Neil  
**Subject:** Re: New England Journal of Medicine - 12-01618 - Availability Request

Where are you? I am in (b)(6)

Rose

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

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Thursday, March 29, 2012 09:21 AM  
**To:** Gabrio, Jenna <jgabrio@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie <mgantz@rti.org>; Vaucher, Yvonne <yvaucher@ucsd.edu>; Das, Abhik <adas@rti.org>  
**Cc:** wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; mperalta@peds.uab.edu <mperalta@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine - 12-01618 - Availability Request

I will be (b)(6) for these dates

I could do the 6th if it is early in the morning here Neil

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

**From:** Gabrio, Jenna [mailto:jgabrio@rti.org]  
**Sent:** Thursday, March 29, 2012 5:09 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Vaucher, Yvonne; Das, Abhik  
**Cc:** Finer, Neil; wcarlo@peds.uab.edu; mperalta@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine - 12-01618 - Availability Request

Hi all,

Please provide your availability for this call for the following dates on this Doodle poll  
(<http://www.doodle.com/tggb53ywrdyvt9ch>):

4/6, F

4/9, M

4/10, Tu

4/11, W

4/12, Th

Thanks,  
Jenna

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Thursday, March 29, 2012 2:00 AM  
To: Gantz, Marie; 'yvaucher@ucsd.edu'; Das, Abhik; Gabrio, Jenna  
Cc: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; 'mperalta@peds.uab.edu'  
Subject: Re: New England Journal of Medicine - 12-01618

Please set up a call with all on the email - perhaps Friday april 6?

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

From: Gantz, Marie [mailto:mgantz@rti.org]  
Sent: Wednesday, March 28, 2012 04:21 PM  
To: Vaucher, Yvonne <yvaucher@ucsd.edu>; Das, Abhik <adas@rti.org>  
Cc: Finer, Neil <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Myriam Peralta, M.D. <MPeralta@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine - 12-01618

Are we planning to get this small group together to discuss specific responses to the NEJM reviewer comments? I think that would be useful.

On the issue of adjusting for SGA, I don't think the suggestion makes sense, because the imbalance in SGA at follow up was a result of the imbalance in death rates between the oximeter groups. Thus, if we really want to know if there is a trade-off between death and NDI in the oximeter groups, we should not adjust for differences in covariates that result from differences between the treatments. My preference is to respond to the reviewer with our reasons for not adjusting (note that the statistician was not the one who suggested it).

We can clarify our power calculations in the paper. That's not a problem.

I am currently working on an approach to the sensitivity analyses for loss to follow up.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Wednesday, March 28, 2012 4:03 PM  
To: Gantz, Marie; Das, Abhik  
Cc: Finer, Neil; Vaucher, Yvonne  
Subject: FW: New England Journal of Medicine - 12-01618

Marie and Abhik,

Here are the comments for the oximeter paper. Most of the statistical comments overlap (i.e. possible interaction between interventions) but one is specific for this paper (i.e., question of need for adjustment for excess SGA in high sat group) I thought we were explicit in the paper about power calculations specifically for NDI based on previous NRN data but the question is raised about power calculations using pre-defined treatment effects by reviewers. Didn't we do this in the protocol (pg 24, N2) although the power was based on the Bayley II estimate of NDI which was substantially higher? Anyway, I guess we need a clearer statement in the paper.

Yvonne

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

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com

[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org

Sent: Thursday, February 09, 2012 3:24 PM

To: mperalta@peds.uab.edu; Vaucher, Yvonne; wcarlo@peds.uab.edu; Finer, Neil; mgantz@rti.org; mcw3@po.CWRU.edu; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; Rich, Wade; Nancy.Newman@UHHospitals.org; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpointex@iupui.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary\_myers@urmc.rochester.edu; higginsr@mail.nih.gov; (b)(6)@aol.com

Subject: New England Journal of Medicine - 12-01618

Dear Dr. Peralta Carcelen and co-authors,

Thank you for submitting your manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets" to the New England Journal of Medicine.

Your manuscript has been forwarded to members of our editorial staff, who will make an initial evaluation and decide whether it merits further consideration. You will be notified of the decision as soon as possible.

Your manuscript ID is 12-01618.

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://mc05.manuscriptcentral.com/nejm> and edit your user information as appropriate. You may also view the status of your manuscript at any time by checking For Authors section of the site.

We are undertaking evaluation of your manuscript with the understanding that neither the substance of the article nor the figures or tables have been published or will be submitted for publication elsewhere during the period of review.

Please provide the editors with copies of other manuscripts by you or your coauthors addressing similar or related research questions that are in preparation or under consideration at other journals. This does not apply to abstracts published in connection with scientific meetings or to news reports based on presentations at such meetings.

The Journal's policy is explained more fully at <http://www.nejm.org/page/author-center/editorial-policies>.

Please call us at 617-734-9800 if you have any questions.

Sincerely,

Jeffrey M. Drazen, M.D.

Editor-in-Chief

New England Journal of Medicine

Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine

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<http://www.nejm.org>

**From:** Vaucher, Yvonne  
**To:** Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik  
**Cc:** Finer, Neil; wcarlo@peds.uab.edu; mperalta@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine - 12-01618 - Availability Request  
**Date:** Thursday, March 29, 2012 11:02:28 AM

---

I can accommodate anytime except Mon 4/9 10-11AM PT/1-2PM EST and Thurs 4/12 from 7-10AM PT/10-1PM EST.

Yvonne

---

From: Gabrio, Jenna [jgabrio@rti.org]  
Sent: Thursday, March 29, 2012 5:08 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Vaucher, Yvonne; Das, Abhik  
Cc: Finer, Neil; wcarlo@peds.uab.edu; mperalta@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine - 12-01618 - Availability Request

Hi all,

Please provide your availability for this call for the following dates on this Doodle poll (<http://www.doodle.com/tggb53ywrdyvt9ch>):

4/6, F

4/9, M

4/10, Tu

4/11, W

4/12, Th

Thanks,  
Jenna

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Thursday, March 29, 2012 2:00 AM  
To: Gantz, Marie; 'yvaucher@ucsd.edu'; Das, Abhik; Gabrio, Jenna  
Cc: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; 'mperalta@peds.uab.edu'  
Subject: Re: New England Journal of Medicine - 12-01618

Please set up a call with all on the email - perhaps Friday april 6?

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

From: Gantz, Marie [mailto:mgantz@rti.org]  
Sent: Wednesday, March 28, 2012 04:21 PM  
To: Vaucher, Yvonne <yvaucher@ucsd.edu>; Das, Abhik <adas@rti.org>  
Cc: Finer, Neil <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Myriam Peralta, M.D. <MPeralta@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine - 12-01618

Are we planning to get this small group together to discuss specific responses to the NEJM reviewer comments? I think that would be useful.

On the issue of adjusting for SGA, I don't think the suggestion makes

sense, because the imbalance in SGA at follow up was a result of the imbalance in death rates between the oximeter groups. Thus, if we really want to know if there is a trade-off between death and NDI in the oximeter groups, we should not adjust for differences in covariates that result from differences between the treatments. My preference is to respond to the reviewer with our reasons for not adjusting (note that the statistician was not the one who suggested it).

We can clarify our power calculations in the paper. That's not a problem.

I am currently working on an approach to the sensitivity analyses for loss to follow up.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
Sent: Wednesday, March 28, 2012 4:03 PM  
To: Gantz, Marie; Das, Abhik  
Cc: Finer, Neil; Vaucher, Yvonne  
Subject: FW: New England Journal of Medicine - 12-01618

Marie and Abhik,

Here are the comments for the oximeter paper. Most of the statistical comments overlap (i.e. possible interaction between interventions) but one is specific for this paper (i.e., question of need for adjustment for excess SGA in high sat group) I thought we were explicit in the paper about power calculations specifically for NDI based on previous NRN data but the question is raised about power calculations using pre-defined treatment effects by reviewers. Didn't we do this in the protocol (pg 24, N2) although the power was based on the Bayley II estimate of NDI which was substantially higher? Anyway, I guess we need a clearer statement in the paper.

Yvonne

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

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf  
Of editorial@nejm.org  
Sent: Thursday, February 09, 2012 3:24 PM  
To: mperalta@peds.uab.edu; Vaucher, Yvonne; wcarlo@peds.uab.edu; Finer,  
Neil; mgantz@rti.org; mcw3@po.CWRU.edu; alaptook@wihri.org;  
Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org;  
kurt.schibler@cchmc.org; Rich, Wade; Nancy.Newman@UHHospitals.org;  
BVohr@wihri.org; kimberly.yolton@cchmc.org;  
roy.heyne@utsouthwestern.edu; (b)(6)@aol.com;

Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu;  
michael.acarregui@providence.org; iadamsc@emory.edu;  
apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu;  
emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu;  
(b)(6)@gmail.com; cbauer@peds.med.miami.edu;  
jafuller@salud.unm.edu; moshea@wfubmc.edu;  
gary\_myers@urmc.rochester.edu; higginsr@mail.nih.gov;  
(b)(6)@aol.com  
Subject: New England Journal of Medicine - 12-01618

Dear Dr. Peralta Carcelen and co-authors,

Thank you for submitting your manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets" to the New England Journal of Medicine.

Your manuscript has been forwarded to members of our editorial staff, who will make an initial evaluation and decide whether it merits further consideration. You will be notified of the decision as soon as possible.

Your manuscript ID is 12-01618.

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://mc05.manuscriptcentral.com/nejm> and edit your user information as appropriate. You may also view the status of your manuscript at any time by checking For Authors section of the site.

We are undertaking evaluation of your manuscript with the understanding that neither the substance of the article nor the figures or tables have been published or will be submitted for publication elsewhere during the period of review.

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Please call us at 617-734-9800 if you have any questions.

Sincerely,

Jeffrey M. Drazen, M.D.  
Editor-in-Chief  
New England Journal of Medicine  
Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115

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Fax: (617) 739-9864

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**From:** [Vaucher, Yvonne](#)  
**To:** [Gantz, Marie](#); [Das, Abhik](#)  
**Cc:** [Finer, Neil](#); [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [Myriam Peralta, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** RE: New England Journal of Medicine - 12-01618  
**Date:** Wednesday, March 28, 2012 11:50:48 PM

---

Thanks. Let's talk soon. I am working on combining the papers.

Yvonne

---

**From:** Gantz, Marie [[mgantz@rti.org](mailto:mgantz@rti.org)]  
**Sent:** Wednesday, March 28, 2012 1:21 PM  
**To:** Vaucher, Yvonne; Das, Abhik  
**Cc:** Finer, Neil; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Myriam Peralta, M.D.; Higgins, Rosemary (NIH/NICHD)  
**Subject:** RE: New England Journal of Medicine - 12-01618

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Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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

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**Sent:** Wednesday, March 28, 2012 4:03 PM  
**To:** Gantz, Marie; Das, Abhik  
**Cc:** Finer, Neil; Vaucher, Yvonne  
**Subject:** FW: New England Journal of Medicine - 12-01618

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

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com

[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org

Sent: Thursday, February 09, 2012 3:24 PM

To: mperalta@peds.uab.edu; Vaucher, Yvonne; wcarlo@peds.uab.edu; Finer, Neil; mgantz@rti.org; mcw3@po.CWRU.edu; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; kurt.schibler@cchmc.org; Rich, Wade; Nancy.Newman@UHHospitals.org; BVohr@wihri.org; kimberly.yolton@cchmc.org; roy.heyne@utsouthwestern.edu; (b)(6)@aol.com; Patricia.W.Evans@uth.tmc.edu; golds005@mc.duke.edu; michael.acarregui@providence.org; iadamsc@emory.edu; apappas@med.wayne.edu; srhintz@stanford.edu; bpoindex@iupui.edu; emcgowan@tuftsmedicalcenter.org; richard.ehrenkranz@yale.edu; (b)(6)@gmail.com; cbauer@peds.med.miami.edu; jafuller@salud.unm.edu; moshea@wfubmc.edu; gary\_myers@urmc.rochester.edu; higginsr@mail.nih.gov; (b)(6)@aol.com

Subject: New England Journal of Medicine - 12-01618

Dear Dr. Peralta Carcelen and co-authors,

Thank you for submitting your manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets" to the New England Journal of Medicine.

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Your manuscript ID is 12-01618.

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://mc05.manuscriptcentral.com/nejm> and edit your user information as appropriate. You may also view the status of your manuscript at any time by checking For Authors section of the site.

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Sincerely,

Jeffrey M. Drazen, M.D.

Editor-in-Chief

New England Journal of Medicine

Distinguished Parker B. Francis Professor of Medicine Harvard Medical School

New England Journal of Medicine

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Boston, MA 02115

(617) 734-9800

Fax: (617) 739-9864

<http://www.nejm.org>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Stevens, Timothy"  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg  
**Date:** Tuesday, March 27, 2012 4:17:00 PM

---

Are you still on the phone??

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

---

**From:** Stevens, Timothy [mailto:Timothy\_Stevens@URMC.Rochester.edu]  
**Sent:** Tuesday, March 27, 2012 3:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

I'm joining now

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 27, 2012 12:57 PM  
**To:** Stevens, Timothy; 'newman@rti.org'  
**Cc:** 'petrie@rti.org'  
**Subject:** Re: Breathing Outcomes analysis update for Follow-up PI Mtg

(b)(6) with pass code (b)(6)

Also, we are running ahead - are you able to join earlier?

---

**From:** Stevens, Timothy [mailto:Timothy\_Stevens@URMC.Rochester.edu]  
**Sent:** Tuesday, March 27, 2012 12:34 PM  
**To:** 'Newman, Jamie' <newman@rti.org>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

Hi Jamie and Rose,

I do not have the call-in number for the update at 3:45. Can you let me know?

Thanks

Tim



---

**From:** Newman, Jamie [mailto:newman@rti.org]  
**Sent:** Tuesday, March 20, 2012 6:14 PM  
**To:** Stevens, Timothy  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik  
**Subject:** Breathing Outcomes analysis update for Follow-up PI Mtg

Dr. Stevens,

Please see below from a message from Rose. We have time slotted in the agenda for a 5 minute update on the Breathing Outcomes analysis at 3:45pm on Thurs Mar 27. Rose has requested handouts (which are optional) by Thursday Mar 22. Attached is the agenda. Are you available to provide the update by phone or do you prefer that someone provide an update on your behalf.

Thanks, Jamie

**From:** Newman, Jamie  
**Sent:** Monday, March 05, 2012 4:34 PM  
**To:** 'Stevens, Timothy'  
**Cc:** Das, Abhik  
**Subject:** Breathing Outcomes analysis update for Follow-up PI Meeting

Dr. Stevens,

Are you available to give a 5 minute update on Breathing Outcomes analysis at 3:45pm for the NRR Follow-up PI Meeting Tuesday March 27? Handouts are optional but we're happy to distribute a handout if you'd like.

Do you know when you'll hear back from your PAS late breaker submission?

Thanks, Jamie

Jamie E. Newman, PhD, MPH  
Statistics and Epidemiology  
RTI International  
Telephone: (919) 485-5719  
Fax: (919) 485-7762  
[newman@rti.org](mailto:newman@rti.org)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 20, 2012 1:03 PM  
**To:** Cunningham, Meg; Cbackstrom@salud.unm.edu; mball@leland.stanford.edu; rbara@med.wayne.edu; mcollins@peds.uab.edu; scosby@peds.uab.edu; cathy.grisby@uc.edu; ehale@emory.edu; ahensman@wihri.org; karen-johnson@uiowa.edu; Georgia.E.McDavid@uth.tmc.edu; Diana.Vasil@utsouthwestern.edu; nxs5@cwru.edu; ldw@iupui.edu; clark@med.unc.edu; bernharj@email.unc.edu; janice\_wereszczak@med.unc.edu; Donia-campbell@uiowa.edu; Iijun.chen@utsouthwestern.edu; JF126@notes.duke.edu; cagauldin@cmh.edu; Toni.Mancini@uphs.upenn.edu; christine.fortney@nationwidechildrens.org; Aasma.Chaudhary@uphs.upenn.edu; rosemary\_jensen@urmc.rochester.edu; kwynn@buffalo.edu;

Kimberley.fisher@duke.edu; sgbrown@salud.unm.edu; tchanlaw@ucla.edu; RGeller@mednet.ucla.edu; tiwusow@salud.unm.edu; Holly\_Wadkins@URMC.Rochester.edu; CUCINOTTA@email.chop.edu; MKeszler@Wihri.org; slakshmi@buffalo.edu; NAmbalavanan@peds.uab.edu; dpcarl@emory.edu; cotte010@mc.duke.edu; woh@wihri.org; rohls@salud.unm.edu; jon.e.tyson@uth.tmc.edu; Matt\_Laughon@med.unc.edu; gsokol@iupui.edu; dan\_ellsbury@pediatrix.com; MGarg@mednet.ucla.edu; bsood@med.wayne.edu; Archer, Stephanie (NIH/NICHD) [E]; edward-bell@uiowa.edu; wcarlo@peds.uab.edu; goldb008@mc.duke.edu; Kathleen.A.Kennedy@uth.tmc.edu; alaptook@WIHRI.org; bpoindex@iupui.edu; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; sshankar@med.wayne.edu; [SCRN] Stoll, Barbara; vanmeurs@leland.stanford.edu; mcw3@cwru.edu; kwatterberg@salud.unm.edu; RAP32@columbia.edu; Luc.Brion@utsouthwestern.edu; dan\_ellsbury@pediatrix.com; wtruog@cmh.edu; KIRPALANIH@email.chop.edu; barbara.schmidt@uphs.upenn.edu; Leif.Nelin@nationwidechildrens.org; nehal.parikh@nationwidechildrens.org; udevaskar@mednet.ucla.edu; carl\_dangio@urmc.rochester.edu; martin.blakely@vanderbilt.edu; dale\_phelps@urmc.rochester.edu; bvohr@wihri.org; DEMAURO@email.chop.edu; jwaidne@emory.edu; gonza025@mc.duke.edu; axt25@po.cwru.edu; Karen.Kirby@UTSouthwestern.edu; lmoore@med.wayne.edu; pamela.neville@duke.edu; Nancy.M.Smith@uth.tmc.edu; StWilliams@peds.uab.edu; bvecchio@careNE.org; jthomp84@iupui.edu; Adele.Lamb@uphs.upenn.edu; KSmiley@mednet.ucla.edu; YDavis@mednet.ucla.edu; Michelle Smith; hk419@mail.cumc.columbia.edu; JRose@WIHRI.org; Deborah.Garcia@uth.tmc.edu; vwilli4@emory.edu; whitte2@email.chop.edu; bvohr@wihri.org; [b](6)@aol.com; golds005@mc.duke.edu; ira\_adams-chapman@oz.ped.emory.edu; srhinz@stanford.edu; MPeralta@PIDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; Kimberly.Yolton@cchmc.org; tarah-colaizy@uiowa.edu; soraya.abbasi@uphs.upenn.edu; hurt@email.chop.edu; GERDES@email.chop.edu; gary\_myers@URMC.Rochester.edu; apappas@med.wayne.edu; ipurdy@mednet.ucla.edu; Keith.Yeates@nationwidechildrens.org; hkilbride@cmh.edu; sgunn@iupui.edu; AFDuncan@salud.unm.edu; diane\_marshall@med.unc.edu; Patrick.M.Jones@uth.tmc.edu; Christopher.Timan@nationwidechildrens.org; Newman, Jamie; jrose@wihri.org  
**Cc:** Auman, Jeanette O.; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn Petrie; Nolen, Tracy; Wallace, Dennis; Zaterka-Baxter, Kristin  
**Subject:** RE: March SC and FU Agenda

If you have items that you wish to use as handouts at the meetings, please send them to us by THURSDAY MARCH 22.

Thanks  
Rose

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

**From:** Cunningham, Meg [mailto:[mcunningham@rti.org](mailto:mcunningham@rti.org)]  
**Sent:** Friday, February 24, 2012 11:48 AM  
**To:** Cbackstrom@salud.unm.edu; mbbail@leland.stanford.edu; rbara@med.wayne.edu; mcollins@peds.uab.edu; scosby@peds.uab.edu; cathy.grisby@uc.edu; ehale@emory.edu; ahensman@wihri.org; karen-johnson@uiowa.edu; Georgia.E.McDavid@uth.tmc.edu;

Diana.Vasil@utsouthwestern.edu; nxs5@cwru.edu; ldw@iupui.edu; ciclarck@med.unc.edu;  
bernharj@email.unc.edu; janice\_wereszczak@med.unc.edu; Donia-campbell@uiowa.edu;  
lijun.chen@utsouthwestern.edu; JF126@notes.duke.edu; cagauldin@cmh.edu;  
Toni.Mancini@uphs.upenn.edu; christine.fortney@nationwidechildrens.org;  
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Kimberley.fisher@duke.edu; sgbrown@salud.unm.edu; tchanlaw@ucla.edu; RGeller@mednet.ucla.edu;  
tiwusow@salud.unm.edu; Holly\_Wadkins@URMC.Rochester.edu; CUCINOTTA@email.chop.edu;  
MKeszler@Wihri.org; slakshmi@buffalo.edu; NAMBALAVANAN@peds.uab.edu; dpcarl@emory.edu;  
cotte010@mc.duke.edu; woh@wihri.org; rohls@salud.unm.edu; jon.e.tyson@uth.tmc.edu;  
Matt\_Laughon@med.unc.edu; gsokol@iupui.edu; dan\_ellsbury@pediatrix.com;  
MGarg@mednet.ucla.edu; bsood@med.wayne.edu; Archer, Stephanie (NIH/NICHD) [E]; edward-  
bell@uiowa.edu; wcarlo@peds.uab.edu; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E];  
Kathleen.A.Kennedy@uth.tmc.edu; alaptook@WIHRI.org; bpoindex@iupui.edu;  
Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; sshankar@med.wayne.edu; [SCRN]  
Stoll, Barbara; vanmeurs@leland.stanford.edu; mcw3@cwru.edu; kwatterberg@salud.unm.edu;  
RAP32@columbia.edu; Luc.Brion@utsouthwestern.edu; dan\_ellsbury@pediatrix.com; wtruog@cmh.edu;  
KIRPALANIH@email.chop.edu; barbara.schmidt@uphs.upenn.edu; Leif.Nelin@nationwidechildrens.org;  
nehal.parikh@nationwidechildrens.org; udevaskar@mednet.ucla.edu; carl\_dangio@urmc.rochester.edu;  
martin.blakely@vanderbilt.edu; dale\_phelps@urmc.rochester.edu; bvohr@wihri.org;  
DEMAURO@email.chop.edu; jwaidne@emory.edu; gonza025@mc.duke.edu; axt25@po.cwru.edu;  
Karen.Kirby@UTSouthwestern.edu; lmoore@med.wayne.edu; pamelaneville@duke.edu;  
Nancy.M.Smith@uth.tmc.edu; StWilliams@peds.uab.edu; bvecchio@careNE.org; jthomp84@iupui.edu;  
Adele.Lamb@uphs.upenn.edu; KSmiley@mednet.ucla.edu; YDavis@mednet.ucla.edu; Michelle Smith;  
hk419@mail.cumc.columbia.edu; JRose@WIHRI.org; Deborah.Garcia@uth.tmc.edu; wwilli4@emory.edu;  
whitec2@email.chop.edu; bvohr@wihri.org; (b)(6)@aol.com; golds005@mc.duke.edu; ira\_adams-  
chapman@oz.ped.emory.edu; srhintz@stanford.edu; MPeralta@PEDS.UAB.EDU;  
Roy.Heyne@utsouthwestern.edu; Kimberly.Yolton@cchmc.org; tarah-colaizy@uiowa.edu;  
soraya.abbasi@uphs.upenn.edu; hurt@email.chop.edu; GERDES@email.chop.edu;  
gary\_myers@URMC.Rochester.edu; apappas@med.wayne.edu; ipurdy@mednet.ucla.edu;  
Keith.Yeates@nationwidechildrens.org; hkilbride@cmh.edu; sgunn@iupui.edu;  
AFDuncan@salud.unm.edu; diane\_marshall@med.unc.edu; Patrick.M.Jones@uth.tmc.edu;  
Christopher.Timan@nationwidechildrens.org; Newman, Jamie; jrose@wihri.org  
**Cc:** Auman, Jeanette O.; Cunningham, Meg; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn Petrie; Nolen,  
Tracy; Wallace, Dennis; Zaterka-Baxter, Kristin  
**Subject:** March SC and FU Agenda

Hi All,

Attached is the agenda for the upcoming meeting at the end of March. Please let me know if you have any questions.

Thanks!

Meg

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Stevens, Timothy"  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg  
**Date:** Tuesday, March 27, 2012 3:37:00 PM

---

Ok Susan is almost done with SUPPORT school age FU

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

---

**From:** Stevens, Timothy [mailto:Timothy\_Stevens@URMC.Rochester.edu]  
**Sent:** Tuesday, March 27, 2012 3:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

I'm joining now

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 27, 2012 12:57 PM  
**To:** Stevens, Timothy; 'newman@rti.org'  
**Cc:** 'petrie@rti.org'  
**Subject:** Re: Breathing Outcomes analysis update for Follow-up PI Mtg

(b)(6) with pass code (b)(6)

Also, we are running ahead - are you able to join earlier?

---

**From:** Stevens, Timothy [mailto:Timothy\_Stevens@URMC.Rochester.edu]  
**Sent:** Tuesday, March 27, 2012 12:34 PM  
**To:** 'Newman, Jamie' <newman@rti.org>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

Hi Jamie and Rose,

I do not have the call-in number for the update at 3:45. Can you let me know?

Thanks

Tim

---

**From:** Newman, Jamie [mailto:newman@rti.org]  
**Sent:** Tuesday, March 20, 2012 6:14 PM  
**To:** Stevens, Timothy  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik  
**Subject:** Breathing Outcomes analysis update for Follow-up PI Mtg

Dr. Stevens,

Please see below from a message from Rose. We have time slotted in the agenda for a 5 minute update on the Breathing Outcomes analysis at 3:45pm on Thurs Mar 27. Rose has requested handouts (which are optional) by Thursday Mar 22. Attached is the agenda. Are you available to provide the update by phone or do you prefer that someone provide an update on your behalf.

Thanks, Jamie

**From:** Newman, Jamie  
**Sent:** Monday, March 05, 2012 4:34 PM  
**To:** 'Stevens, Timothy'  
**Cc:** Das, Abhik  
**Subject:** Breathing Outcomes analysis update for Follow-up PI Meeting

Dr. Stevens,

Are you available to give a 5 minute update on Breathing Outcomes analysis at 3:45pm for the NRN Follow-up PI Meeting Tuesday March 27? Handouts are optional but we're happy to distribute a handout if you'd like.

Do you know when you'll hear back from your PAS late breaker submission?

Thanks, Jamie

Jamie E. Newman, PhD, MPH  
Statistics and Epidemiology  
RTI International  
Telephone: (919) 485-5719  
Fax: (919) 485-7762  
[newman@rti.org](mailto:newman@rti.org)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 20, 2012 1:03 PM  
**To:** Cunningham, Meg; Cbackstrom@salud.unm.edu; mball@leland.stanford.edu; rbara@med.wayne.edu; mcollins@peds.uab.edu; scosby@peds.uab.edu; cathy.grisby@uc.edu; ehale@emory.edu; ahensman@wihri.org; karen-johnson@uiowa.edu; Georgia.E.McDavid@uth.tmc.edu; Diana.Vasil@utsouthwestern.edu; nxs5@cwru.edu; ldw@iupui.edu; dclark@med.unc.edu; bernharj@email.unc.edu; janice\_wereszczak@med.unc.edu; Donia-campbell@uiowa.edu; lijun.chen@utsouthwestern.edu; JF126@notes.duke.edu; cagauldin@cmh.edu; Toni.Mancini@uphs.upenn.edu; christine.fortney@nationwidechildrens.org; Aasma.Chaudhary@uphs.upenn.edu; rosemary\_jensen@urmc.rochester.edu; kwynn@buffalo.edu;

Kimberley.fisher@duke.edu; sgbrown@salud.unm.edu; tchanlaw@uca.edu; RGeller@mednet.ucla.edu; tiwussow@salud.unm.edu; Holly\_Wadkins@URMC.Rochester.edu; CUCINOTTA@email.chop.edu; MKeszler@Wihri.org; slakshmi@buffalo.edu; NAmbalavanan@peds.uab.edu; dpcarl@emory.edu; cotte010@mc.duke.edu; woh@wihri.org; rohls@salud.unm.edu; jon.e.tyson@uth.tmc.edu; Matt\_Laughon@med.unc.edu; gsokol@iupui.edu; dan\_ellsbury@pediatrix.com; MGarg@mednet.ucla.edu; bsood@med.wayne.edu; Archer, Stephanie (NIH/NICHD) [E]; edward-bell@uiowa.edu; wcarlo@peds.uab.edu; goldb008@mc.duke.edu; Kathleen.A.Kennedy@uth.tmc.edu; alaptook@WIHRI.org; bpoindex@iupui.edu; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; sshankar@med.wayne.edu; [SCRN] Stoll, Barbara; vanmeurs@leland.stanford.edu; mcw3@cwru.edu; kwatterberg@salud.unm.edu; RAP32@columbia.edu; Luc.Brion@utsouthwestern.edu; dan\_ellsbury@pediatrix.com; wtruog@cmh.edu; KIRPALANI@email.chop.edu; barbara.schmidt@uphs.upenn.edu; Leif.Nelin@nationwidechildrens.org; nehal.parikh@nationwidechildrens.org; udevaskar@mednet.ucla.edu; carl\_dangio@urmc.rochester.edu; martin.blakely@vanderbilt.edu; dale\_phelps@urmc.rochester.edu; bvohr@wihri.org; DEMAURO@email.chop.edu; jwaidne@emory.edu; gonza025@mc.duke.edu; axt25@po.cwru.edu; Karen.Kirby@UTSouthwestern.edu; lmoore@med.wayne.edu; pamela.neville@duke.edu; Nancy.M.Smith@uth.tmc.edu; StWilliams@peds.uab.edu; bvecchio@careNE.org; jthomp84@iupui.edu; Adele.Lamb@uphs.upenn.edu; KSmiley@mednet.ucla.edu; YDavis@mednet.ucla.edu; Michelle Smith; hk419@mail.cumc.columbia.edu; JRose@WIHRI.org; Deborah.Garcia@uth.tmc.edu; wwilli4@emory.edu; whitte2@email.chop.edu; bvohr@wihri.org; [b](6)@aol.com; golds005@mc.duke.edu; ira\_adams-chapman@oz.ped.emory.edu; srhintz@stanford.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; Kimberly.Yolton@cchmc.org; tarah-colaizy@uiowa.edu; soraya.abbasi@uphs.upenn.edu; hurt@email.chop.edu; GERDES@email.chop.edu; gary\_myers@URMC.Rochester.edu; apappas@med.wayne.edu; ipurdy@mednet.ucla.edu; Keith.Yeates@nationwidechildrens.org; hkilbride@cmh.edu; sgunn@iupui.edu; AFDuncan@salud.unm.edu; diane\_marshall@med.unc.edu; Patrick.M.Jones@uth.tmc.edu; Christopher.Timan@nationwidechildrens.org; Newman, Jamie; jrose@wihri.org  
**Cc:** Auman, Jeanette O.; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn Petrie; Nolen, Tracy; Wallace, Dennis; Zaterka-Baxter, Kristin  
**Subject:** RE: March SC and FU Agenda

If you have items that you wish to use as handouts at the meetings, please send them to us by THURSDAY MARCH 22.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

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

**Sent:** Friday, February 24, 2012 11:48 AM

**To:** Cbackstrom@salud.unm.edu; mball@leland.stanford.edu; rbara@med.wayne.edu; mcollins@peds.uab.edu; scosby@peds.uab.edu; cathy.grisby@uc.edu; ehale@emory.edu; ahensman@wihri.org; karen-johnson@uiowa.edu; Georgia.E.McDavid@uth.tmc.edu;

Diana.Vasil@utsouthwestern.edu; nxs5@cwru.edu; ldw@iupui.edu; clark@med.unc.edu; bernharj@email.unc.edu; janice\_wereszczak@med.unc.edu; Donia-campbell@uiowa.edu; lijun.chen@utsouthwestern.edu; JF126@notes.duke.edu; cagauldin@cmh.edu; Toni.Mancini@uphs.upenn.edu; christine.fortney@nationwidechildrens.org; Aasma.Chaudhary@uphs.upenn.edu; rosemary\_jensen@urmc.rochester.edu; kwynn@buffalo.edu; Kimberley.fisher@duke.edu; sgbrown@salud.unm.edu; tchanlaw@ucla.edu; RGeller@mednet.ucla.edu; tiwusow@salud.unm.edu; Holly\_Wadkins@URMC.Rochester.edu; CUCINOTTA@email.chop.edu; MKesler@Wihri.org; slakshmi@buffalo.edu; NAmbalavanan@peds.uab.edu; dpcarl@emory.edu; cotte010@mc.duke.edu; woh@wihri.org; rohls@salud.unm.edu; jon.e.tyson@uth.tmc.edu; Matt\_Laughon@med.unc.edu; gsokol@iupui.edu; dan\_ellsbury@pediatrix.com; MGarg@mednet.ucla.edu; bsood@med.wayne.edu; Archer, Stephanie (NIH/NICHD) [E]; edward-bell@uiowa.edu; wcarlo@peds.uab.edu; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; alaptook@WIHRI.org; bpoindex@iupui.edu; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; sshankar@med.wayne.edu; [SCRN] Stoll, Barbara; vanmeurs@leland.stanford.edu; mcw3@cwru.edu; kwatterberg@salud.unm.edu; RAP32@columbia.edu; Luc.Brion@utsouthwestern.edu; dan\_ellsbury@pediatrix.com; wtruog@cmh.edu; KIRPALANIH@email.chop.edu; barbara.schmidt@uphs.upenn.edu; Leif.Nelin@nationwidechildrens.org; nehal.parikh@nationwidechildrens.org; udevaskar@mednet.ucla.edu; carl\_dangio@urmc.rochester.edu; martin.blakely@vanderbilt.edu; dale\_phelps@urmc.rochester.edu; bvohr@wihri.org; DEMAURO@email.chop.edu; jwaidne@emory.edu; gonza025@mc.duke.edu; axt25@po.cwru.edu; Karen.Kirby@UTSouthwestern.edu; lmoore@med.wayne.edu; pamela.neville@duke.edu; Nancy.M.Smith@uth.tmc.edu; StWilliams@peds.uab.edu; bvecchio@careNE.org; jthomp84@iupui.edu; Adele.Lamb@uphs.upenn.edu; KSmiley@mednet.ucla.edu; YDavis@mednet.ucla.edu; Michelle Smith; hk419@mail.cumc.columbia.edu; JRose@WIHRI.org; Deborah.Garcia@uth.tmc.edu; wwilli4@emory.edu; whitec2@email.chop.edu; bvohr@wihri.org; (b)(6)@aol.com; golds005@mc.duke.edu; ira\_adams-chapman@oz.ped.emory.edu; srhintz@stanford.edu; MPeralta@PEDS.UAB.EDU; Roy.Heyne@utsouthwestern.edu; Kimberly.Yolton@cchmc.org; tarah-colaizy@uiowa.edu; soraya.abbasi@uphs.upenn.edu; hurt@email.chop.edu; GERDES@email.chop.edu; gary\_myers@URMC.Rochester.edu; apappas@med.wayne.edu; ipurdy@mednet.ucla.edu; Keith.Yeates@nationwidechildrens.org; hkilbride@cmh.edu; sgunn@iupui.edu; AFDuncan@salud.unm.edu; diane\_marshall@med.unc.edu; Patrick.M.Jones@uth.tmc.edu; Christopher.Timan@nationwidechildrens.org; Newman, Jamie; jrose@wihri.org  
**Cc:** Auman, Jeanette O.; Cunningham, Meg; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn Petrie; Nolen, Tracy; Wallace, Dennis; Zaterka-Baxter, Kristin  
**Subject:** March SC and FU Agenda

Hi All,

Attached is the agenda for the upcoming meeting at the end of March. Please let me know if you have any questions.

Thanks!

Meg

*Meg Cunningham, CCRP*  
*RTI International*  
*701 13th St. NW, Ste. 750*  
*Washington, DC 20005*  
*tel: 202-974-7837*  
*fax: 202-773-2095*  
[www.rti.org](http://www.rti.org)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "mgantz@rti.org"  
**Subject:** Fw: New England Journal of Medicine 12-01618  
**Date:** Tuesday, March 27, 2012 8:04:37 AM

---

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

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]  
Sent: Monday, March 26, 2012 06:01 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: FW: New England Journal of Medicine 12-01618

Here are the reviews, sorry I could not forward it before, my phone was not working.  
I am traveling to the meeting tomorrow, I should arrive around 11:30 am or so I hope we can talk then. thanks

---

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[onbehalfof+editorial+nejm.org@manuscriptcentral.com] on behalf of editorial@nejm.org [editorial@nejm.org]  
Sent: Monday, March 26, 2012 8:40 AM  
To: Myriam Peralta, M.D.  
Subject: New England Journal of Medicine 12-01618

Dear Dr. Peralta Carcelen:

I am writing about your manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets." We found your study interesting but do not consider it acceptable for publication in the Journal in its present form. We would be interested, however, in receiving a single manuscript that combines the results in this paper with those currently included in your companion manuscript, "Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood." We believe that the results of these 2 reports are best presented as a single manuscript.

As raised by the statistician, whose comments on both manuscripts are included below, it is important to address whether there is (b)(4),(b)(6) We would underscore the recommendations of reviewer 1 and the statistical consultant that you report results of (b)(4),(b)(6) (b)(4),(b)(6)

If you choose to resubmit, as we hope that you will, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy.

We ask that the final version of your manuscript not exceed 2700 words (text) and that there be no more than 5 tables or figures in the print version. It is fine to include additional material (methodologic, and other tables or figures as needed) in a supplemental web appendix.

To resubmit your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter "For Authors." Under "My Manuscripts," click on "Manuscripts with Decisions." Your manuscript will appear at the bottom of the screen under "Manuscripts with Decisions." Click on "Create a Resubmission," and follow the instructions for resubmitting your manuscript. When your manuscript has been submitted, a new manuscript ID will be assigned.

Thank you for submitting your work to the Journal.

Sincerely,

Caren G. Solomon, MD



Deputy Editor

Michael F. Greene, MD  
Associate Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Reviewer: 1

<b>Comments for the Author</b>

This multicenter randomized controlled trial sought to determine a lower target range of oxygen saturation compared to a higher target oxygen saturation range on the composite outcome of death or neurodevelopment impairment at 18 to 22 months corrected age in extremely premature infants. (b)(4)

(b)(4)

Reviewer: 2

<b>Comments for the Author</b>

(b)(4)

(b)(4)



Statistical Reviewer: 1  
Comments for the Author:

(b)(4)



(b)(4)



**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Myriam Peralta, M.D."](#)  
**Cc:** ["wacarlo@uab.edu"](#)  
**Subject:** NEJM  
**Date:** Monday, March 26, 2012 5:47:00 PM  
**Importance:** High

---

Myriam

We are having a discussion at 10 am tomorrow regarding the SUPPORT FU paper(s). Please forward us the reviews from NEJM as soon as you can

Thanks for all your help!

Rose

**Rosemary D. Higgins, MD**  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** [Finer, Neil](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Rich, Wade](#)  
**Cc:** [Carlo, Wally \(wcarlo@peds.uab.edu\)](#); [Rich, Wade](#); [Vaucher, Yvonne](#); [Meg Cunningham](#); [Abhik Das](#); "Myriam Peralta, M.D."  
**Subject:** RE: NEJM getting the SUPPORT subcommittee together.  
**Date:** Monday, March 26, 2012 3:01:42 PM

---

Great  
Talk to you then  
Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, March 26, 2012 11:57 AM  
**To:** Finer, Neil; Rich, Wade  
**Cc:** Carlo, Wally ([wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)); Rich, Wade; Vaucher, Yvonne; Meg Cunningham; Abhik Das; 'Myriam Peralta, M.D.'  
**Subject:** RE: NEJM getting the SUPPORT subcommittee together.

We will move things around to accommodate a 7 am call in for you (10 am ET)

Please call (b)(6) with passcode (b)(6)  
Myriam.– please send your email to us from NEJM>  
Thanks

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

---

**From:** Finer, Neil [<mailto:nfiner@ucsd.edu>]  
**Sent:** Monday, March 26, 2012 1:15 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade  
**Cc:** Carlo, Wally ([wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)); Rich, Wade; Vaucher, Yvonne  
**Subject:** RE: NEJM getting the SUPPORT subcommittee together.

Hi Rose  
I can be available at 7:00AM as I have other commitments after 8:00AM  
Yvonne can also do 7:00AM tomorrow  
Can that work for you?  
Otherwise I can do Wednesday after 9:15 AM as I have early meetings that day  
Did Wally/Marion get a letter from NEJM about their paper or are these combined comments for both? – I assume the latter.

Be well  
Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, March 26, 2012 8:50 AM  
**To:** Finer, Neil; Rich, Wade  
**Subject:** NEJM getting the SUPPORT subcommittee together.

Are you available tomorrow at 1205 pm (905 PT)?  
Let me know and I can see about getting the SUPPORT subcommittee together – the only other possible time is 6 PM ET but I think many of the PI's will already be gone.

Thanks

Rose

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

**From:** Vaucher, Yvonne  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo, M.D."; Finer, Neil  
**Cc:** Abhik Das  
**Subject:** RE: New England Journal of Medicine 12-01547  
**Date:** Monday, March 26, 2012 12:16:38 PM

---

All,

I agree with the recommendation to combine the papers as there is so much overlap. The comments are reasonable and I think can all be adequately addressed for resubmission to the NEJM. Rose, can you report this change in plans at the FUP meeting?

Yvonne

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, March 26, 2012 7:46 AM  
**To:** "Wally Carlo, M.D."; Finer, Neil  
**Cc:** Vaucher, Yvonne; Abhik Das  
**Subject:** RE: New England Journal of Medicine 12-01547

Ok

Can you send the comments on the saturation paper?

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov>

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, March 26, 2012 10:46 AM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Vaucher, Yvonne  
**Subject:** Re: New England Journal of Medicine 12-01547

I agree also with combining the papers so we can get it into NEJM. I am available for a call this week.

Wally

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

**From:** "Finer, Neil" <nfiner@ucsd.edu>  
**To:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, rose higgins <higginsr@mail.nih.gov>  
**Cc:** "Vaucher, Yvonne" <yvaucher@ucsd.edu>  
**Sent:** Mon, Mar 26, 2012 14:14:27 GMT+00:00  
**Subject:** Fwd: New England Journal of Medicine 12-01547

I know you guys are at a Network meeting and I would guess that you have got the same response to the Marions

paper

Can we arrange a phone call to discuss these and whether we want a combined paper in NEJM?

I am OK with that

be well

Neil

Begin forwarded message:

From: "editorial@nejm.org<mailto:editorial@nejm.org>" <editorial@nejm.org<mailto:editorial@nejm.org>>  
Date: March 26, 2012 6:46:45 AM PDT  
To: "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>  
Subject: New England Journal of Medicine 12-01547

Dear Dr. Finer:

I am writing about your manuscript, "Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood." We found your study interesting but do not consider it acceptable for publication in the Journal in its present form. We would be interested, however, in receiving a single manuscript that combines the results in this paper with those currently included in your companion manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets." We believe the results of these two reports are best presented as a single manuscript.

As raised by the statistician, whose comments on both manuscripts are included below, it is important to address whether there is a (b)(4),(b)(6) We would underscore the recommendation of the statistical consultant that you report the (b)(4),(b)(6) (b)(4),(b) In addition, effects of the (b)(4),(b)(6) should be more explicitly acknowledged.

If you choose to resubmit, as we hope that you will, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy.

We ask that the final version of your manuscript not exceed 2700 words (text) and that there be no more than 5 tables or figures in the print version. It is fine to include additional material (methodologic, and other tables or figures as needed) in a supplemental web appendix.

To resubmit your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter "For Authors." Under "My Manuscripts," click on "Manuscripts with Decisions." Your manuscript will appear at the bottom of the screen under "Manuscripts with Decisions." Click on "Create a Resubmission," and follow the instructions for resubmitting your manuscript. When your manuscript has been submitted, a new manuscript ID will be assigned.

Thank you for submitting your work to the Journal.

Sincerely,

Caren G. Solomon, MD  
Deputy Editor

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**Reviewer: 1**

**<b>Comments for the Author</b>**

This is a sub-study of the original SUPPORT Trial published in NEJM in May 2010. The background, methods, and discussion is well written.

**Suggestions and questions that I have for the authors are as follows:**

(b)(4)



**Reviewer: 2**

**<b>Comments for the Author</b>**

(b)(4)



**From:** Phelps, Dale  
**To:** "Kennedy, Kathleen A"  
**Cc:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann (wrage@rti.org)  
**Subject:** RE: Poster for SUPPORT Secondary Study  
**Date:** Monday, March 26, 2012 10:46:07 AM

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Thanks Kathleen,

It might be most pertinent to the purpose of the poster to ask if any of these 14 met criteria for not doing further examinations. I think only 1, maybe.

Clearly the infants with zone I or zone II vessels should still be in frequent follow up

So....

The one with zone III vessels (that went on to treatment) is in question.

Was this his first examination with zone III vessels ? if so, repeat examination needed, (recommendations supported)

Were his zone III vessels with ROP of prethreshold severity? If so needed follow up exams (recommendations supported).

Were his zone III vessels with less than prethreshold ROP seen on at least two consecutive examinations? If so, then he is an exception to the examination guidelines and the most worrisome.

Dale

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**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Monday, March 26, 2012 5:36 AM  
**To:** Phelps, Dale  
**Cc:** Finer, Neil; Higgins, Rosemary (NIH/NICHD); Wrage, Lisa Ann (wrage@rti.org)  
**Subject:** RE: Poster for SUPPORT Secondary Study

We have this information. It's in the draft manuscript but didn't make it into the paper. We were focusing on ROP exam factors. I interpreted this as showing that the babies diagnosed after discharge are a little different as a group, but there's nothing that sets them apart.

**ROP exam prior to discharge for infants with final ROP status determined after discharge home**

<b>Worst exam findings prior to discharge either or both eyes:</b>	<b>Severe ROP Group N=14</b>	<b>No Severe ROP Group N=535</b>
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0

No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

We also have the PMA information that's in the poster. We could ask Lisa for more medical information, but I think we need to compare these two groups, not just list the information for the 14 infants with no comparison. I can ask her to include all the medical info you've requested to the table that's in the poster (for the manuscript version). Lisa can work on that after she revises the figures for the poster.

I'll work on Dale's other suggestions as well as Wally's in a revised version of the poster.

Kathleen A. Kennedy, MD, MPH  
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713 500-6708

---

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Sunday, March 25, 2012 6:17 PM  
**To:** 'Finer, Neil'; Kennedy, Kathleen A; Carlo, Wally ([wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)); Faix, Roger; Laptook, Abbot; Walsh, Michele; Brad Yoder ([Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu)); Das, Abhik; Gantz, Marie ; Rich, Wade  
**Cc:** Higgins, Rosemary (NIH/NICHD); Archer, Stephanie; Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org))  
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Neil asks a very interesting question. You probably can't put it on the poster, but you will very likely get questions about 'what's different about them?'

My guess is that reasons might group:

1. did really well and went home earlier than usual, so maybe PMA 33-36 weeks while they were still really at risk, or their ROP was just starting and looked mild, but was actually taking off down the wrong road.
2. Had concerning ROP known at time of discharge, but clinicians judged family stable and reliable enough to bring them back in for follow up examinations as scheduled.
3. A total surprise -- no one identified a particular risk factor (other than they were <28 weeks GA at birth)

Could Lisa make us a table for you of the 14 ?

GA, BW, days on oxygen, early onset sepsis, late onset sepsis, Candida sepsis, PMA at first ROP detected, PMA at discharge or transfer, PMA at time of surgical treatment? What I have I forgotten? :-)

Dale

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**From:** Finer, Neil [<mailto:nfiner@ucsd.edu>]  
**Sent:** Sunday, March 25, 2012 4:09 PM  
**To:** Kennedy, Kathleen A; Carlo, Wally ([wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)); Faix, Roger; Laptook, Abbot; Walsh, Michele; Brad Yoder ([Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu)); Das, Abhik; Gantz, Marie ; Rich, Wade  
**Cc:** Higgins, Rosemary (NIH/NICHD); Archer, Stephanie; Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org)); Phelps, Dale  
**Subject:** RE: Poster for SUPPORT Secondary Study

Hi Kathleen

Thanks for sharing this poster

Very useful and worrying information

How different are the 14 infants with late post discharge Severe ROP – ie more immature, sicker, with severe IVH, NEC, other surgery, etc?

Do you have any of this?

Nicely done

Thanks Neil

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Friday, March 23, 2012 1:24 PM  
**To:** Finer, Neil; Carlo, Wally ([wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)); Faix, Roger; Laptook, Abbot; Walsh, Michele; Brad Yoder ([Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu)); Das, Abhik; Gantz, Marie ; Rich, Wade  
**Cc:** Higgins, Rosemary (NIH/NICHD); Archer, Stephanie; Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Myriam Peralta, M.D."; "wacarlo@uab.edu"  
**Subject:** NEJM???  
**Date:** Monday, March 26, 2012 10:21:00 AM

---

Can you send Abhik< Neif and I the NEJM comments on the SUPPORT paper

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**From:** [Finer, Neil](#)  
**To:** [Phelps, Dale](#); [Kennedy, Kathleen A](#); [Carlo, Wally \(wcarlo@peds.uab.edu\)](#); [Faix, Roger](#); [Laptook, Abbot](#); [Walsh, Michele](#); [Brad Yoder \(Bradley.Yoder@hsc.utah.edu\)](#); [Das, Abhik](#); [Gantz, Marie](#); [Rich, Wade](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Wrage, Lisa Ann \(wrage@rti.org\)](#)  
**Subject:** RE: Poster for SUPPORT Secondary Study  
**Date:** Sunday, March 25, 2012 7:18:58 PM

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Thanks Dale

You forgot much less than I did!

Be well

Neil

---

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**From:** Phelps, Dale  
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**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Wraga, Lisa Ann (wraga@rti.org)  
**Subject:** RE: Poster for SUPPORT Secondary Study  
**Date:** Sunday, March 25, 2012 6:17:20 PM

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Hi Kathleen,

Here are my 4 comments on the poster. (I also agree that some brighter colors would be nice for the bar graph).

Nicely pulled together, clear content, logically sequenced and objective.

I do have some editorial concerns and include them here. (I didn't want to mess up your poster).  
Dale

1. Background: Comments from Dale Phelps

- Timely detection of treatable ROP is important for optimal outcomes.
- The current (2006) screening guidelines are based on infants born in 1986-1997:
  - screening should begin by 31 wks postmenstrual age (PMA) (or 4 weeks after birth, if later)
  - and continue until vessels have reached fully to the ora serrata (mature), zone III without prior ROP ~~at~~ after 35 wks or, for infants who have had ROP less severe than ~~without~~ prethreshold ROP and is regressing until 45 wks PMA.
- Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I; or stage 2-3 with plus disease in zone II) is now recommended.

2. Objective:

To validate the 2006 ROP screening guidelines for 24-27 wk GA infants Comment: the word 'validate' has, I believe, specific statistical meaning. I don't think we did this. I would say rather:  
To evaluate the 2006 ROP screening guidelines for 24-27 wk GA infants born in 2006-2008 {are those the right dates for SUPPORT?}

3. In Methods: or in the Results.... we need to add the years of recruitment, particularly since we are making the point that the current guidelines are based on old data. Could be above, or here or in Results.

- Inborn infants 24 <sup>0</sup>/<sub>7</sub> to 27 <sup>6</sup>/<sub>7</sub> wks GA with consent prior to delivery and born 2006-20?? were eligible.

4. Number Discrepancy:

In your table of when things happen (Table at the bottom in the center). It reports 128 infants who reached Type I ROP.

but in the table on the right showing timing in relation to going home, you report 138 infants who got treatment. There are probably explanations for these, but it will be hard to remember, so put the explanations in a foot note.... probably they had worse disease at the time of discovery for treatment so their age of onset was not known.



---

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**Subject:** Poster for SUPPORT Secondary Study  
**Date:** Friday, March 23, 2012 4:22:52 PM  
**Attachments:** [NRN SUPPORT ROP Observational Study \(resized\).pptx](#)

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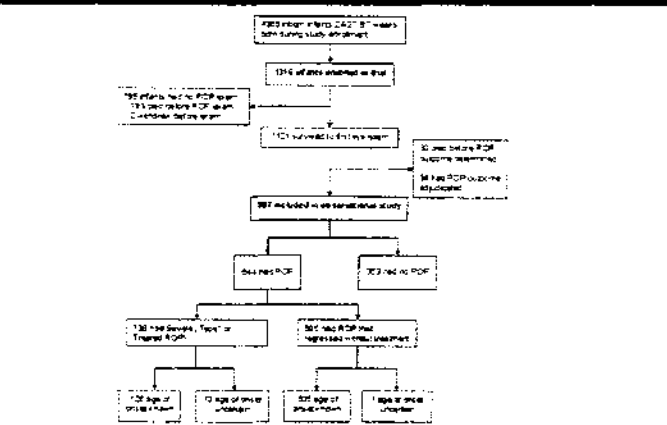
# Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants

Kathleen A Kennedy MD MPH, Lisa A Wrage MPH, Dale Phelps MD, Rosemary Higgins MD and the SUPPORT Subcommittee of the NICHD Neonatal Research Network

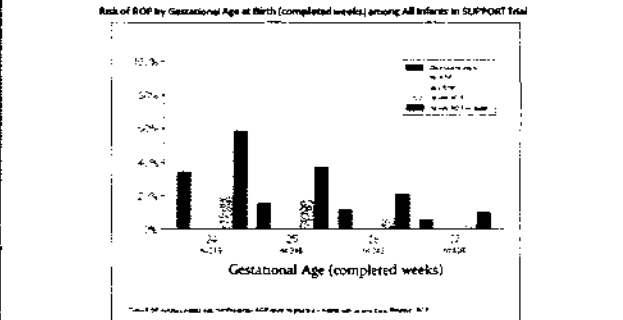
- Timely detection of treatable ROP is important for optimal outcomes.
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  - and continue until vessels have reached zone III at 35 wks or, for infants without prethreshold ROP, until 45 wks PMA.
- Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

To validate the 2006 ROP screening guidelines for 24-27 wk GA infants

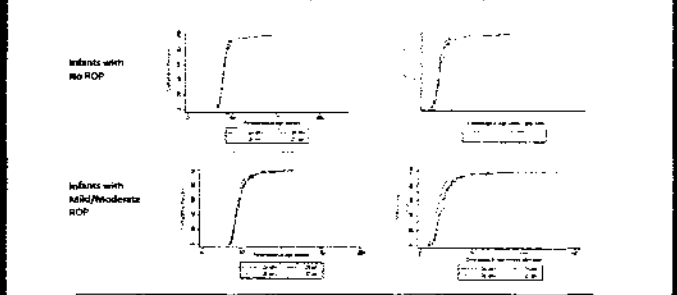
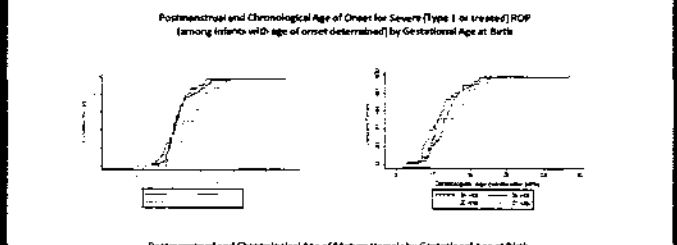
- Descriptive natural history study using outcome data from the NICHD Network SUPPORT trial
- In this trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial trial.
- Inborn infants 24 2/7, to 27 6/7 wks GA with consent prior to delivery were eligible.
- Examinations followed current screening recommendations.
- Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA.
- For this observational study, age of onset is defined as age of detection.
- Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 wks (1 wk if the previous exam had ROP in zone I) were defined as having an uncertain age of onset.



Characteristic	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Selected Baseline Characteristics)			
		All ROP Outcomes	No ROP	Any ROP	Severe Type 1 or Treated ROP
n	1316	997	223	644	138
Gestational Age (Weeks) (SD)	26.2 (1.3)	26.3 (1.3)	26.6 (1.0)	26.0 (1.0)	25.5 (1.0)
Birth Weight (kg) (SD)	1.23 (0.2)	1.24 (0.2)	1.43 (0.2)	1.18 (0.2)	1.18 (0.2)
Race/Ethnicity (%)					
White	48 (3.6)	34 (3.4)	13 (5.8)	22 (3.4)	4 (2.9)
Black	52 (3.9)	38 (3.8)	12 (5.4)	23 (3.6)	4 (2.9)
Hispanic	239 (18.2)	190 (19.0)	49 (22.0)	131 (20.3)	28 (20.3)
Other	47 (3.6)	35 (3.5)	6 (2.7)	29 (4.5)	7 (5.1)
Male (%)	712 (54.1)	519 (52.1)	195 (87.4)	534 (82.8)	73 (53.6)
Antenatal Steroids (%)	1285 (97.7)	853 (85.6)	340 (152.0)	613 (95.2)	135 (97.8)
Multiple Birth (%)	127 (9.6)	25 (2.5)	91 (40.8)	162 (25.2)	41 (29.7)



ROP type	Postmenstrual Age (weeks)												Chronological Age (months)											
	n	min	1%	5%	25%	50%	75%	90%	95%	100%	min	1%	5%	25%	50%	75%	90%	95%	100%					
Any ROP	642	29.2	30.4	31.6	32.7	33.9	35.1	37.9	43.0	46.7	4.0	4.8	5.4	6.7	8.0	9.4	11.8	15.8	19.7					
Type 1 ROP	158	29.3	31.7	31.1	34.1	38.1	40.4	45.4	45.9	48.7	4.4	4.6	5.3	5.7	10.9	12.5	15.0	21.5	22.7					
Severe Type 1/Treated ROP	138	32.1	33.7	33.9	35.1	36.9	38.6	43.6	45.0	53.2	6.4	7.1	8.4	9.8	11.3	13.1	17.0	23.0	24.4					



Infants with Severe ROP (n=138)	First exam with severe ROP occurred before discharge (n=25)	First exam with severe ROP after discharge (n=113)
Postmenstrual age at first occurrence of severe ROP: weeks (range)	36.0 (32.1-45.0)	40.8 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-76.9)	38.9 (26.6-71.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

- In these 997 infants, we did not observe treatable ROP before 32 wks PMA; only 1 infant developed severe ROP after 45 wks PMA.
- Our contemporary data support continued use of the 2006 ROP screening guidelines.
- Some infants who are stable enough for back transfer or discharge home are still at risk to develop treatable ROP.
- A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to report. This poster is for informational purposes only and does not constitute an offer of medical or pharmaceutical products. Acknowledgements: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Pittsburg State University; Tulane University; University of Alabama at Birmingham; University of California - San Diego; University of Iowa; University of Michigan; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kennedy, Kathleen A"  
**Cc:** "dale\_phelps@urmc.rochester.edu"  
**Subject:** RE: Poster Draft  
**Date:** Friday, March 23, 2012 12:48:00 PM

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I meant "brighter colors"

You can tell the differences, but would it be possible to use other colors?

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**From:** Kennedy, Kathleen A [mailto:[Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)]  
**Sent:** Friday, March 23, 2012 12:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** dale\_phelps@urmc.rochester.edu  
**Subject:** RE: Poster Draft

The conclusion previously said "our data support". Dale suggested changing it to "our data are consistent with". I didn't think that sounded right. We could say that our data were consistent with prior natural history study data but it seems that the data either support or do not support a change in the screening guidelines. I'm happy to change it to what you're suggesting if that's ok with Dale.

I'm still trying to figure out how to work with RTI on the figures. It would be much easier for me if I were making them myself but I don't have the data. What do you mean by "better" colors? Do you think it's too hard to tell one bar from another or that they don't look good with the Network poster template?

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Friday, March 23, 2012 11:24 AM  
**To:** Kennedy, Kathleen A  
**Subject:** RE: Poster Draft

2<sup>nd</sup> conclusion – can we restate as a positive such as  
Our data affirm continued ROP screening as per the 2006 guidelines in a contemporary trial....

For the bar graph in the middle of the poster – any way to have better colors??

I am ok with the other figures – those who are interested will take a close look.

Thanks – I think this is ready for the SUPPORT Subcommittee

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](mailto:higginsr@mail.nih.gov)

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Friday, March 23, 2012 12:01 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org))  
**Subject:** Poster Draft

I've attached a draft of the poster. The content is taken from the revised manuscript draft.

Dale and Rose: If you could pay particular attention to what's in the figures (and if you think these are the best figures to include), that would be great. They don't look very good right now and I'm still trying to figure out how to address that when I'm not making them myself. I've plastered some text boxes on top of the copied figures to cover up titles etc that need to be removed and axis labels that need to be changed. I'm hoping that Lisa can look at what's on the poster draft to see what we need. If you have suggestions for modification to the tables and text, those will be easy for me to do; I'll work on making those look better when we agree on the content.

Lisa: I'm not sure what program you use to make the figures and how much flexibility you have to change the appearance and resolution. Some of the figures are very grainy when copied and enlarged. They don't all seem to be the same shape so it's hard to line them up. There are a number of changes that need to be made to the axes, titles and axis labels. I put some comments about that in the manuscript draft but I think it might be easier to see what's needed in the draft of the poster.

When we get some better looking versions of the figures, we can send it to the SUPPORT Subcommittee for their review.

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]  
**To:** Hoult, Ben (NIH/OD) [E]  
**Subject:** RE: Breathing Outcomes analysis handout for Follow-up PI Mtg  
**Date:** Friday, March 23, 2012 12:16:00 PM

---

yes

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**From:** Hoult, Ben (NIH/OD) [E]  
**Sent:** Friday, March 23, 2012 12:12 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes analysis handout for Follow-up PI Mtg

Double sided and stapled?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, March 23, 2012 11:57 AM  
**To:** Hoult, Ben (NIH/OD) [E]  
**Cc:** Langham, Amira (NIH/OD) [E]; Rose, Michele (NIH/OD) [E]  
**Subject:** FW: Breathing Outcomes analysis handout for Follow-up PI Mtg

30 copies of each in a folder labeled "BREATHING OUTCOMES"

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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Newman, Jamie [<mailto:newman@rti.org>]  
**Sent:** Friday, March 23, 2012 11:53 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** FW: Breathing Outcomes analysis handout for Follow-up PI Mtg

Rose,

Tim Stevens just confirmed that he intends for the attached to be distributed as a handout at the Follow-up Mtg (I misinterpreted his email below to mean that he didn't want it distributed due to length). He will also join by phone to give a summary.

Thanks, Jamie

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**From:** Stevens, Timothy [[mailto:Timothy\\_Stevens@URMC.Rochester.edu](mailto:Timothy_Stevens@URMC.Rochester.edu)]

**Sent:** Thursday, March 22, 2012 4:19 PM

**To:** Newman, Jamie

**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

Hi Jamie

Here is a copy of the late breaker abstract and a draft of the analysis plan that Steven Thomas wrote based on discussion with Abhik, me and others.

As a handout it is a bit long, but I'll provide a synopsis over the phone.

Thanks

Tim

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**From:** Newman, Jamie [<mailto:newman@rti.org>]

**Sent:** Wednesday, March 21, 2012 7:30 PM

**To:** Stevens, Timothy

**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

Ok, I'll keep an eye out for it. I'm out of the office Thurs but I'm in all day on Friday.

Thanks, Jamie

---

**From:** Stevens, Timothy [[mailto:Timothy\\_Stevens@URMC.Rochester.edu](mailto:Timothy_Stevens@URMC.Rochester.edu)]

**Sent:** Wednesday, March 21, 2012 6:24 PM

**To:** Newman, Jamie

**Subject:** Re: Breathing Outcomes analysis update for Follow-up PI Mtg

Hi Jamie,

I'll get a handout to you tomorrow (Thurs) and plan to speak by phone.

Thanks

Tim

On Mar 20, 2012, at 6:13 PM, "Newman, Jamie" <[newman@rti.org](mailto:newman@rti.org)> wrote:

Dr. Stevens,



Please see below from a message from Rose. We have time slotted in the agenda for a 5 minute update on the Breathing Outcomes analysis at 3:45pm on Thurs Mar 27. Rose has requested handouts (which are optional) by Thursday Mar 22. Attached is the agenda. Are you available to provide the update by phone or do you prefer that someone provide an update on your behalf.

Thanks, Jamie

**From:** Newman, Jamie  
**Sent:** Monday, March 05, 2012 4:34 PM  
**To:** 'Stevens, Timothy'  
**Cc:** Das, Abhik  
**Subject:** Breathing Outcomes analysis update for Follow-up PI Meeting

Dr. Stevens,  
Are you available to give a 5 minute update on Breathing Outcomes analysis at 3:45pm for the NRN Follow-up PI Meeting Tuesday March 27? Handouts are optional but we're happy to distribute a handout if you'd like.

Do you know when you'll hear back from your PAS late breaker submission?

Thanks, Jamie

Jamie E. Newman, PhD, MPH  
Statistics and Epidemiology  
RTI International  
Telephone: (919) 485-5719  
Fax: (919) 485-7762  
[newman@rti.org](mailto:newman@rti.org)

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, March 20, 2012 1:03 PM  
**To:** Cunningham, Meg; [Cbackstrom@salud.unm.edu](mailto:Cbackstrom@salud.unm.edu); [mbball@leland.stanford.edu](mailto:mbball@leland.stanford.edu); [rbarat@med.wayne.edu](mailto:rbarat@med.wayne.edu); [mcollins@peds.uab.edu](mailto:mcollins@peds.uab.edu); [scosby@peds.uab.edu](mailto:scosby@peds.uab.edu); [cathy.grisby@uc.edu](mailto:cathy.grisby@uc.edu); [ehale@emory.edu](mailto:ehale@emory.edu); [ahensman@wihri.org](mailto:ahensman@wihri.org); [karen-johnson@uiowa.edu](mailto:karen-johnson@uiowa.edu); [Georgia.E.McDavid@uth.tmc.edu](mailto:Georgia.E.McDavid@uth.tmc.edu); [Diana.Vasil@utsouthwestern.edu](mailto:Diana.Vasil@utsouthwestern.edu); [nxs5@cwru.edu](mailto:nxs5@cwru.edu); [ldw@iupui.edu](mailto:ldw@iupui.edu); [clark@med.unc.edu](mailto:clark@med.unc.edu); [bernharij@email.unc.edu](mailto:bernharij@email.unc.edu); [janice\\_wereszczak@med.unc.edu](mailto:janice_wereszczak@med.unc.edu); [Donia-campbell@uiowa.edu](mailto:Donia-campbell@uiowa.edu); [lijun.chen@utsouthwestern.edu](mailto:lijun.chen@utsouthwestern.edu); [JF126@notes.duke.edu](mailto:JF126@notes.duke.edu); [cagauldin@cmh.edu](mailto:cagauldin@cmh.edu); [Toni.Mancini@uphs.upenn.edu](mailto:Toni.Mancini@uphs.upenn.edu); [christine.fortney@nationwidechildrens.org](mailto:christine.fortney@nationwidechildrens.org); [Aasma.Chaudhary@uphs.upenn.edu](mailto:Aasma.Chaudhary@uphs.upenn.edu); [rosemary\\_jensen@urmc.rochester.edu](mailto:rosemary_jensen@urmc.rochester.edu); [kwynn@buffalo.edu](mailto:kwynn@buffalo.edu); [Kimberley.fisher@duke.edu](mailto:Kimberley.fisher@duke.edu); [sgbrown@salud.unm.edu](mailto:sgbrown@salud.unm.edu); [tchanlaw@ucla.edu](mailto:tchanlaw@ucla.edu); [RGeller@mednet.ucla.edu](mailto:RGeller@mednet.ucla.edu); [tiwussow@salud.unm.edu](mailto:tiwussow@salud.unm.edu); [Holly.Wadkins@URMC.Rochester.edu](mailto:Holly.Wadkins@URMC.Rochester.edu); [CUCINOTTA@email.chop.edu](mailto:CUCINOTTA@email.chop.edu); [MKeszler@Wihri.org](mailto:MKeszler@Wihri.org); [slakstani@buffalo.edu](mailto:slakstani@buffalo.edu); [NAmbalavanan@peds.uab.edu](mailto:NAmbalavanan@peds.uab.edu); [dpcarl@emory.edu](mailto:dpcarl@emory.edu); [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [woh@wihri.org](mailto:woh@wihri.org); [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [jon.e.tyson@uth.tmc.edu](mailto:jon.e.tyson@uth.tmc.edu); [Matt.Laughon@med.unc.edu](mailto:Matt.Laughon@med.unc.edu); [gsokol@iupui.edu](mailto:gsokol@iupui.edu); [dan\\_ellsbury@pediatrix.com](mailto:dan_ellsbury@pediatrix.com); [MGen@mednet.ucla.edu](mailto:MGen@mednet.ucla.edu); [bsood@med.wayne.edu](mailto:bsood@med.wayne.edu); Archer, Stephanie (NIH/NICHD) [E]; [edward.bell@uiowa.edu](mailto:edward.bell@uiowa.edu); [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); [bpointindex@iupui.edu](mailto:bpointindex@iupui.edu);

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**Cc:** Auman, Jeanette O.; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn Petrie; Nolen, Tracy;  
Wallace, Dennis; Zaterka-Baxter, Kristin

**Subject:** RE: March SC and FU Agenda

If you have items that you wish to use as handouts at the meetings, please send them to us by THURSDAY MARCH 22.

Thanks

Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal  
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**From:** Cunningham, Meg [mailto:mcunningham@rti.org]

**Sent:** Friday, February 24, 2012 11:48 AM

**To:** Cbackstrom@salud.unm.edu; mball@leland.stanford.edu; rbara@med.wayne.edu;  
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[goldb005@mc.duke.edu](mailto:goldb005@mc.duke.edu); [ira\\_adams-chapman@oz.ped.emory.edu](mailto:ira_adams-chapman@oz.ped.emory.edu); [srhintz@stanford.edu](mailto:srhintz@stanford.edu);  
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[GERPES@email.chop.edu](mailto:GERPES@email.chop.edu); [gary\\_myers@URMC.Rochester.edu](mailto:gary_myers@URMC.Rochester.edu); [apappas@med.wayne.edu](mailto:apappas@med.wayne.edu);  
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**Cc:** Arman, Jeanette O.; Cunningham, Meg; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn  
Petrie; Nolen, Tracy; Wallace, Dennis; Zaterka-Baxter, Kristin

**Subject:** March SC and FU Agenda

Hi All,

Attached is the agenda for the upcoming meeting at the end of March. Please let me know if you have any questions.

Thanks!

Meg

*Meg Cunningham, CCRP  
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fax: 202-728-2095  
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<Agenda as of March 20.docx>

**From:** Kennedy, Kathleen A  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; dale\_phelps@urmc.rochester.edu; Wraga, Lisa Ann (wraga@rti.org)  
**Subject:** Poster Draft  
**Date:** Friday, March 23, 2012 12:00:01 PM  
**Attachments:** NRN SUPPORT RQP Observational Study.pptx

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I've attached a draft of the poster. The content is taken from the revised manuscript draft.

Dale and Rose: If you could pay particular attention to what's in the figures (and if you think these are the best figures to include), that would be great. They don't look very good right now and I'm still trying to figure out how to address that when I'm not making them myself. I've plastered some text boxes on top of the copied figures to cover up titles etc that need to be removed and axis labels that need to be changed. I'm hoping that Lisa can look at what's on the poster draft to see what we need. If you have suggestions for modification to the tables and text, those will be easy for me to do; I'll work on making those look better when we agree on the content.

Lisa: I'm not sure what program you use to make the figures and how much flexibility you have to change the appearance and resolution. Some of the figures are very grainy when copied and enlarged. They don't all seem to be the same shape so it's hard to line them up. There are a number of changes that need to be made to the axes, titles and axis labels. I put some comments about that in the manuscript draft but I think it might be easier to see what's needed in the draft of the poster.

When we get some better looking versions of the figures, we can send it to the SUPPORT Subcommittee for their review.

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NICHD  
NEONATAL RESEARCH NETWORK



# Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants

Kathleen A Kennedy MD MPH, Lisa A Wrage MPH, Dale Phelps MD, Rosemary Higgins MD and the SUPPORT Subcommittee of the NICHD Neonatal Research Network

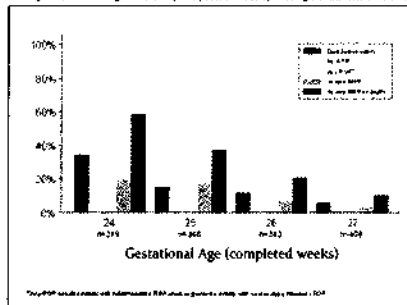
- Timely detection of treatable ROP is important for optimal outcomes.
- The current (2006) screening guidelines are based on infants born in 1986-1997:
  - screening should begin by 31 wks postmenstrual age (PMA)
  - and continue until vessels have reached zone III at 35 wks or, for infants without prethreshold ROP, until 45 wks PMA.
- Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

To validate the 2006 ROP screening guidelines for 24-27 wk GA infants.

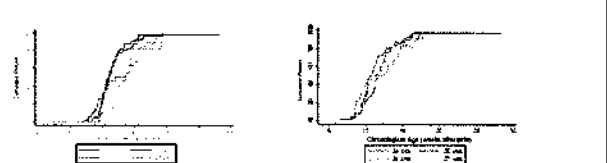
- Descriptive natural history study using outcome data from the NICHD Network SUPPORT trial
- In this trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial trial.
- Inborn infants 24 1/2 to 27 1/2 wks GA with consent prior to delivery were eligible.
- Examinations followed current screening recommendations.
- Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA.
- For this observational study, age of onset is defined as age of detection.
- Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 wks (1 wk if the previous exam had ROP in zone I) were defined as having an uncertain age of onset.

Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Randomized Trial ROP Outcome)			
	All ROP Outcomes	By ROP Outcome Category		
		No ROP	Any ROP	Severe (Type 1 or Treated) ROP
Total	127	73	54	125
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)
Mean (SD) Age (wks)	26.3 (1.0)	26.8 (1.0)	26.0 (1.0)	26.3 (1.0)

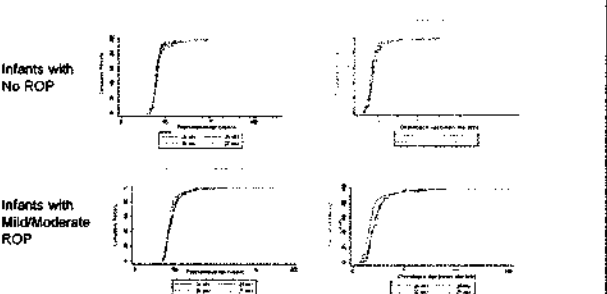
Risk of ROP by Gestational Age at Birth (completed weeks) among All Infants in SUPPORT Trial



Postmenstrual and Chronological Age of Onset for Severe (Type 1 or treated) ROP (among infants with age of onset determined) by Gestational Age at Birth



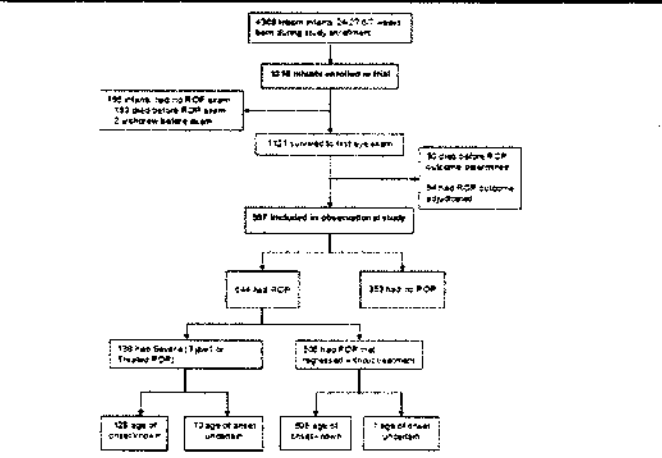
Postmenstrual and Chronological Age of Mature Vessels by Gestational Age at Birth



Through First Exam Meeting Severe ROP Criteria (Retinopathy, Vascularization, and Treatment)

First exam with severe ROP occurred before discharge to home	First exam with severe ROP criteria occurred after discharge to home
36.9 (30.4-45.0)	49.9 (37.9-55.8)
43.4 (34.9-52.5)	35.3 (26.9-43.3)

- In these 997 infants, we did not observe treatable ROP before 32 wks PMA; only 1 infant developed severe ROP after 45 wks PMA.
- Our data do not support a change in the 2006 guidelines.
- Some infants who are stable enough for back transfer or discharge home are still at risk to develop treatable ROP.
- A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.



Gestational Age (wks)	Postmenstrual Age (wks)										Chronological Age (wks)									
	24	25	26	27	28	29	30	31	32	33	24	25	26	27	28	29	30	31	32	33
Severe (Type 1 or Treated) ROP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Any ROP	0	10.1	30.4	34.1	33.7	32.9	32.1	31.9	31.0	30.7	0	4.0	14.0	24.0	30.0	34.0	36.0	36.0	35.0	33.0
Type II ROP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Severe (Type 1 or Treated) ROP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug. Acknowledgements: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Penn State Hershey; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California - San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Hoult, Ben (NIH/OD) [E]  
**Cc:** Langham, Amira (NIH/OD) [E]; Rose, Michele (NIH/OD) [E]  
**Subject:** FW: Breathing Outcomes analysis handout for Follow-up PI Mtg  
**Date:** Friday, March 23, 2012 11:56:00 AM  
**Attachments:** Print - PAS 2012 - Late Breaking Submission-Final.pdf  
Draft Statistical Analysis Plan V3.doc

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30 copies of each in a folder labeled "BREATHING OUTCOMES"

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**From:** Newman, Jamie [mailto:[newman@rti.org](mailto:newman@rti.org)]  
**Sent:** Friday, March 23, 2012 11:53 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Breathing Outcomes analysis handout for Follow-up PI Mtg

Rose,  
Tim Stevens just confirmed that he intends for the attached to be distributed as a handout at the Follow-up Mtg (I misinterpreted his email below to mean that he didn't want it distributed due to length). He will also join by phone to give a summary.  
Thanks, Jamie

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**From:** Stevens, Timothy [mailto:[Timothy\\_Stevens@URMC.Rochester.edu](mailto:Timothy_Stevens@URMC.Rochester.edu)]  
**Sent:** Thursday, March 22, 2012 4:19 PM  
**To:** Newman, Jamie  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

Hi Jamie

Here is a copy of the late breaker abstract and a draft of the analysis plan that Steven Thomas wrote based on discussion with Abhik, me and others.

As a handout it is a bit long, but I'll provide a synopsis over the phone.

Thanks

Tim

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**From:** Newman, Jamie [mailto:[newman@rti.org](mailto:newman@rti.org)]  
**Sent:** Wednesday, March 21, 2012 7:30 PM  
**To:** Stevens, Timothy  
**Subject:** RE: Breathing Outcomes analysis update for Follow-up PI Mtg

Ok, I'll keep an eye out for it. I'm out of the office Thurs but I'm in all day on Friday.

Thanks, Jamie

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**From:** Stevens, Timothy [mailto:[Timothy\\_Stevens@URMC.Rochester.edu](mailto:Timothy_Stevens@URMC.Rochester.edu)]  
**Sent:** Wednesday, March 21, 2012 6:24 PM  
**To:** Newman, Jamie  
**Subject:** Re: Breathing Outcomes analysis update for Follow-up PI Mtg

Hi Jamie,  
I'll get a handout to you tomorrow (Thurs) and plan to speak by phone.  
Thanks  
Tim

On Mar 20, 2012, at 6:13 PM, "Newman, Jamie" <[newman@rti.org](mailto:newman@rti.org)> wrote:

Dr. Stevens,  
Please see below from a message from Rose. We have time slotted in the agenda for a 5 minute update on the Breathing Outcomes analysis at 3:45pm on Thurs Mar 27. Rose has requested handouts (which are optional) by Thursday Mar 22. Attached is the agenda. Are you available to provide the update by phone or do you prefer that someone provide an update on your behalf.

Thanks, Jamie

**From:** Newman, Jamie  
**Sent:** Monday, March 05, 2012 4:34 PM  
**To:** 'Stevens, Timothy'  
**Cc:** Das, Abhik  
**Subject:** Breathing Outcomes analysis update for Follow-up PI Meeting

Dr. Stevens,  
Are you available to give a 5 minute update on Breathing Outcomes analysis at 3:45pm for the NRN Follow-up PI Meeting Tuesday March 27? Handouts are optional but we're happy to distribute a handout if you'd like.

Do you know when you'll hear back from your PAS late breaker submission?

Thanks, Jamie

Jamie E. Newman, PhD, MPH  
Statistics and Epidemiology

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newman@rti.org

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 20, 2012 1:03 PM  
**To:** Birmingham, Meg; Cbackstrom@salud.unm.edu; mball@leland.stanford.edu; rbaron@med.wayne.edu; mcollins@peds.uab.edu; scosby@peds.uab.edu; callycrisby@uc.edu; ehale@emory.edu; ahensman@wihri.org; karen-johnson@uiowa.edu; Georgia.E.McDavid@uth.tmc.edu; Diana.Vasil@utsouthwestern.edu; nxs@cwru.edu; ldw@iupui.edu; clark@med.unc.edu; bernharj@email.unc.edu; janice.wereszczak@med.unc.edu; Donia-campbell@uiowa.edu; lijun.zhen@utsouthwestern.edu; JF126@notes.duke.edu; cagauldin@cmh.edu; Tom.Jancini@uphs.upenn.edu; christine.fortney@nationwidechildrens.org; Aashish.Chaudhary@uphs.upenn.edu; rosemary.jensen@urmc.rochester.edu; kwan@buffalo.edu; Kimberley.fisher@duke.edu; sgbrown@salud.unm.edu; tchew@ucla.edu; RGeller@mednet.ucla.edu; tiwussow@salud.unm.edu; Holly.Wadkins@URMC.Rochester.edu; CUCINOTTA@email.chop.edu; MKeszler@Wihri.org; slaf@u@buffalo.edu; NAmbalavanan@peds.uab.edu; dpcarl@emory.edu; colin@mc.duke.edu; woh@wihri.org; rohls@salud.unm.edu; jon.e.tyson@uth.tmc.edu; Mary.McLaughon@med.unc.edu; gsokol@iupui.edu; dan\_ellsbury@pediatrix.com; MG@mcdnet.ucla.edu; bsood@med.wayne.edu; Archer, Stephanie (NIH/NICHD) [E]; edwardbell@uiowa.edu; wcarlo@peds.uab.edu; goldb008@mc.duke.edu; Kathleen.A.Kennedy@uth.tmc.edu; alaptook@Wihri.org; bpointindex@iupui.edu; Pablo.Ramirez@UTSouthwestern.edu; kurt.schibler@cchmc.org; sshahar@med.wayne.edu; [SCRN] Stoll, Barbara; vanmeurs@leland.stanford.edu; mc@cwru.edu; kwatterberg@salud.unm.edu; RAP32@columbia.edu; Luc.Henon@utsouthwestern.edu; dan\_ellsbury@pediatrix.com; wtruog@cmh.edu; KIRBY@ANIH@email.chop.edu; barbara.schmidt@uphs.upenn.edu; Leif.Lin@nationwidechildrens.org; nehal.parikh@nationwidechildrens.org; ude@kar@mednet.ucla.edu; carl\_dangio@urmc.rochester.edu; marie.blakely@vanderbilt.edu; dale.phelps@urmc.rochester.edu; bvohr@wihri.org; DEBRA@RO@email.chop.edu; jwaidne@emory.edu; gonza025@mc.duke.edu; axt@cwru.edu; Karen.Kirby@UTSouthwestern.edu; lmoore@med.wayne.edu; parr@neville@duke.edu; Nancy.M.Smith@uth.tmc.edu; StWilliams@peds.uab.edu; bwh@careNE.org; jthomp84@iupui.edu; Adele.Lamb@uphs.upenn.edu; KShah@mednet.ucla.edu; YDavis@mednet.ucla.edu; Michelle Smith; hks@mail.cumc.columbia.edu; JRose@Wihri.org; Deborah.Garcia@uth.tmc.edu; vwh@emory.edu; whitec2@email.chop.edu; bvohr@wihri.org; (b)(6)@aol.com; gonza025@mc.duke.edu; ira\_adams-chapman@oz.ped.emory.edu; srhinz@stanford.edu; ME@ta@Peds.UAB.EDU; Roy.Heyne@utsouthwestern.edu; Kimberly.Yolton@cchmc.org; tara@olajzy@uiowa.edu; soraya.abbasi@uphs.upenn.edu; hurt@email.chop.edu; GEL@S@email.chop.edu; gary\_myers@URMC.Rochester.edu; apappas@med.wayne.edu; ipu@mednet.ucla.edu; Keith.Yeates@nationwidechildrens.org; hkilbride@cmh.edu; sm@iupui.edu; AFDuncan@salud.unm.edu; diane\_marshall@med.unc.edu; Patricia.M.Jones@uth.tmc.edu; Christopher.Timan@nationwidechildrens.org; Newman, Jamie; jrose@wihri.org  
**Cc:** Anan, Jeanette O.; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn Petrie; Nolen, Tracy; Wadley, Dennis; Zaterka-Baxter, Kristin  
**Subject:** RE: March SC and FU Agenda

If you have items that you wish to use as handouts at the meetings, please send them to us by THURSDAY MARCH 22.



Thank you  
Rose

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301-496-3790 (FAX)  
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**From:** Cunningham, Meg [<mailto:mcunningham@rti.org>]  
**Sent:** Friday, February 24, 2012 11:48 AM  
**To:** [Clackstrom@salud.unm.edu](mailto:Clackstrom@salud.unm.edu); [mbball@leland.stanford.edu](mailto:mbball@leland.stanford.edu); [rbara@med.wayne.edu](mailto:rbara@med.wayne.edu); [mcolts@peds.uab.edu](mailto:mcolts@peds.uab.edu); [scosby@peds.uab.edu](mailto:scosby@peds.uab.edu); [cathy.grisby@uc.edu](mailto:cathy.grisby@uc.edu); [ehale@emory.edu](mailto:ehale@emory.edu); [aherlihan@wihri.org](mailto:aherlihan@wihri.org); [karen-johnson@uiowa.edu](mailto:karen-johnson@uiowa.edu); [Georgia.E.McDavid@uth.tmc.edu](mailto:Georgia.E.McDavid@uth.tmc.edu); [Diana.Jasli@utsouthwestern.edu](mailto:Diana.Jasli@utsouthwestern.edu); [nxs5@cwru.edu](mailto:nxs5@cwru.edu); [ldw@iupui.edu](mailto:ldw@iupui.edu); [cldark@med.unc.edu](mailto:cldark@med.unc.edu); [bernie.j@med.unc.edu](mailto:bernie.j@med.unc.edu); [janice\\_wereszczak@med.unc.edu](mailto:janice_wereszczak@med.unc.edu); [Donia-campbell@uiowa.edu](mailto:Donia-campbell@uiowa.edu); [lijun.zhou@utsouthwestern.edu](mailto:lijun.zhou@utsouthwestern.edu); 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**Cc:** Auman, Jeanette O.; Cunningham, Meg; Das, Abhik; Gabrio, Jenna; Huitema, Carolyn  
Petrie; Nolan, Tracy; Wallace, Dennis; Zaterka-Baxter, Kristin  
**Subject:** March SC and FU Agenda

Hi All,

Attached is the agenda for the upcoming meeting at the end of March. Please let me know if you have any questions.

Thanks!

Meg

*Meg Cunningham, CCRP  
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<Agenda as of March 20.docx>

**Please select Print from the file menu to print your Late Breaking Abstract.**

**First Author:** Timothy P Stevens, MD, MPH

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**Presenting Author:** Timothy P Stevens, MD, MPH

## 2012 PAS Annual Meeting

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### QUESTIONNAIRE INFORMATION

**Research Type:** Clinical

**Reason why the November deadline could not be met:**

Analysis had not been completed.

**Title:** Respiratory Outcomes of The NICHD SUPPORT Trial

Timothy P Stevens, MD, MPH<sup>1</sup> and for the Neonatal Research Network (NRN)<sup>2</sup>. <sup>1</sup>Pediatrics (Neonatology), Univ. of Rochester, Rochester, NY, United States and <sup>2</sup>The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda, MD, United States.

**Background:** The NICHD SUPPORT Trial, a randomized trial using a 2x2 factorial design, compared initial therapy with either prophylactic surfactant or nasal CPAP (Surf v. CPAP) and low (85-89%) or high (91-95%) oxygen saturation targets (Low v. High Sat). Primary outcomes were reported in 2010.

**Objective:** The Breathing Outcomes Study (BOS), a secondary study to SUPPORT, tested the hypotheses that treatment with CPAP v. Surf or Low v. High Sat reduces the incidences of recurrent wheezing and chronic cough at 18-22 months corrected age (m).

**Design/Methods:** Patients 24-27 6/7 wks gestation who were enrolled in SUPPORT were eligible to consent to the BOS. For each BOS patient, a validated questionnaire of respiratory symptoms, medication use and healthcare utilization was administered verbally to the subject's caregiver at 6, 12 and 18-22m. Questionnaire responses are reported as unadjusted results according to the primary treatment assignment of SUPPORT: Surf v. CPAP and Low v. High Sat.

**Results:** Of 1315 patients enrolled in SUPPORT, 1079 survived to hospital discharge and, of these, 922 (85.4%) consented to participate in BOS. Survey response rates exceeded 94% at each of the 6, 12 and 18-22m time points. As in SUPPORT, there were no differences between either Surf v. CPAP or Low v. High Sat in the incidence of either traditional BPD (oxygen at 36 wks) or physiologic BPD among pts in BOS. However, at 6m, patients treated with Low v. High Sat targets were less likely to have parental report of wheezy breathing (27.8% v. 36.4%,  $p < 0.04$ ), documented wheezing (36.3% v. 43.4%,  $p < 0.05$ ) or use a home nebulizer (1.2% v. 3.9%,  $p < 0.02$ ). Differences in these outcomes or in incidence of chronic cough were not seen in the Surf v. CPAP groups at 6m or between either the Surf v. CPAP or Low v. High Sat groups at 12 or 18-22m. Hospitalization, physician visit and emergency department visit rates, overall and for respiratory conditions, were similar between the Surf v. CPAP and Low v. High Sat groups at each time point.

**Conclusions:** Preterm infants managed with Low compared with High Sat targets were less likely to have wheezing or use a home nebulizer at 6m. Differences in these outcomes were not seen at 12 and 18-22m. Based upon the finding of greater mortality with Low vs. High Sat targets seen in SUPPORT, the benefit of reduced wheezing and nebulizer use at 6m does not justify Low Sat targets in patients 24 - 27 6/7 wks gestation.

Analyses to adjust for baseline group differences are ongoing and may affect results.

**Other Preview:**

[Abstract Disclosure Info:](#)

[Disclosures](#)

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## **Draft Statistical Analysis Plan**

### **Breathing Outcomes SUPPORT Study**

SAP Version: 1.0

SAP Date: March 9, 2012

Author: Steven Thomas

Revisions/Notes:

# 1 Study Hypotheses and Outcomes

## 1.1 Primary

1) We hypothesize that relative to infants managed with a higher SpO<sub>2</sub> range (91% to 95%), infants managed with a lower SpO<sub>2</sub> range (85% to 89%) will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

2) We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

## 1.2 Secondary Hypotheses

1) We hypothesize that among infants with CLD, infants managed with a lower SpO<sub>2</sub> range relative to those managed with a higher SpO<sub>2</sub> target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

2) We hypothesize that among infants without CLD, infants managed with a lower SpO<sub>2</sub> range relative to those managed with a higher SpO<sub>2</sub> target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

## 1.3 Primary Outcomes

Question(s)	Description	Specifications	Variables
9,9a, 10	Symptomatic airway dysfunction	Yes to questions 9, 9a, or 10. "Don't Know" will be considered as a "No" response	
7a	Outpatient pulmonary Care		SF2ERBP

## 1.4 Secondary Outcomes

Question	Description	Variables																																																																					
9e, 10e	<p><b>Classification of Asthma Severity (Children 0-4 years of age)</b></p> <table border="1"> <thead> <tr> <th rowspan="2">Components of Severity</th> <th colspan="4">Persistence</th> </tr> <tr> <th>Intermittent</th> <th>Mild</th> <th>Moderate</th> <th>Severe</th> </tr> </thead> <tbody> <tr> <td>Symptoms</td> <td>&lt; 2 days/week</td> <td>2-3 days/week but not daily</td> <td>Daily</td> <td>Throughout the day</td> </tr> <tr> <td>Nighttime awakenings</td> <td>0-2</td> <td>1-2/ month</td> <td>3-4/ month</td> <td>&gt; 1x/week</td> </tr> <tr> <td>Impairment</td> <td>Short acting</td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th colspan="7">Nighttime 9e or 10e</th> </tr> <tr> <th></th> <th></th> <th>Never</th> <th>Once or twice every two weeks</th> <th>Once a week</th> <th>Two or three times a week</th> <th>Frequently</th> </tr> </thead> <tbody> <tr> <th rowspan="5">Daytime 9e or 10e</th> <th>Never</th> <td>None</td> <td>Mild</td> <td></td> <td></td> <td></td> </tr> <tr> <th>Twice a week or less</th> <td>Intermittent</td> <td>Mild</td> <td></td> <td></td> <td></td> </tr> <tr> <th>Two or more times a week</th> <td>Mild</td> <td>Mild</td> <td></td> <td></td> <td></td> </tr> <tr> <th>Everyday</th> <td>Moderate</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <th>Everyday all the time</th> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Components of Severity	Persistence				Intermittent	Mild	Moderate	Severe	Symptoms	< 2 days/week	2-3 days/week but not daily	Daily	Throughout the day	Nighttime awakenings	0-2	1-2/ month	3-4/ month	> 1x/week	Impairment	Short acting				Nighttime 9e or 10e									Never	Once or twice every two weeks	Once a week	Two or three times a week	Frequently	Daytime 9e or 10e	Never	None	Mild				Twice a week or less	Intermittent	Mild				Two or more times a week	Mild	Mild				Everyday	Moderate					Everyday all the time						
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26	Oxygen therapy	SF2OXYTH																																																																					
27	Any Medications includes all medications listed in medication codes except 'other'	med_rescue med_cromo  med_istero id_ med_sstero id_ med_leuko  med_meth  med_diure  med_nebu																																																																					

## 2 Analysis Populations

The follow-up study included all surviving infants enrolled in the NICHD Neonatal Research Network SUPPORT main trial and who gave consent and completed at least one questionnaire in the Breathing Outcomes trial. Because the study was implemented on, date?, after the main study only 1100 of the 1316 participates we eligible for the BO study. Of the

1100, 918 participants were alive at screening, provided consent to be in the BO study, and completed at least one questionnaire.

Subjects	Count	Denominator	Percent
Eligible for BO Study	1100	1,316	83.5866
Survived to Discharge Eligible	1067	1,100	97.0000
Transferred and Eligible	2	1,100	0.1818
Death and Eligible	26	1,100	2.3636
Hospitalized at one Year and Eligible	5	1,100	0.4545
Given Consent and Eligible	938	1,100	85.2727
Survived to Discharge and Enrolled	918	938	97.8678
Transferred and Enrolled	2	938	0.2132
Death and Enrolled	16	938	1.7058
Hospitalized at one Year and Enrolled	2	938	0.2132
Enrolled and Alive	922	938	0.9829
Received CPAP, Not Death and Enrolled	476	922	51.6269
Surfactant, Not Death and Enrolled	446	922	48.3731
High SPO2, Not Death and Enrolled	482	922	52.2777
Low SPO2, Not Death and Enrolled	440	922	47.7223
Completed at least one questionnaire, Not Death and Enrolled	918	922	99.5662
Made 6 Month FU, Not Death and Enrolled	893	922	96.8547
Made 12 Month FU, Not Death and Enrolled	896	922	97.1800
Made 18-22 Month FU, Not Death and Enrolled	905	922	98.1562

## 2.2 Treatment or Comparison Groups

Groups	Description	Specifications	Variables
CPAP treatment arm	Early CPAP or Surfactant		CPAP
Oxygen treatment arm	SpO2 Low or High		oximeter
BPD			



### 2.3 Candidate covariates

Question	Candidate Covariates	Recommend by Literature	Description	Variable
4a to 4d Look at grandparents and parents.	Lung Scaring family history	Suggested	Yes if any family member has indicated history of COPD chronic bronchitis, emphysema, or bronchiectasis.  Don't know and missing considered No History	Look at the 24 variables Starting with: FHM FHF FHMM FHMF FHPM FHFP  Ending with: ----COPD ----CBROC ----EMPHY ----BRONC
4e (parents only)	Asthma	Yes	Any Family history of asthma.  Don't know and missing considered No History	FHMasthm FHFasthm
4f or 4g (parents only)	Family history of inhaled or food allergies	Suggested	Yes if any parent has indicated an allergy.  Don't know and missing considered No History	FHFIALGY FHFFALGY FHMIALGY FHMFALGY
4h(parents only)	Family history of chronic respiratory disease.	Suggested	Yes if any parent.	FHFOCR FHMOCRD
	Time		Time of follow-up in months 6, 12, 18.	SF2BAGE
	GA	Yes	Gestational age in weeks	GESTAGE
	Site	Yes		Sitenm
16, 16a, 16b	Breast feed	Yes	Use question 16, received breast milk Yes/No.  However use 16a or 16b if the information provides significant improvement to the model.	SF2BRSMK SF2BMMTN SF2MNHLE

17,18, 20	Smoking Ban	Yes	<p>No smoking is allowed in the home or car with no exceptions and there are no smokers in the child's home.</p> <p>Q17=3 and Q17a=2</p> <p>Q18=5 and Q18a=2</p> <p>Q20=0</p>	<p>SF2SMKEX SF2EXCPT SF2SMCAR SF2EXCP SF2NPSMK</p>
21	Daycare	Yes	<p>Continuous variable in hours per week.</p> <p>In our data the majority of subjects report zero daycare use.</p>	sf2hrsdc
22	Siblings	Yes	variable	SF2NUM12
23,	Pets	Suggested	Yes/No	<p>SF2PETS SF2NDOGS SF2NCATS SF2NOPET</p>
24	RSV shots	Yes	<p>Yes/No</p> <p>Treat Don't know as No</p>	SF2RSVSH
25	Flu Shots	Suggested	Yes/No	SF2FLUSH

## **3 Statistical Methods**

### **3.1 Overview**

Standard descriptive and longitudinal analysis techniques will be utilized at two different stages. In the first stage simple bivariate tests will be conducted between comparison groups at each follow-up visit. Each test will compare the mean or proportion of the select questions of interest. No adjustment will be made for multiple testing. In the second stage confounding variables will adjusted for with a generalized linear model.

All analyses involving the trial treatment groups will adjust for the design variables such as center and gestational age groups, as well as familial clustering and repeated measures. Candidate covariates may be selected both on statistical significance and known confounding variables that may not have been significant in our data. Sources of variation such as repeated measures and familial clustering will be accounted for through random effects. The final association between outcomes and treatment groups will be assessed with their corresponding relative risk estimates.

### **3.2 Task list**

1. Summary statistics and bivariate comparisons (Original analysis for the poster)
2. Descriptive comparison of baseline characteristics between study population (918 subjects) and the 398 subjects excluded from the BO study but included in the SUPPORT main study.
3. Exploratory analysis of control variables. Select variables may be included regardless of statistical significance.
4. Statistical models that account for sources of correlation. If multiple source of correlation needs to be considered *the analysis will use GLIMMIX with random effects. However if only repeated measures are we may consider GEEs.*
5. Summarize statistical output. This will include multilevel simple models and multivariate models for each outcome and randomization arm.

## **4 Statistical / Analytical Issues**

### **4.1 Family Clusters**

It is logical to assume that subjects from the same family will be correlated. If possible this source of correlation and repeated measures will be considered. However statistical models may not converge because eighty percent of the observations come from subjects without siblings presented in the study. If family clusters and repeated measure show a high degree of linear dependence a sensitivity analysis will be conducted. All siblings will be excluded and testing results inspected.

### **4.2 Missing Follow-up Visits**

Missing follow-up data can be correctly accounted with GEE using the within option. Mixed models should construct the correct structure with the random statement.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** "[Susan Hintz](#)"  
**Subject:** RE: time and date of PAS presentation for Vaucher and Peralta  
**Date:** Friday, March 23, 2012 10:24:00 AM  
**Attachments:** [NRN PAS 2012.pdf](#)  
[SPR Presentations and Schedule 2012.xls](#)

---

Here are the abstracts and the schedule  
Let me know if you need anything else

Rose

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

From: Susan Hintz [<mailto:srhintz@stanford.edu>]  
Sent: Friday, March 23, 2012 10:23 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: time and date of PAS presentation for Vaucher and Peralta

Hi Rose

Do you have the dates and times of the Vaucher and Peralta SUPPORT  
main trial follow up presentations? I want to put it in my  
presentation -

thanks

s

**Title:** Blood Pressure Values in the First 24 Hours for Infants 23 – 26 weeks Gestation

**Authors:** Beau J. Batton, MD,<sup>1</sup> Lei Li, PhD,<sup>2</sup> Nancy S. Newman, RN,<sup>1</sup> Steven Thomas, MS,<sup>2</sup> Abhik Das, PhD,<sup>3</sup> Kristi L. Watterberg, MD,<sup>4</sup> Bradley A. Yoder, MD,<sup>5</sup> Roger G. Faix, MD,<sup>5</sup> Matthew M. Laughon, MD, MPH,<sup>6</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD,<sup>8</sup> & Michele C. Walsh, MD, MS<sup>1</sup> for the *Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

<sup>1</sup>Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; <sup>2</sup>Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; <sup>3</sup>Statistics and Epidemiology Unit, RTI International, Rockville, MD; <sup>4</sup>University of New Mexico Health Sciences Center, Albuquerque, NM; <sup>5</sup>Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT; <sup>6</sup>Department of Pediatrics, the University of North Carolina at Chapel Hill, Chapel Hill, NC; <sup>7</sup>Emory Department of Pediatrics and Children's Healthcare of Atlanta, Atlanta, GA; <sup>8</sup>*Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD*  
Funded by the Best Pharmaceuticals for Children Act

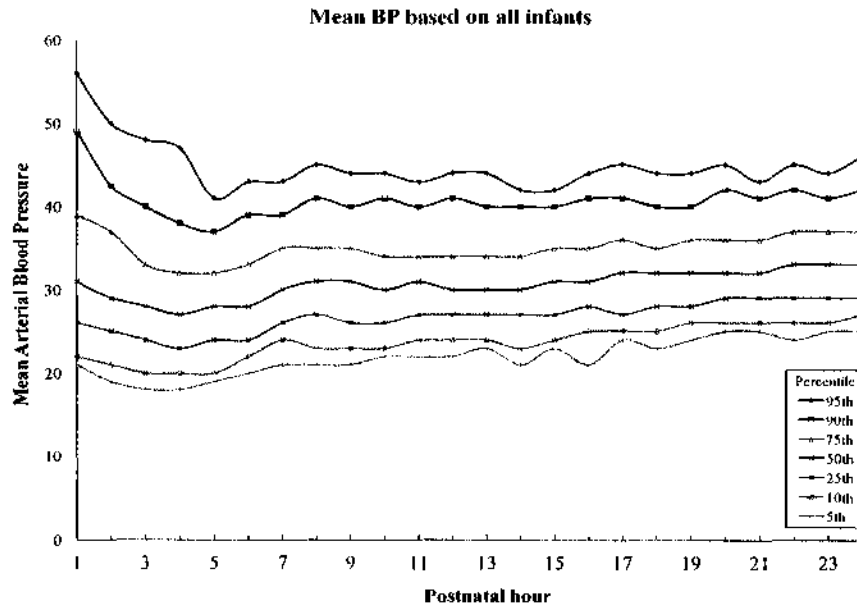
**Background:** Data are limited on blood pressure (BP) measurements in the first 24 hrs for extremely preterm infants. Identifying the expected trends in BP values during this time may aid in the decision to administer antihypotensive therapy.

**Objective:** To identify the range and changes in BP values during the first 24 hrs for extremely preterm infants.

**Methods:** Prospective observational study of infants 23<sup>0/7</sup> – 26<sup>6/7</sup> weeks GA born at 16 academic centers of the NICHD Neonatal Research Network from 7/20/10 – 1/20/11. Systolic (S), diastolic (D), and mean (M) arterial BP measurements were made at least hourly for the first 24 hrs.

**Results:** 12,460 BP measurements were taken for 367 infants: 9,420 (76%) from an umbilical arterial catheter, 2,750 (22%) from a BP cuff, and 290 (2%) from a peripheral arterial line. 203 (55%) infants received at least one antihypotensive therapy and 104 (28%) received an inotrope. S/D/M BP values decreased for the first three hours, reached a nadir at the 4<sup>th</sup> hour, and then slowly increased over the next 20 hours (figure). The 5<sup>th</sup>, 50<sup>th</sup>, and 95<sup>th</sup> percentiles for S/D/M BP were higher for 88% of the hours investigated for infants who survived the first 24 postnatal hours without receiving any antihypotensive therapy (n=156) as compared to the entire cohort. GA specific trends were similar. At any given postnatal hour, BP values tended to be lower as GA decreased, but they varied widely at each GA with significant overlap across the GA range. 49% of infants had  $\geq 2$  mean BP values less than their GA equivalent.

**Conclusion:** Similar to more mature infants, BP increases spontaneously over the first 24 hours for infants 23 – 26 weeks GA. BP values tend to increase with increasing GA, but there is tremendous overlap in the range of S/D/M BP values at any given postnatal hour for infants in the 23 – 26 weeks GA range.



**Title:** Prospective Observational Study of Blood Pressure Management in Infants 23 – 26 weeks Gestation

**Authors:** Beau J. Batton, MD,<sup>1</sup> Lei Li, PhD,<sup>2</sup> Nancy S. Newman, RN,<sup>1</sup> Steven Thomas, MS,<sup>2</sup> Abhik Das, PhD,<sup>3</sup> Kristi L. Watterberg, MD,<sup>4</sup> Bradley A. Yoder, MD,<sup>5</sup> Roger G. Faix, MD,<sup>5</sup> Matthew M. Laughon, MD, MPH,<sup>6</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD<sup>8</sup>, & Michele C. Walsh, MD, MS<sup>1</sup> for the *Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

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Funded by the Best Pharmaceuticals for Children Act

**Background:** Optimal management of low blood pressure (BP) in extremely preterm infants remains unclear.

**Objectives:** To identify differences in early BP management in the 1<sup>st</sup> 24 hrs for extremely preterm infants and investigate the relationship between BP, antihypotensive therapy and infant outcomes.

**Methods:** Prospective observational study of infants 23<sup>0/7</sup> – 26<sup>0/7</sup> wks gestation born at 16 academic centers of the NICHD Neonatal Research Network between 7/20/10 and 1/20/11. Antihypotensive therapy included: fluid bolus, dopamine, dobutamine, hydrocortisone, vasopressin, and (any) blood product. Multiple definitions of low BP were examined.

**Results:** 367 infants were enrolled, including 203 (55%) who received at least one antihypotensive therapy and 104 (28%) who received a vasoactive drug. A fluid bolus was the most common therapy administered (37% of all infants), followed by blood products (28%), dopamine (25%), hydrocortisone (7%), and dobutamine (5%). With logistic regression analysis, infants not given antihypotensive therapy (n=164) were less likely to have low BP (p<0.001). However, for the definitions of low BP investigated, 18 – 32% of the infants with low BP were not treated for hypotension and 28 – 41% of infants without low BP received antihypotensive therapy. The odds of receiving any therapy increased as BW decreased (p<0.001). Compared to untreated infants, treated infants were more likely to have a 1 minute Apgar score ≤3 (60% vs. 43%, p<0.01), a pH <7.10 in the 1<sup>st</sup> 24 hrs (13% vs 3%, p<0.01), ROP requiring laser surgery (15% vs 8%, p=0.03), grade III/IV IVH (22% vs 11%, p<0.01) and less likely to survive to hospital discharge (67% vs 78%, p=0.02). The frequency of low BP values, administration of antihypotensive therapy, in-hospital morbidity, and survival varied considerably across NRN centers. However, center rate of treatment did not have a significant effect on the rates of survival or IVH.

**Conclusion:** Antihypotensive therapies are frequently administered to extremely preterm infants in the 1<sup>st</sup> 24 hrs. Factors other than BP values contribute to the decision to use these therapies. Regardless of the definition of low BP, antihypotensive therapy was not associated with an improvement of in-hospital outcomes.

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## 2012 PAS Annual Meeting

**Subspecialty:** Neonatal Fetal Nutrition & Metabolism  
**Theme:** Neonatal - Patient-Oriented Research

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**Title:** TOCOPHEROL LEVELS IN VERY PRETERM INFANTS AFTER A SINGLE ENTERAL DOSE OF VITAMIN E GIVEN SOON AFTER BIRTH.

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**Background:** Preterm infants are born with vitamin E deficiency. Systematic reviews show that vitamin E supplementation can reduce the risk of intracranial hemorrhage in very preterm infants.  $\alpha$ -Tocopherol levels rise during the first week as a result of nutritional intake but are low during the first days of life, when hemorrhage is most likely to occur.  $\alpha$ -Tocopherol levels of 0.5-3.0 mg/dl are normal, and levels above 3.5 mg/dl have been associated with increased sepsis and NEC.

**Objective:** Our objective was to examine  $\alpha$ -tocopherol levels after a single enteral dose of vitamin E, given soon after birth.

**Design/Methods:** 93 infants <27 weeks and <1 kg were randomized in a 2:1 ratio to receive a single enteral dose of vitamin E or placebo within 4 h of birth. The vitamin E group received a 50-IU/kg (1.0-ml/kg) dose of dl- $\alpha$ -tocopheryl acetate diluted with an equal volume of sterile water. The placebo group received a 2.0-ml/kg dose of water. Blood samples were taken for serum  $\alpha$ -tocopherol levels at 0 h, 24 h, and 7 d after dosing. The samples were analyzed by HPLC.

**Results:** 88 infants received the study drug. The mean birth weight was 718 (SD 132) g, and the mean gestational age was 24.7 (SD 1.0) weeks. For these infants, there were 225 correctly-timed blood samples of adequate volume for tocopherol analysis.  $\alpha$ -Tocopherol levels were significantly higher in the vitamin E group than the placebo group at 24 h and 7 d (Table 1).

Table 1.  $\alpha$ -Tocopherol levels, mg/dl, median (interquartile range).

	Baseline	24 h	7 d
Vitamin E	0.31 (0.26-0.38)	0.63 (0.47-0.80)	2.21 (1.75-3.13)
Placebo	0.33 (0.27-0.42)	0.42 (0.28-0.54)	1.86 (1.40-2.37)
p-value (Wilcoxon)	0.49	0.003	0.040

At 24 h, fewer infants in the vitamin E group had levels below 0.5 mg/dl, and more had levels in the desirable range of 0.5-3.0 mg/dl (Table 2). Only 4% of infants in the vitamin E group had levels above 3.5 mg/dl.

Table 2. Distribution of  $\alpha$ -tocopherol levels (%) at 24 h.

Levels (mg/dl)	<0.50	0.50-0.99	1.00-3.00	3.01-3.50	>3.50
Vitamin E	30	52	14	0	4
Placebo	62	27	12	0	0

**Conclusions:** A single 50-IU/kg enteral dose of vitamin E soon after birth achieves acceptable serum  $\alpha$ -tocopherol levels in most infants. This dose rarely produces potentially toxic levels of  $\alpha$ -



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tocopherol.

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**Title:** Genome-wide association study of morbidities of extreme prematurity

C. M. Cotten, MD MHS<sup>1</sup>, G. Page, PhD<sup>2</sup>, W. Carlo, MD<sup>3</sup>, R. Higgins, MD<sup>4</sup> and J. C. Murray, MD<sup>5</sup>.  
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**Background:** Extremely low birthweight (ELBW) infants with bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intracranial hemorrhage (ICH) and patent ductus arteriosus (PDA) are at high risk of mortality or survival with impairment. Unbiased assessments of associations between genetic loci and these morbidities have not been published.

**Objective:** Conduct a genome-wide scan to identify genetic variants associated with major morbidities of extreme prematurity.

**Design/Methods:** An anonymized DNA biorepository of blood spot samples and clinical dataset from ELBW infants enrolled in a prior NRN study were developed. An NHGRI-GENEVA supported genome wide scan was performed with repository samples. Genomic DNA was extracted from the filter cards; 20% of samples required whole genome amplification of DNA. The Illumina Human660W-Quad1\_A, with 1.2 million single nucleotide polymorphisms (SNPs) was used for genotyping. Standard quality checks were applied to samples and SNPs. Associations were tested for BPD, NEC, ROP, IVH and PDA in single and multiple logistic regression models which included covariates: antenatal steroids, gestational age, gender, small for gestational age status and 5 minute Apgar score. For this number of statistical tests our target for reporting was  $p < 10^{-5}$ . Associations were tested separately for infants of different ancestry with metaanalysis for significance across ethnicities.

**Results:** Of 764 infants included, 47% were male. 54% (411) were classified as African-American. Average gestational age and birthweight were 26 weeks and 757 grams. Incidence of BPD, NEC, ROP, IVH3/4 and PDA were 49%, 11%, 70%, 37% and 52%, respectively. Genotypes were successfully identified for > 95% of SNPs. Associations stronger than  $10^{-5}$  across all ethnicities were found between BPD and loci on 11 chromosomes; ICH3/4 and 3 loci; NEC and 4 loci and ROP and 7 loci. The strongest association was identified among African American infants

between SNP rs4358081 on chromosome 2 and ROP ( $p = 8.2 \times 10^{-7}$ ). Several SNPs in a region of chromosome 1 which included neuronal nitric oxide synthase were associated with BPD.

**Conclusions:** The genome wide scan on a cohort of ELBW infants identified loci of interest associated with morbidities of prematurity, particularly for BPD and ROP. This collection of genetic information linked to phenotypes is valuable for understanding genetic contributions to risk of morbidities of extreme prematurity.

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## 2012 PAS Annual Meeting

**Subspecialty:** Neonatology - General

**Theme:** Neonatal - Patient-Oriented Research

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**Title:**

**Hypotension and Adverse Short Term Outcomes in Critically Ill Term and Late Preterm Newborns**

Erika F Fernandez, MD<sup>1</sup>, Kristi L Watterberg, MD<sup>1</sup>, Roger Faix, MD<sup>2</sup>, Bradley Yoder, MD<sup>3</sup>, Michele Walsh, MD<sup>4</sup>, Conra Lacy, RN<sup>1</sup>, Karen Osborne, RN<sup>2</sup>, Abhik Das, PhD<sup>5</sup>, Dennis Kendrick, MS<sup>6</sup>, Gregory Sokol, MD<sup>7</sup>, Barbara Stoll, MD<sup>8</sup> and Rosemary Higgins, MD<sup>9</sup>. <sup>1</sup>Pediatrics/ Division of Neonatology, University of New Mexico Health Sciences Center, Albuquerque, NM, United States; <sup>2</sup>Pediatrics/ Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT, United States; <sup>3</sup>Pediatrics/ Division of Neonatology, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH, United States; <sup>4</sup>Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC, United States; <sup>5</sup>Pediatrics/ Division of Neonatology, Indiana University School of Medicine, Indianapolis, IN, United States; <sup>6</sup>Department of Pediatrics, Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA, United States and <sup>7</sup>Term Hypotension Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

**Background:** Hypotension is common in critically ill term & late preterm infants. However, because there is no clear definition of hypotension, data on the association of hypotension with adverse short term outcomes is rare in this population. We have reported a higher incidence of short term adverse outcomes in infants with hypotension compared to those without (Fernandez et al EPAS 2011:305), but did not evaluate the effect of using different definitions of hypotension.

**Objective:** To determine the definition of hypotension most associated with adverse short term outcomes in infants  $\geq 34$  weeks GA who are on mechanical ventilation (MV) at  $< 72$  hrs in NICHD NRN NICUs.

**Design/Methods:** Multicenter, prospective cohort. Hypotension in the 1<sup>st</sup> 72 postnatal hours was defined as (1) 2 mean blood pressures (MAP)  $< GA$ ; (2)  $\# 1$  plus  $\geq 1$  sign of low systemic blood flow (cap refill  $> 3$ "; urine out  $< 1$ ml/kg/hr; HCO<sub>3</sub>  $< 18$  &/or base deficit  $> 5$ ); (3) receipt of any therapy (tx) for hypotension; or (4) of inotropic tx. Days to full nipple feedings, days in NICU, intubated, and on O<sub>2</sub> were log-transformed & analyzed by linear regression; death was analyzed by logistic regression. Outcomes were adjusted for BW, GA, 5<sup>th</sup> APGAR, gender, delivery room intubation, INO, race & center. Exclusions: omphalocele, congenital diaphragmatic hernia, hypoxic ischemic encephalopathy & whole body cooling.

**Results:** 65% (419/647) of enrolled infants met at least 1 definition of hypotension. 618 infants had complete data for modeling

	Days to full feeds	Days NICU	Days MV	Days O2	Death
	AMD, p	AMD, p	AMD, p	AMD, p	OR, p

MAP<GA	0.1, 0.3	0.8, 0.2	0.2, 0.02	0.2, 0.003	2.3 (0.9,6), 0.07
MAP<GA+sign	0.2, 0.1	0.1, 0.1	0.3, 0.001	0.3, 0.01	3.3 (1.8), 0.01
Any tx for hypotension	0.3, 0.001	0.3, <.0001	0.3, <.0001	0.3, 0.001	3.9 (1.14), 0.04
Inotrope tx	0.4, 0.003	0.2, 0.01	0.5, <.0001	0.6, <.0001	4.6 (2.13), 0.003

**Adjusted mean difference (AMD) in log; p = p-value**

All definitions were associated with greater number of days on MV & days on O<sub>2</sub>. Definitions (2), (3) and (4) were associated with higher numbers of deaths; (4) had the highest odds ratio for death.

**Conclusions:** Blood pressure, + / - evidence of low systemic blood flow, was not consistently associated with these adverse short term outcomes; however tx for hypotension was significantly associated with all outcomes & inotrope tx was highly associated with death.

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**FINAL November 14<sup>th</sup> SUBMITTED**

**Title: Early and late cranial ultrasound (CUS) to predict 18-22 month outcomes in extremely preterm infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) cohort**

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**Background:** Cranial US (CUS) is routinely used to identify acute brain injury and assist in prognosis for extremely preterm (EPT) infants. Studies vary regarding the capability of neonatal CUS to predict childhood outcomes.

**Objective:** To determine associations and predictive value of early and late CUS findings with 18-22 months outcomes in a large contemporary EPT cohort.

**Design/Methods:** NEURO was a prospective study of early (4-14 days) and late (34-42 wks PMA) CUS and near-term MRI in a subcohort of 24-27+6/7 wk EGA infants in the NRN SUPPORT study. All neuroimaging was centrally read. Follow up (FU) outcomes at 18-22 mo corrected age included Bayley III Scales, cerebral palsy (CP), neurodevelopmental impairment (NDI), and unimpaired.

**Results:** 480 infants had all neuroimaging within protocol timing. 444 had FU (15 died, 21 lost, 95% FU rate). Rates of adverse CUS findings and impairment at FU were low. Selected results are shown.

Relation of early and late CUS to 18-22 mo outcomes

Outcome	Early CUS		Late CUS			Early or Late
	Normal (n=321)	IVH 3/4 or PVL (n=44)	Normal (n=320)	Mod/severe ventriculomegaly (VM) (n=17)	cPVL, cyst, mod/severe VM or shunt (n=26)	Any cerebellar lesions (n=7)
Cognitive score <70	16/318 (5%)	5 (11%)	13/316 (4.1%)	3 (18%)	6 (23%)	2 (29%)
Mod/severe CP	2 (0.6%)	9 (20%)	1 (0.3%)	8 (47%)	9 (35%)	6 (86%)
NDI	18/318 (5.7%)	13 (30%)	16/316 (5.1%)	10 (59%)	13 (50%)	6 (86%)
Unimpaired	154/312 (49%)	14/43 (33%)	157/310 (50%)	3 (18%)	5 (19%)	1 (14.3%)

NDI: any of Cog <70, mod/sev CP, GMFCS ≥ 2, bilat blind or deaf; Unimpaired: all of Cog & Lang >85, no CP, blindness, or deafness

Predictive associations of CUS findings with 18-22 mo outcomes

	CUS finding*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cognitive <70	Early adverse	19	91	11	95
	Late adverse	23	95	23	95
Mod/severe CP	Early adverse	69	92	21	99
	Late adverse	69	96	35	99
Death or NDI	Early adverse	31	92	34	91
	Late adverse	29	97	54	91
Unimpaired	Normal both Early and Late	66	44	52	59

\*Early adverse CUS: IVH grade 3/4 or PVL; Late adverse CUS: cPVL, p-cyst, mod-severe VM or shunt

**Conclusions:** Early and late CUS findings were associated with 18-22 mo outcomes. Sensitivity and PPV were

poor, but specificity and NPV were excellent. Having normal early and late CUS was poorly predictive of unimpaired outcome. Cerebellar lesions on CUS were rare; relation to outcomes will be further explored by MRI.

**FINAL November 14<sup>th</sup> submitted**

**Title: Brain MRI and outcomes at 18-22 months in extremely preterm infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) cohort**

S R Hintz, MD MS Epi<sup>1</sup>, L A Wragge, MPH<sup>2</sup>, P D Barnes, MD<sup>1</sup>, D Bulas, MD<sup>3</sup>, T Slovis, MD<sup>4</sup>, A Das, PhD<sup>5</sup>, N Finer, MD<sup>6</sup> and R Higgins, MD<sup>6</sup>. <sup>1</sup>Stanford University, Palo Alto, CA, United States; <sup>2</sup>RTI International, Research Triangle Park, NC, United States; <sup>3</sup>Children's National Medical Center, Washington, DC, United States; <sup>4</sup>Children's Hospital of Michigan, Detroit, MI, United States; <sup>5</sup>UCSD, San Diego, CA, United States and <sup>6</sup>the SUPPORT subcommittee and the NICHD Neonatal Research Network (NRN), Bethesda, MD, United States.

**Background:** Extremely preterm (EPT) infants are at high risk for adverse neurodevelopmental outcomes. Cranial ultrasound (CUS) is standard practice for brain imaging, but near-term brain MRI has been reported to better predict outcomes in this population.

**Objective:** To assess associations of near-term brain MRI findings including severity of white matter abnormalities (WMA) and cerebellar (BEL) lesions, and early and late CUS findings, with early childhood neurodevelopmental outcomes in a large EPT cohort.

**Design/Methods:** NEURO was a prospective study of early (4-14 days) and late (34-42 wks PMA) CUS and near-term MRI in a subcohort of 24-27+6/7 wk EGA infants in the NRN SUPPORT study. Follow Up (FU) outcomes at 18-22 mo corrected age included Bayley III Scales, neurodevelopmental impairment (NDI) (any of Cognitive<70, mod/severe CP, GMFCS>= 2, blindness or deafness), and unimpaired. Logistic regression analysis evaluated associations of CUS and MRI with outcomes, adjusting for multiple other factors.

**Results:** 480 infants had both CUS, and MRI within 2 weeks of late CUS. 444 had FU (15 died; 21 lost). Outcomes by severity of WMA and BEL lesions on MRI are shown.

18-22 mo outcomes and WMA on brain MRI					
	Severity of WMA (Inder TE, et al, J Peds 2003)				
	Normal (n=98)	Mild (n=260)	Moderate (n=68)	Severe (n=18)	p value
Cognitive score, mean (SD)	94 (14)	93 (13)	90 (15)	78 (15)	<.0001
Cognitive<70	4.1%	4.3%	11%	22%	0.01
Mod/severe CP	0	1.2%	1.5%	50%	<.0001
NDI	4.1%	5.8%	11%	61%	<.0001
Unimpaired	57%	47%	43%	17%	0.01

18-22 mo outcomes and cerebellar lesions on brain MRI			
	No BEL lesions (n=373)	Any BEL lesions (n=71)	p value
Cognitive score, mean (SD)	93.1 (13.5)	85.0 (14.9)	<.0001
Cognitive<70	4.1%	16%	<.0001
Mod/severe CP	1.6%	9.9%	0.002
NDI	5.7%	23%	<.0001
Unimpaired	51%	31%	0.003

In regression models including both early and late CUS, brain MRI findings (BEL) remained independently associated with outcomes including death or NDI (OR 3.1, 95%CI 1.4-7.1, p=0.008), or cognitive<70 (OR 2.6, 1.1-6.4, p=0.03). Late CUS findings also remained independently associated with adverse outcomes, but predictive accuracy of models was improved with inclusion of MRI.

**Conclusions:** Brain MRI abnormalities were associated with adverse outcomes, independent of multiple factors including early and late CUS findings. Near-term brain MRI may augment CUS in prediction of early childhood outcomes for EPT infants.

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## 2012 PAS Annual Meeting

**Subspecialty:** Neonatology - General

**Theme:** Neonatal - Patient-Oriented Research

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**Eastern Society for Pediatric Research:** No, Do not consider this abstract for the Eastern SPR

**Pediatric Hospital Medicine:** No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012

**Research Type:** Clinical

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### AWARDS APPLIED FOR:

SPR House Officer Research Award

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**Title:** Concurrent Administration Of Enteral Nutrition And Prophylactic Indomethacin Is Not Associated With Spontaneous Intestinal Perforation In Extremely Low Birth Weight Infants

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**Background:** Prophylactic indomethacin use in extremely-low-birth-weight (ELBW) infants decreases severe IVH. Concerns regarding spontaneous intestinal perforation (SIP) following indomethacin prophylaxis have contributed to varied early feeding practices.

**Objective:** Our hypothesis was that concurrent prophylactic indomethacin (I+) and early enteral nutrition defined as any feeds at 3 days (E+) increases the risk for SIP or death from suspected SIP (SIP/death) at 14 days of life in ELBW infants as compared to infants who do not receive prophylactic indomethacin (I-) and early enteral nutrition (E-).

**Design/Methods:** This was an observational study of 15,751 ELBW infants who survived to day 14 of life and were ever fed, using the 1999-2010 Neonatal Research Network Generic Database. The primary outcome was SIP/death. Secondary outcomes included death/severe neurodevelopmental impairment (NDI) at 18 - 22 months. The risk of the outcome in exposed groups (I+E+, I+E-, and I-E+) was compared to the risk in the unexposed group (I-E-). All estimates were adjusted for gestation, birth weight, gender, race, antenatal steroids, surfactants, SGA, and 5 minute Apgar scores.

**Results:** SIP/death did not differ between either I+E+ (2.71%) or I-E+ group (3.79%) and the I-E- referent group (3.09%) in both the unadjusted and adjusted models (Table). Among infants exposed to indomethacin, the risk of SIP/death did not differ between the E+ and E- groups (I+E+ vs. I+E-, RR 0.90, 95% CI 0.61, 1.33 p = 0.59). Prophylactic indomethacin with early feeding was associated with lower death/severe NDI (I+E+: RR 0.77, 95% CI 0.66, 0.90, p < 0.001) but not in the absence of early feeds. Early feeding, regardless of indomethacin, was associated with lower death/severe NDI (both p < 0.001, Table).

	Table		
	I-E+ (n = 3128)	I+E+ (n = 1186)	I+E- (n = 4668)
	Adj RR (95% CI)	Adj RR (95% CI)	Adj RR (95% CI)
SIP/death from SIP at < 14 days	0.60 (0.41, 0.87)	1.01 (0.69, 1.49)	1.13 (0.91, 1.39)
Death/severe NDI	0.71 (0.63, 0.80)	0.77 (0.66, 0.90)	1.02 (0.93, 1.12)

I+E+, I+E- and I-E+ are compared to RR (1.0) in unexposed group I-E- (n = 6749)

**Conclusions:** The combination of prophylactic indomethacin and concurrent early feeds is not associated with increased SIP/death. The association of early enteral nutrition with better prognosis may indicate unmeasured illness confounders in the models.

**Other Previews:**  
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Abstract Award Info:

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**Research Type:** Clinical

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No awards selected

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**Title:**

**Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants**

Kathleen A Kennedy, MD, MPH<sup>1</sup>, Lisa A Wrage, MPH<sup>2</sup>, Dale Phelps, MD<sup>3</sup> and Rosemary Higgins, MD<sup>4</sup>.  
<sup>1</sup>Pediatrics, UT Houston Medical, Houston, TX, United States; <sup>2</sup>RTI International, Research Triangle Park, NC, United States; <sup>3</sup>University of Rochester, Rochester, NY, United States and <sup>4</sup>the SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

**Background:** Timely detection of treatable ROP is important for optimal outcomes. The 2006 screening guidelines are based on infants born in 1986-1997: screening should begin by 31 wks postmenstrual age (PMA) and continue until vessels have reached zone III at ≥ 35 wks or, for infants without prethreshold ROP, until 45 wks PMA. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

**Objective:** To validate current ROP screening guidelines for 24-27 wk infants.

**Design/Methods:**

In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial trial. Infants 24 0/7 to 27 6/7 wks GA with consent prior to delivery were eligible. Examinations followed current screening recommendations. Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA.

**Results:** 1316 infants were enrolled. 1091 (83%) survived to ROP determination. 997 (91%) of these infants had a definitive ROP outcome. 644 infants developed ROP (138 met criteria for severe ROP); 353 had no ROP. 128/138 (93%) with severe ROP had sufficient data (no missing or delayed exams) to determine the age of onset of ROP. Infants with severe ROP were less mature [mean(SD) 25.5(0.9) wks vs 26.8(0.9) wks, p<0.0001] and lower birth weight [mean (SD) 708(148)g vs 942(173)g, p<0.0001] than infants with no ROP. The PMAs at which selected percentiles reached diagnosis are shown below:

	Cumulative % with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
ROP type (number of infants)	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=642)	30.4	31.4	32.7	33.9	35.1	37.9	41.0



Diagnosis of Severe (Type 1/Treated) ROP (n=128) 32.7 33.9 35.1 36.4 38.6 43.3 45.0

**The PMA at onset of severe ROP ranged from 32.1 to 53.1 wks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer; 1.0% (7% of infants with severe ROP) reached severe ROP after discharge.**

**Conclusions: Our data support the 2006 guidelines. In these 997 infants, we did not observe treatable ROP before 32 wks PMA; only 1 infant developed severe ROP after 45 wks. A limitation of this study is that Infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.**

**Other Previews:**

Abstract Disclosure Info:

Disclosures

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**Title:** Early Use of Surfactant and Inhaled Nitric Oxide (INO) Decreases the Risk of Death/ECMO in Neonates with Moderate Respiratory Failure: Sub-group Analysis of Early INO Trial in Term/Near Term Infants with Hypoxic Respiratory Failure (HRF)

Girija G Konduri, MD<sup>1</sup>, Gregory M Sokol, MD<sup>2</sup>, Krisa Van Meurs, MD<sup>3</sup>, Joel Singer, PhD<sup>4</sup>, N. Ambalavanan, MD<sup>5</sup>, Terry Lee, PhD<sup>4</sup>, Alfonso Solimano, MD<sup>6</sup> and Neonatal Inhaled Nitric Oxide Study Group. <sup>1</sup>Pediatrics, Medical College of Wisconsin, Milwaukee, WI, United States; <sup>2</sup>Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States; <sup>3</sup>Pediatrics, Stanford University, Palo Alto, CA, United States; <sup>4</sup>Center for Health Evaluation and Outcome Sciences, St Paul's Hospital, Vancouver, BC, Canada; <sup>5</sup>Pediatrics, University of Alabama at Birmingham, Birmingham, AL, United States and <sup>6</sup>Pediatrics, University of British Columbia, Vancouver, BC, Canada.

**Background:** In a previous RCT of early INO given at an oxygenation index (OI) of 15-25 versus standard INO at OI>25 in term/near term neonates with HRF, we observed no effect on ECMO/death rates (Pediatrics, 113:559, 2004). However, the mean OI at study enrollment was 19.6 and the control group received INO when OI increased to >25, which led to little separation in treatment between the 2 groups.

**Objective:** To identify risk factors for death/ ECMO by sub-group analysis of early INO RCT data for infants enrolled at OI strata of 15-20 and 20-25.

**Design/Methods:** Univariate, step-wise logistic regression and CART analyses were used to determine if OI at enrollment, PaO<sub>2</sub> response at study gas initiation, surfactant therapy and primary diagnosis influenced the rate of death/ECMO and progression to higher OI.

**Results:** Of 299 infants enrolled between 1998 and 2001, 150 received early INO and 149 received standard INO. An OI of 20 at enrollment was the optimum cut point to predict death/ECMO by ROC. In the early INO group, death/ECMO rate was 10.2% at OI 15-20 (n=88) versus 25.8% at OI 20-25 (n=62), p=0.02. For the control group, death/ECMO rates were 17.4% at OI 15-20 (n=92) vs 22.8% at OI 20-25 (n=57), p=0.52. Early INO group at OI 15-20 showed a trend for lower death/ECMO rate compared to controls at same OI (p=0.19). For babies enrolled at OI>20, early INO decreased progression to OI>30 or death/ECMO (early INO 29%, controls 56%, p<0.01). Stepwise log regression analysis showed that OI at enrollment >20 (OR 1.89, CI 1.02-3.54), diagnosis of PPHN relative to RDS (OR 3.92, CI: 1.19-17.81) and no surfactant therapy (OR 1.85, CI 0.99-3.47) were

independently associated with death/ECMO. Death/ECMO rate was 13.5% for infants receiving surfactant (n=192) vs 26.2% for those not treated (n=107),  $p < 0.01$ . Benefit of surfactant therapy was seen in RDS, perinatal aspiration syndromes and pneumonia/sepsis, but not for primary PPHN. CART analysis showed that babies receiving INO at OI > 20 had lower death/ECMO rates if they were on high frequency oscillation.

**Conclusions:** Post-hoc analysis of early INO RCT suggests that use of surfactant for parenchymal lung disease and INO use at an OI 15-20 are associated with lower death/ECMO rates in HRF.

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## 2012 PAS Annual Meeting

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**Theme:** Neonatal Medicine: Clinical Trials

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**Title: Outcome at 6-7 years of Infants with Elevated Temperatures Following Hypoxia-Ischemia**

Abbot Laptook, MD<sup>1</sup>, Scott McDonald, BS<sup>2</sup>, Seetha Shankaran, MD<sup>3</sup>, Bonnie Stephens, MD<sup>1</sup>, Betty Vohr, MD<sup>1</sup>, Ronnie Guillet, MD<sup>4</sup> and Rose Higgins, MD<sup>5</sup>. <sup>1</sup>Women & Infants Hospital, Providence, RI, United States; <sup>2</sup>RTI International, Research Triangle, NC, United States; <sup>3</sup>Wayne State University, Detroit, MI, United States; <sup>4</sup>University of Rochester, Rochester, NY, United States and <sup>5</sup>for the Extended Hypothermia FU Committee of NICHD NRN,, NICHD, Rockville, MD, United States.

**Background:** Higher temperatures (T) after perinatal HI are associated with poor 18mon outcome in infants cared without hypothermia in the NRN hypothermia trial (Ped 2008).

**Objective:** To determine if higher esophageal (Tes) or skin (Tsk) temperature is associated with death or IQ < 70 at 6-7 yr following perinatal HI for infants cared without hypothermia.

**Design/Methods:** Control infants (non-cooled, n=106) of the NRN hypothermia trial (NEJM 2005) had Tes and Tsk recorded every 4hr over 72hrs. Each infant's T was ranked to derive an average value for the upper quartile (Q4, index of high T) and median of the Es and Sk sites. Average values of Q4 for Tes were ranked and logistic regression was used to determine associations with death or IQ < 70 adjusted for race, gender and encephalopathy level. Similar regressions were performed for median Tes, and for Q4 and median Tsk. Regressions for 6-7 yr survivors were also adjusted for maternal education. Secondary outcomes were death alone, IQ < 70, and moderate/severe CP. IQ and motor function were assessed with Wechsler scales and Gross Motor Function Classification Scores. Results are odds ratio (OR, per °C increment within the quartile or median) and 95% confidence interval (CI).

**Results:** Primary outcome was available for 89 infants (84% of control group). Excluded infants lacked follow-up (13) or T (4) and were similar except for a higher cord pH. Infants with any Tes ≥ 38 °C (n = 44) differed from infants with all Tes < 38 °C in BW (3.6±.6 vs 3.1±.5kg, p < .001) but were similar for GA, gender, resuscitation at birth, and encephalopathy level. At 6-7 yrs death or IQ < 70 occurred in 54 infants (37 deaths, 17 survivors with IQ < 70). For all survivors median IQ was 81 (inter-quartile range 48-91). Average of mean Q4 for Tes was 37.9±.7 °C (range 36.5/41.1 °C). Average of mean Q4 for Tsk was 37.1±.6 °C (range 35.9/39.6 °C). Adjusted OR and 95% CI for associations between T and outcomes are in the table.

**Associations Between Temperature and Outcomes**

	Death or IQ <70	Death	IQ <70	CP
Tes				
Q4	7.3 (2.0-26.3)	4.8 (1.7-13.9)	9.1 (.7-112)	12.5 (1.02-155)
Median	3.3 (.9-12.2)	4.4 (1.2-16.5)	.7 (.1-7.8)	.7 (.1-7.2)
Tsk				

Q4	3.5 (1.2-10.4)	2.7 (1.02-7.2)	5.4 (.8-34.9)	10.3 (1.3-80.2)
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**Conclusions:** Elevated Tes and Tsk following perinatal HI are associated with death or IQ < 70 at 6-7 yr among non-cooled RCT participants. The results support the importance of T control for infants with HI.

**Other Previews:**

Abstract Disclosure Info:

Disclosures

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**Title: Association between Apgar scores (AS) and school-age outcomes following hypoxic-ischemic encephalopathy (HIE)**

**Girija Natarajan MD, Seetha Shankaran MD, Abbot R Laptook MD, Athina Pappas MD<sup>1</sup>, Carla Bann PhD for the Extended Hypothermia Subcommittee of the NICHD Neonatal Research Network (NRN), Bethesda, MD, United States.**

**Background:** In the NICHD whole body cooling randomized controlled trial (RCT) for HIE, lower 10 minute AS were associated with death/ disability at 18-22 months. The correlation between AS and school-age outcomes has not been examined in the era of therapeutic cooling.

**Objective:** To examine the association of 10 minute AS with outcomes at 6-7 years among children with HIE and to determine predictors of death/IQ < 70 among those with 10 minute AS of 0-3.

**Design/Methods:** This was a secondary analysis of 6-7 year follow-up data of the NICHD whole body cooling RCT for HIE. Evaluations included the WPPSI-III or WISC-IV and Gross Motor Functional Classification Scale. Primary outcome was death/IQ < 70; secondary outcomes were death, IQ < 70, death or moderate/severe cerebral palsy (CP), and moderate/severe CP. Logistic regression models were used to generate odds ratios with 95% CI of outcomes per unit increase in 10 minute AS, after adjusting for birth weight, gestational age, gender, outborn status, treatment group (hypothermia vs. standard care) and center as a random effect.

**Results:** The study cohort comprised 179 children enrolled in the NICHD whole body cooling RCT in whom both 10 minute AS and 6-7 year outcome data were available. Death/IQ < 70 was noted in 19/24 (79%) of those with 10 minute AS of 0, 62/85 (73%) of those with AS of 0-3 and 38/94 (40%) of those with AS >3. AS at 10 minutes were significantly associated with outcomes (Table 1). Among children with 10 minute AS of 0-3, those who died or had IQ < 70 (n=62) differed significantly from those who did not (n=23) in the following variables: severe encephalopathy (66% vs. 17%), delivery room chest compressions (90% vs. 65%), time to spontaneous respirations  $\geq$  10 minutes (96% vs. 78%), cord pH < 7 (92% vs. 67%) and hypothermia (37% vs. 65%) respectively.

Table: Association between increasing 10 minute AS and 6-7 year outcomes

Outcome	Adjusted OR (95% CI)
Death / IQ < 70	0.70 (0.58-0.83)*
Death	0.68 (0.57-0.81)*
IQ < 70	0.83 (0.67-1.03)
Death or moderate to severe CP	0.65 (0.54-0.78)*
Moderate to severe CP	0.74 (0.59-0.94)*

**Conclusions:** In a cohort of children with perinatal HIE enrolled in the NICHD cooling

**RCT, 10 minute AS were significantly associated with school-age outcomes. Even among those with AS of 0 at 10 minutes, death or cognitive impairment at school age was not universal. These data suggest caution in determining guidelines for the duration of resuscitation.**





# PEDIATRIC ACADEMIC SOCIETIES ANNUAL MEETING APRIL 28 - MAY 1

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Filename: 752262

### 2012 PAS Annual Meeting

**Subspecialty:** Neonatology - General  
**Theme:** Not yet indicated

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**Pediatric Hospital Medicine:** No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012

**Research Type:** Clinical

**Presentation Sabbath Conflict on:** N/A

**APA Special Interest Groups, Committees or Regions:** None

### AWARDS APPLIED FOR:

No awards selected

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**Title:** Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

Cristina Navarrete, MD<sup>1</sup>, Shahnaz Duara, MD<sup>1</sup> and Rosemary Higgins, MD<sup>2</sup>, <sup>1</sup>University of Miami, Miami, FL, United States and <sup>2</sup>the SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

**Background:** Post-natal growth restriction is a major morbidity in preterm infants. Perturbations in oxygenation may influence

somatic growth: a recent study showed that infants exposed to higher oxygen saturation (SpO<sub>2</sub>) targets experience poorer growth (Tin, Arch Child Dis FN 2001). The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) showed that a lower target range of SpO<sub>2</sub> from birth, as compared with a higher range, resulted in less retinopathy of prematurity in survivors but an increase in mortality (Carr, NEJM 2010).

**Objective:** To test the hypotheses that infants kept in the low SpO<sub>2</sub> target range from birth will have better growth trajectories and better growth at 36 weeks and at 18-22 months corrected age (fewer babies <10% for weight).

**Design/Methods:** A sub-cohort of 810 preterm infants enrolled in SUPPORT (n=1,316), randomized at birth to low (85-89%, n=402, GA 26.2 ± 1.1wks, BW 838.6 ± 185 gm) or high (91-95%, n=408, GA 26.2 ± 1.1wks, BW 839.6 ± 191gm) SpO<sub>2</sub> target range was studied. Anthropometric measures were obtained at birth, postnatal days 7, 14, 21, and 28, 32 and 36 weeks post-menstrual age, and at 18-22 months corrected age. Longitudinal growth trajectories were constructed for each target group using the means of each measure per time point. Poor growth (weight, length, head circumference <10<sup>th</sup> %ile) at 36 weeks and 18-22 months was analyzed using robust Poisson regression.

**Results:** Growth trajectories for Wt, L, and HC showed no differences in growth between the low and high SpO<sub>2</sub> assignment groups. There was no difference in mortality by 36 weeks and the rate of poor growth at 36 wks and at 18-22 month was not different for any measure (Table1).

**Conclusions:** Early oxygen saturation target assignment did not impact on growth in a large subgroup of infants enrolled in the SUPPORT Trial.

Growth Outcomes by Assigned Groups

	Low SpO <sub>2</sub> (n=402)	High SpO <sub>2</sub> (n=408)	p-value
n (%) death by 36wk	69 (17.2)	60 (14.7)	0.32
n/N(%) with Wt <10th %ile at 36wk	155/333 (46.6)	172/342 (50.3)	0.30
n/N(%) with Wt <10th %ile at 18-22m	48/296 (16.2)	45/313 (14.4)	0.49
n/N(%) with L <10th %ile at 36wk	203/314 (64.7)	218/315 (69.2)	0.21
n/N(%) with L <10th %ile at 18-22m	79/296 (26.7)	98/313 (31.3)	0.28
n/N(%) with HC <10th %ile at 36wk	124/319 (38.9)	130/325 (40.0)	0.87
n/N(%) with HC <10th %ile at 18-22m	46/296 (15.5)	49/313 (15.7)	0.92

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### 2012 PAS Annual Meeting

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**Theme:** Not yet indicated

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**Research Type:** Clinical  
**Presentation Sabbath Conflict on:** N/A  
**APA Special Interest Groups, Committees or Regions:** None

#### AWARDS APPLIED FOR:

No awards selected

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American Academy of Pediatrics

**Title:** PREDICTING COGNITIVE OUTCOMES AT SCHOOL AGE AMONG CHILDREN WITH NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY AT BIRTH

Athina Pappas, MD<sup>1</sup>, Seetha Shankaran, MD<sup>1</sup>, Scott McDonald, BS<sup>1</sup>, Betty Vohr, MD<sup>3</sup>, Rebecca Bara, RN BSN<sup>1</sup>, Richard Ehrenkranz, MD<sup>4</sup>, Susan Hintz, MD MS Epi<sup>5</sup>, Jon Tyson, MD MPH<sup>6</sup>, Kimberly Yolton, PhD<sup>7</sup>, Abhik Das, PhD<sup>8</sup>, Jane Hammond, PhD<sup>2</sup>, Rosemary Higgins, MD<sup>9</sup> and on behalf of the NICHD Neonatal Research Network. <sup>1</sup>Wayne State University, Detroit, MI, United States; <sup>2</sup>RTI International, Research Triangle Park, NC, United States; <sup>3</sup>Brown University, Providence, RI, United States; <sup>4</sup>Yale University, New Haven, CT, United States; <sup>5</sup>Stanford University, Palo Alto, CA, United States; <sup>6</sup>University of Texas Medical School at Houston, Houston, TX, United States; <sup>7</sup>University of Cincinnati, Cincinnati, OH, United States; <sup>8</sup>RTI International, Rockville, MD, United States and <sup>9</sup>Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD, United States.

**Background:** Children with hypoxic ischemic encephalopathy at birth are at risk for cognitive impairment. Accurate assessment of outcomes and prediction of school age functioning is important.

**Objective:** To describe the relationship between the Bayley Scales of Infant Development II (BSID II) at 18-22mo and IQ at 6-7y among children with moderate-severe HIE at birth.

**Design/Methods:** The participants of this trial were the survivors of the original NRN trial of whole body hypothermia for HIE (NEJM 2005; 353:1574) followed to school age. Measures included the BSID II at 18-22mo and Wechsler intelligence scales at 6-7y administered by blinded examiners trained to reliability. The relationship between the BSID II MDI and Wechsler Composite IQ scores was assessed via sensitivity testing, Spearman's rank-order correlation and logistic regression adjusted for important covariates. Scores categorized at 1 and 2 SD of the mean (<70, 70-84, >84) were examined.

**Results:** The study cohort included 110/140 surviving children (18 lost; 12 missing 21 test score). Except for race, baseline and demographic characteristics were similar for those with and without assessments (higher % non-white among those without). Overall, 72% of children remained in the same cognitive range from 18-22mo to 6-7y (Table 1). A Bayley MDI score of <70 had a sensitivity of 0.87, a specificity of 0.96, a positive predictive value of 0.90 and a negative predictive value of 0.95 for detecting school age IQ<70. Spearman's rank correlation for MDI and IQ scores was 0.74, p<0.0001. Logistic regression analyses indicated that, even after adjusting for maternal education, treatment group and level of encephalopathy, a low Bayley MDI score (<70) at 18-22mo increased the odds of low IQ (<70) at 6-7 years 96-fold compared to those with mild delay or normal MDI at 18-22mo, p<0.0001. Adjusting for center as a random effect did not appreciably change the results.

**Conclusions:** For children with HIE, severe developmental impairment at 18-22mo was highly predictive of IQ<70 at school age. Prediction of less severe impairment is challenging and requires further study.

Neurodevelopmental Outcomes

MDI at 18-22 mo, n	IQ at 6-7 years, n			Total, n
	>84	70-84	<70	
>84	39	12	2	53
70-84	12	13	2	27
<70	1	2	27	30
Total, n	52	27	31	110

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## 2012 PAS Annual Meeting

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**Theme:** Neonatal Medicine: Clinical Trials

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**Research Type:** Clinical  
**Presentation Sabbath Conflict on:** N/A  
**APA Special Interest Groups, Committees or Regions:** None

### AWARDS APPLIED FOR:

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**Title:** INOSITOL SERUM CONCENTRATIONS AND SAFETY IN A DAILY DOSE RANGING STUDY FOR EXTREMELY PRETERM INFANTS

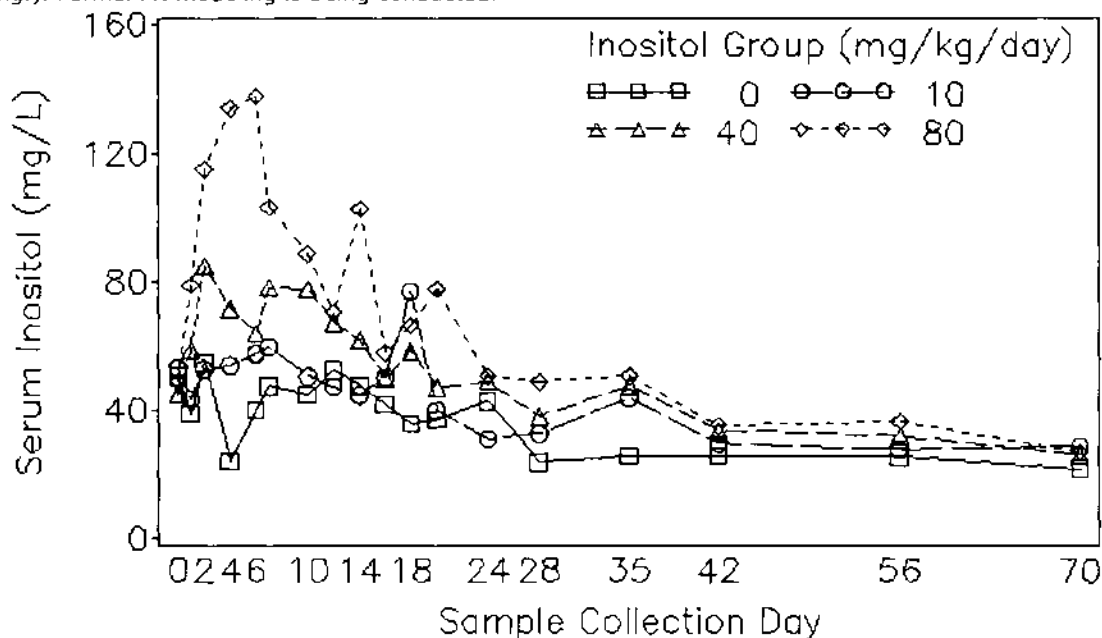
Dale Phelps<sup>1</sup>, Kristi Watterberg<sup>2</sup>, Tracy Nolen<sup>3</sup>, Robert Ward<sup>4</sup> and for the Inositol Subcommittee<sup>5</sup>.  
<sup>1</sup>Univ of Rochester, Rochester, NY, United States; <sup>2</sup>Univ of New Mexico, Albuquerque, NM, United States; <sup>3</sup>RTI International, Research Triangle Park, NC, United States; <sup>4</sup>Univ of Utah, Salt Lake City, UT, United States and <sup>5</sup>NICHD Neonatal Research Network, Rockville, MD, United States.

**Background:** Early trials of IV myo-inositol(Ins) show reductions in death, BPD and ROP in extremely preterm infants. Few data are available on extended daily Ins or its pharmacokinetics(PK) in this population.

**Objective:** Determine the safety and PK of Ins in extremely preterm infants at 3 doses.

**Design/Methods:** Infants of 23<sup>0/7</sup>-29<sup>6/7</sup> wks &  $\geq 400$ g BW were randomized to placebo, 10, 40, or 80mg/kg/d of Ins IV(divided q 12hr) from enrollment(1-3d) to: 10 wks, 34 wks postmenstrual age or discharge. Once feedings were established, the same dose converted to enteral. Adverse events(AE) were prospectively monitored, serum collected in a sparse sampling population PK design of 7-9 per infant, and Ins excretion measured in four, 24-hr urine collections during wks 1, 2, 4 & 6.

**Results:** 122 infants were randomized and treated(Rx), stratified by GA (23-26 vs 27-29wks). Serum Ins rose from baseline ( $50 \pm 25$ mg/L,  $m \pm s$ d) in proportion to dose, reaching the target range of 130-150mg/L in the 80mg/kg/d group in wk 1. Levels then gradually fell despite ongoing Rx. Avg. levels in all 4 groups converged by 6 wks, continuing to slowly decline (raw mean levels in fig.). Formal PK modeling is being conducted.



In wk 1, 24-hr urine excretion was proportional to dose ( $108 \pm 30$  vs  $33 \pm 24$ mg/kg/24 hr in the 80mg/kg/d vs placebo infants respectively). In wk 2, excretion fell in the 2 high dose groups, and continued to fall in wks 4 & 6. AEs were not significantly different across groups (avg 6 events/subject). Death, ROP requiring surgery, BPD and severe IVH were lowest in the 80mg/kg/d group, however the study was not powered to detect significant differences in these outcomes.

**Conclusions:** Daily IV Ins(80mg/kg/d) reached the target range in wk 1, elevating levels for 2 to 3 wks with no serum accumulation, no toxicity and outcomes consistent with previous reports of reduced morbidity, justifying our intent to pursue an adequately powered phase 3 RCT.

Funding: NIH: NICHD and NEI. Abbott Nutrition provided study drug.

**Title:** Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD,MPH<sup>1</sup>, Marie Gantz, PhD<sup>2</sup>, Neil N Finer, MD<sup>1</sup> and SUPPORT Study Group<sup>3</sup>. <sup>1</sup>Division of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; <sup>2</sup>Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and <sup>3</sup>Neonatal research Network, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, United States.

**Background:** The multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

**Objective:** We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

**Design/Methods:** The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive either CPAP in the delivery room with a limited ventilation for strategy for two weeks (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary, pre-specified composite outcome was death or NDI including at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification Score (GMFCS)  $\geq 2$ , moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

**Results:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants. Death or NDI occurred in 27.9% (173/621) of CPAP and 29.9% (183/613) of SURF infants ( $p=0.39$ ). Rates of death (CPAP-18.4 vs. SURF-21.9%,  $p=0.10$ ), NDI alone (CPAP-0.9 vs. SURF 9.1%,  $p=0.44$ ), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%,  $p=0.84$ ), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%,  $p=0.82$ ), GMFCS  $\geq 2$  (CPAP-5.1 vs. SURF 4.8%,  $p=0.95$ ); blindness (CPAP-0.8 vs. SURF 1.5%,  $p=0.31$ ), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%,  $p=0.06$ ) were similar in both treatment arms. There were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

**Conclusions:** We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.



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## 2012 PAS Annual Meeting

**Subspecialty:** Neonatal Epidemiology & Follow-Up

**Theme:** Neonatal Medicine: Clinical Trials

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**APA Special Interest Groups, Committees or Regions:** None

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**Title:** Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD, MPH<sup>1</sup>, Marie G Gantz, PhD<sup>2</sup>, Neil N Finer, MD<sup>3</sup> and Rosemary D Higgins, MD<sup>1</sup>. <sup>1</sup>Division of Neonatology, Department of Pediatrics, University of California, San Diego, CA, United States; <sup>2</sup>Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and <sup>3</sup>SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

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**Objective:** We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

**Design/Methods:** The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive either CPAP in the delivery room with a limited ventilation strategy for two weeks (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary, pre-specified composite outcome was death or NDI including at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification System (GMFCS) score 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

**Results:** Death or NDI was determined for 1234/1316 (93.8%) enrolled infants. Death or NDI occurred in 27.9% (173/621) of CPAP and 29.9% (183/613) of SURF infants ( $p=0.38$ ). Rates of death (CPAP-18.4 vs. SURF-21.9%,  $p=0.10$ ), NDI alone (CPAP-10.9 vs. SURF 9.1%,  $p=0.44$ ), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%,  $p=0.84$ ), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%,  $p=0.82$ ), GMFCS 2 (CPAP-5.1 vs. SURF 4.8%,  $p=0.95$ ); blindness (CPAP-0.8 vs. SURF 1.5%,  $p=0.31$ ), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%,  $p=0.06$ ) were similar in both treatment arms. There were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

**Conclusions:** We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.

**Other Previews:**

Abstract Disclosure Info:

Please select Print from the file menu to print your Abstract.

**First Author:** Betty Vohr, MD  
**Responsible Author:** Betty Vohr, MD  
**Presenting Author:** Betty Vohr, MD  
**Contact Person:** Betty R. Vohr, MD

**Filename:** 750504

## 2012 PAS Annual Meeting

**Subspecialty:** Neonatal Epidemiology & Follow-Up  
**Theme:** Neonatal - Disease-Oriented Research

**Contact Author:** Betty R. Vohr, MD  
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**Phone:** (401) 274-1122, ext. 7435 **Fax:** (401) 453-7571 **E-mail:** bvohr@wihri.org

**Responsible Author:** Betty Vohr, MD  
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**Responsible Author Declaration:** As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

**Presenting Author:** Betty Vohr, MD  
**Department/Institution/Address:** Pediatrics, Women and Infants Hospital, 101 Dudley Street, Providence, RI, 02905, United States  
**Phone:** (401) 274-1122, ext. 7435 **Fax:** (401) 453-7571  
**Presenting Author E-mail:** bvohr@wihri.org

**The presenting author is member of these Alliance Societies:**

Society for Developmental and Behavioral Pediatrics

**Is Presenting Author a Trainee?** No, Not a Trainee

**Presenter Copyright Declaration:**

I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

### QUESTIONNAIRE INFORMATION

**Eastern Society for Pediatric Research:** No, Do not consider this abstract for the Eastern SPR

**Pediatric Hospital Medicine:** No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012

**Research Type:** Clinical

**Presentation Sabbath Conflict on:** N/A

**APA Special Interest Groups, Committees or Regions:** None

**AWARDS APPLIED FOR:**

No awards selected

- Title:** *The effect of sepsis on subsequent PCV7 vaccine responses in very low birth weight infants*  
*JL Wynn, L Li, CM Cotten, RN Goldberg, BJ Stoll, and CT D'Angio for the PCV 7 Subcommittee of the Neonatal Research Network (NRN)*
- Background:** Sepsis in older children and adults may decrease immune system function and alter the capacity to respond to infectious challenge. The impact of sepsis on subsequent function of the preterm infant's developing adaptive immune system is unknown.
- Objective:** Compare serotype specific antibody responses to heptavalent pneumococcal conjugate vaccine (PCV7) in very low birth weight infants (<1500g,VLBW) with and without a history of sepsis.
- Design/methods:** Retrospective analysis of data collected in an NRN study of PCV7 vaccine among VLBW infants. Infants received PCV7 at 2, 4, and 6 months after birth and had blood drawn 4-6 weeks after the 3rd dose. Vaccine serotype antibodies (4, 6B, 9V, 14, 18C, 19F, 23F) were measured by ELISA. Percentages of infants that reached cutoff antibody titers of  $\geq 0.35$  and  $> 1.0 \mu\text{g/mL}$  were compared between infants with/without a history of sepsis by 60 days of life. Opsonization titers (OT) were the serum dilution that killed 50% of the target bacteria. Logistic regression models for serum antibody cutoffs were constructed with birth weight group ( $\leq 1000\text{g}$  or  $> 1000\text{g}$ ) and other confounding factors identified in the primary study (gender, race, postnatal glucocorticoids, Z-score of weight for corrected age at blood draw and age at 1st vaccination).
- Results:** 249 infants (67% of enrolled) completed the vaccine series and 244 (66%) had serum antibody available. Sepsis (96% between day of life 3-60) occurred in 33% (81/244). Mean BW and gestational age was greater in uninfected infants (1094g, 28wk) than those with sepsis (837g, 26wk),  $p < 0.01$  for both variables between groups. After adjustment, sepsis reduced the odds of having serum antibody  $> 1.0 \text{ mcg/mL}$  against serotype 23F (OR=0.38, 95% confidence interval [0.20, 0.73]) compared to infants without sepsis. No other differences were found between groups for all other vaccine serotypes at either cutoff concentration. When restricted to infants with BW < 1000 grams, the reduced response to 23F remained significant (OR=0.38,[0.15, 0.93]), and was comparable with only infants < 28 weeks (OR=0.42[0.17, 1.04],  $p = 0.06$ ). Infants with sepsis had reduced percentage of OT > 1:8 against serotype 6B compared vs infants without sepsis (82 vs 97%,  $p < 0.01$ ).
- Conclusions:** Sepsis was independently associated with reduced odds of protection following PCV7 against serotypes 6B and 23F.

**Title:** *Risk of subsequent infection in very low birth weight neonates after early sepsis*

*JL Wynn, NI Hansen, CM Cotten, RN Goldberg, DK Benjamin Jr, BJ Stoll for the NICHD Neonatal Research Network (NRN).*

**Background:** Sepsis in children and adults results in alterations of immune system function that may increase the risk of subsequent infection. It is unknown whether preterm infants have an increased risk of subsequent infection following early onset sepsis (EOS).

**Objective:** Determine if preterm infants who survived EOS have an increased risk of subsequent late onset sepsis (LOS).

**Design/methods:** Very low birth weight (VLBW) infants (401-1500g) born between Sept. 1998 and Dec. 2009 who survived >72 hours (hr) and were cared for within the NICHD NRN were studied. Sepsis was defined by growth of bacteria or fungi in a blood culture obtained  $\leq 72$  hr of birth (EOS) or >72 hr (LOS) and antimicrobial therapy for  $\geq 5$  days (d) or death <5d while receiving therapy. Poisson regression models were used to assess risk of the composite of LOS or death by 120d and LOS by 120d among survivors to discharge or 120d while adjusting for study center, gestational age (GA), BW, gender, and race.

**Results:** Of 34,396 infants studied 504 (1.5%) had EOS. Infants with EOS had lower median GA [27 vs 28 week (wk)] and lower BW (909 vs 1040g) than infants without EOS. Death or LOS by discharge or 120d occurred in 196 (39%) infants who had EOS and in 9906 (29%) infants who did not have EOS  $p < 0.001$ . After adjustment, no overall difference was found in the risk for death or LOS within 120d of life for infants with EOS compared to those without EOS [RR: 0.99 (0.89-1.09),  $p = 0.79$ ]. However, a reduction in death or LOS risk was found for infants <25wk who had EOS compared to those who did not [RR: 0.87(0.76-0.99),  $p = 0.048$ ]. Among survivors to discharge or 120d, LOS was diagnosed in 26% of infants who had EOS and 23% of infants who did not have EOS,  $p = 0.09$ . After adjustment, no difference in the overall risk of LOS by discharge or 120d was found for infants with and without EOS [RR: 0.87 (0.75-1.02),  $p = 0.07$ ]. A reduction in LOS risk was found for infants <25wk who had EOS compared to those who did not [RR: 0.76 (0.59-0.98),  $p = 0.03$ ]. A similar reduction in risk of LOS was found for infants with BW 401-750g who had EOS compared to those without EOS [RR: 0.79 (0.63-0.98),  $p = 0.03$ ].

**Conclusions:** In contrast to children and adults, the risk of subsequent infection was not increased after EOS in this cohort of VLBWs. Our findings highlight the need for age-specific analyses of immune function and infection risk.

Saturday, April 28, 2012

Beau Batton	Prospective Observational Study of Blood Pressure Management in Infants 23-26 Weeks Gestation	Platform	1150 - Neonatal - Patient-Oriented Research: NICU Research	8:15 AM	Ballroom B (Hynes Convention Center)	1150.2
Erika Fernandez	Hypotension and Adverse Short Term Outcomes in Critically Ill Term and Late Preterm Newborns	Platform		8:30 AM		1150.3
Ed Bell	Tocopherol Levels in Very Preterm Infants after a Single Enteral Dose of Vitamin E Given Soon after Birth	Platform	1335 - Neonatal Fetal Nutrition & Metabolism I	10:30 AM	309 (Hynes Convention Center)	1335.1
Susan Hintz	Brain MRI and Outcomes at 18-22 Months in Extremely Preterm Infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) Cohort	Platform	1670 - Neonatal - Patient-Oriented Research: Neonatal Neurology	2:45 PM	Ballroom B (Hynes Convention Center)	1670.1
Susan Hintz	Early and Late Cranial Ultrasound (CUS) To Predict 18-22 Month Outcomes in Extremely Preterm Infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) Cohort	Platform	1670 - Neonatal - Patient-Oriented Research: Neonatal Neurology	3:15 PM	Ballroom B (Hynes Convention Center)	1670.3
Ganesh Konduri	Early Use of Surfactant and Inhaled Nitric Oxide (INO) Decreases the Risk of Death/ECMO in Neonates with Moderate Respiratory Failure: Sub-Group Analysis of Early INO Trial in Term/Near Term Infants with Hypoxic Respiratory Failure (HRF)	Platform	1675 - Neonatal Medicine: Clinical Trials	3:15 PM	Ballroom C (Hynes Convention Center)	1675.3

Sunday, April 29, 2012

James Wynn	Risk of Subsequent Infection in Very Low Birth Weight Neonates after Early Sepsis	Platform	2430 – New Findings in Neonatal Infectious Diseases	11:45 AM	309 (Hynes Convention Center)	2430.6
Athina Pappas	Predicting Cognitive Outcomes at School Age among Children with Hypoxic Ischemic Encephalopathy at Birth	Poster Symposium	2760 – Neonatal Outcomes at School Age & Beyond	1:00 PM - 3:00 PM	304 (Hynes Convention Center)	2760.1
Cristina Navarrete	Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth	Platform	2755 – Neonatal – Patient-Oriented Research: Neonatal Nutrition	2:00 PM	Ballroom B (Hynes Convention Center)	2755.5
Kathleen Kennedy	Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24–27 Week Gestational Age (GA) Infants	Poster	2916 – Neonatology – General	4:15 PM - 7:15 PM	Exhibit Halls A/B (Hynes Convention Center)	2919.293
Betty Vohr	Associations between Disability and Growth at 6–7 Years in the NICHD Trial of Whole Body Hypothermia for HIE	Poster				2916.246
Girija Natarajan	Association between Apgar Scores (AS) and School–Age Outcomes Following Hypoxic–Ischemic Encephalopathy (HIE)	Poster				2916.236

Monday, April 30, 2012

Andrea Duncan	Evaluation of Early Executive Function in Extremely Preterm Children	Platform	3325 – Neonatal Outcomes Before School Age	11:15 AM	Ballroom B (Hynes Convention Center)	3325.4
Seetha Shankaran	Management of Post Hemorrhagic Ventricular Dilatation: Impact of Early vs. Late Intervention, a Single Center Observational Study	Platform		11:30 AM		3325.5
James Wynn	The Effect of Sepsis on Subsequent PCV7 Vaccine Responses in Very Low Birth Weight Infants	Platform	PIDS Blue Ribbon Research Session	12:30 PM	302 (Hynes Convention Center)	N/A
Dale Phelps	Inositol Serum Concentrations and Safety in a Daily Dose Ranging Study for Extremely Preterm Infants	Poster	1536 – Neonatology – General	1:00 PM - 4:00 PM	Exhibit Halls A/B (Hynes Convention Center)	1536.654
Beau Batton	Blood Pressure Values in the First 24 Hours for Infants 23–26 Weeks Gestation	Poster	3853 – Neonatology – General	4:15 PM - 7:30 PM	Exhibit Halls A/B (Hynes Convention Center)	3853.668



Tuesday, May 1, 2012

Mike Cotten	Genome-Wide Association Study of Morbidities of Extreme Prematurity	Poster	4526 – Neonatology – General	10:00 AM - 2:00 PM	Exhibit Halls A/B (Hynes Convention Center)	4526.381
J Kelleher	Concurrent Administration of Enteral Nutrition and Prophylactic Indomethacin Is Not Associated with Spontaneous Intestinal Perforation in Extremely Low Birth Weight Infant	Poster	4530 – Neonatology – General			4530.52
Yvonne Vaucher	Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT Trial: Early CPAP Versus Intubation with Surfactant Administration	Platform	4630 – Neonatal Medicine: Clinical Trials	2:00 PM	Ballroom B (Hynes Convention Center)	4630.1
Myriam Peralta-Carcelen	Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targ	Platform		2:15 PM		4630.2
Abbot Laptok	Outcome at 6–7 Years of Infants with Elevated Temperatures Following Hypoxia-Ischemia	Platform	4630 – Neonatal Medicine: Clinical Trials	3:15 PM		4630.6

**From:** Kennedy, Kathleen A  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: ROP Natural History Study Manuscript  
**Date:** Thursday, March 22, 2012 8:45:21 PM

---

I'm still trying to figure out what to do with the author list for this secondary study. I've made some changes to the manuscript based on comments from you and Dale. I've added Lisa and I've sent her the revised version because we need some additional information from her. Once I get that, I'll have a draft of the poster to send to the subcommittee. I left a comment in what I sent Lisa that we're still working on the author list.

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:** Kennedy, Kathleen A  
**Sent:** Friday, March 16, 2012 4:55 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** RE: ROP Natural History Study Manuscript

Based on a prior email from you (during the abstract submission process), I thought that everyone on the subcommittee was supposed to be included as an author. Maybe that's what always happens, in effect, when it's up to the subcommittee to decide who should be an author. Based on what I understand about principles of authorship (should be based on scientific contribution to the effort), it doesn't seem like the importance of the paper should determine authorship. I'm still a little confused about when this gets decided in the course of writing and revising the manuscript. I was thinking that the next version (after it's reviewed by you and Dale and Lisa) would go to the subcommittee for their review. Are there more steps before that to decide on the author list?

As far as I can tell, neither Marie nor Abhik has been involved in the secondary analyses. But I don't know what discussions, if any, have happened behind the scenes. All of my communications have been with Lisa Wrage.

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  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, March 16, 2012 3:26 PM  
**To:** Kennedy, Kathleen A  
**Subject:** RE: ROP Natural History Study Manuscript

Kathleen –

The policies and procedures state:

### **6.6.2 Secondary Protocols**

The protocol subcommittee, with Steering Committee approval, determines the authorship of secondary protocol papers.

I would suggest we come up with a list (and you are correct about the 4 folks who have contributed). Was Marie Gantz involved at all as she was the main SUPPORT statistician??

How the paper gets cited comes up after the fact – as a little history, after Jon's outcome tool paper was published, I received some comments about "why wasn't the entire network included on such an important paper?" In going back over things, Jon had updated the steering committee on several occasions as well as sending the paper through the publication process and to the steering committee – this authorship issue came up AFTER publication (no one said anything prior to this and I am happy to discuss with you). No one mentioned it before – I am simply trying to be pro-active. Jon was aware of this after the fact as we discussed this and were somewhat dismayed that folks didn't speak up – they may have been a little shy given that there were survivors (albeit few) at 22-23 weeks. I brought it up with Wally's antenatal steroids JAMA paper and folks were included. I also brought this up with a trisomy 21 paper from Iowa and folks decided not to be included.

I am happy to discuss the authorship issues with you!!

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](mailto:higginsr@mail.nih.gov)

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]

**Sent:** Friday, March 16, 2012 2:19 PM

**To:** Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** RE: ROP Natural History Study Manuscript

The main question I had about authorship had to do with Lisa Wrage. She has done all the analyses

for this and she was included as an author on the abstract. You and Dale are the only others who have contributed to this effort so far. Can I assume that the 4 of us should be the first 4 authors? Do we still include 2 more authors from RTI (that seems like a lot of authors from RTI)? As I understand it, there will also be 9 other authors from the original subcommittee. That's 15 already. I wasn't aware that consideration of how that paper might be cited affects the Networks authorship policies. Is that what you're saying?

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

**Sent:** Friday, March 16, 2012 12:52 PM

**To:** Kennedy, Kathleen A

**Subject:** ROP Natural History Study Manuscript

Kathleen –

This is coming together nicely – my comments are in track changes and comments in the text. This paper is likely to be cited by the practicing bodies for ROP screening (affirms what is already recommended). Should all sites that contributed patients be authors?? I am unsure – perhaps we should ask the SC??

Thanks for all the hard work!!

Rose

**From:** Roger Faix  
**To:** Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; "Wally Carlo, M.D."; "Schibler, Kurt"; "Michele Walsh"; Bradley Yoder; Gantz, Marie; Laptook, Abbot; "Das, Abhik"; nancy newman  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Truog, William (MD)"  
**Subject:** RE: SUPPORT letter and commentary  
**Date:** Monday, March 19, 2012 8:43:15 PM

---

Wade and Neil have articulated the resolution of the issue better than I can. I believe no response is needed from the SUPPORT group.

Roger

---

**From:** Rich, Wade [wrich@ucsd.edu]  
**Sent:** Monday, March 19, 2012 11:11 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'Wally Carlo, M.D.'; 'Schibler, Kurt'; 'Michele Walsh'; Roger Faix; Bradley Yoder; Gantz, Marie; Laptook, Abbot; 'Das, Abhik'; nancy newman  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Truog, William (MD)'  
**Subject:** RE: SUPPORT letter and commentary

Hi Rose,

Neil and I talked about these, and agreed that Dr. Whitney's comment was probably an opportunity for him to express an opinion, and not truly related to the manuscript in any way, and that the response letter pretty much said what we would have said in reply. Interested in others take on them.

Wade

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 19, 2012 9:44 AM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; 'Schibler, Kurt'; 'Michele Walsh'; 'ROGER.FAIX@HSC.UTAH.EDU'; Bradley.Yoder@hsc.utah.edu; Rich, Wade; Gantz, Marie; Laptook, Abbot; 'Das, Abhik'; nancy newman  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Truog, William (MD)'  
**Subject:** SUPPORT letter and commentary  
**Importance:** High

Hi,

There is a letter and a commentary with Wade's paper that came out in Pediatrics:

[http://pediatrics.aappublications.org/content/129/3/480.short/reply#pediatrics\\_ei\\_53118](http://pediatrics.aappublications.org/content/129/3/480.short/reply#pediatrics_ei_53118)

<http://pediatrics.aappublications.org/content/129/3/576.full>

Let me know if you want a call to discuss.

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](mailto:higginsr@mail.nih.gov)

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT letter and commentary  
**Date:** Monday, March 19, 2012 2:28:54 PM

---

I agree.

*Michele Walsh, MD*  
*Chief, Division of Neonatology*  
216.844.3759

*It's not what you look at that matters, it's what you see. Thoreau*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 19, 2012 1:42 PM  
**To:** 'Rich, Wade'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Schibler, Kurt'; 'Michele Walsh'; 'ROGER.FAIX@HSC.UTAH.EDU'; Bradley.Yoder@hsc.utah.edu; Gantz, Marie; Laptook, Abbot; 'Das, Abhik'; nancy newman  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Truog, William (MD)'  
**Subject:** RE: SUPPORT letter and commentary

My take is that these go beyond the scope of the mission of the network – to perform studies to provide evidence for change in practice and patient care—  
Rose

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**From:** Rich, Wade [mailto:wrich@ucsd.edu]  
**Sent:** Monday, March 19, 2012 1:12 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Schibler, Kurt'; 'Michele Walsh'; 'ROGER.FAIX@HSC.UTAH.EDU'; Bradley.Yoder@hsc.utah.edu; Gantz, Marie; Laptook, Abbot; 'Das, Abhik'; nancy newman  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Truog, William (MD)'  
**Subject:** RE: SUPPORT letter and commentary

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take on them.  
Wade

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 19, 2012 9:44 AM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; 'Schibler, Kurt'; 'Michele Walsh'; 'ROGER.FAIX@HSC.UTAH.EDU'; Bradley.Yoder@hsc.utah.edu; Rich, Wade; Gantz, Marie; Laptook, Abbot; 'Das, Abhik'; nancy newman  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Truog, William (MD)'  
**Subject:** SUPPORT letter and commentary  
**Importance:** High

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<http://pediatrics.aappublications.org/content/129/3/576.full>

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Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Kennedy, Kathleen A"](#)  
**Subject:** ROP Natural History Study Manuscript  
**Date:** Friday, March 16, 2012 1:52:00 PM  
**Attachments:** [ROP Natural History Study Manuscript.doc](#)

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Kathleen –

This is coming together nicely – my comments are in track changes and comments in the text. This paper is likely to be cited by the practicing bodies for ROP screening (affirms what is already recommended). Should all sites that contributed patients be authors?? I am unsure – perhaps we should ask the SC??

Thanks for all the hard work!!  
Rose

## Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy MD MPH, Rosemary D. Higgins MD, Dale L. Phelps MD, Neil Finer, Waldemar Carlo, Roger Faix, Abbot Laptook, Kurt Schibler, Michelle Walsh, Brad Yoder, Abhik Das, Gantz, N. Newman, Rich

### Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to achieve optimal outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower gestational age (GA) infants has increased.<sup>7</sup> For infants 501-750g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002. The timing of onset of ROP is related to both gestational age and postnatal age. The impact of increased survival of ELBW infants on the incidence and timing of the onset and regression of ROP have not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). Based on the results of ET-ROP study, earlier treatment is now recommended.<sup>8</sup> With these new treatment criteria, screening must be initiated early enough to reliably identify infants with Type 1 ROP (ET-ROP treatment criteria), defined as stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II, rather than CRYO-ROP threshold ROP. In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4,9</sup> We need updated information about the evolution of ROP in a contemporary cohort to determine when screening must be initiated to capture all infants as soon as Type 1 ROP develops. There have been two more recent publications of the timing of ROP onset from the ET-ROP Study<sup>9</sup> and from a population-based cohort of infants born 2004-2007 in Sweden,<sup>10</sup> but the age distribution of onset of Type 1 ROP was not reported in either publication.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This observational study was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of infants 24-27 6/7 weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) to determine if the current ROP screening guidelines were appropriate to identify treatable Type 1 ROP in a contemporary cohort of infants.

### Methods

In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design. Extensive ROP outcome data were prospectively collected for all enrolled infants. Infants 24 0/7 - 27 6/7 weeks gestation (no birth weight limits) were eligible for this study if prenatal consent was obtained. Ophthalmology exams began before 33 weeks postmenstrual age. The following data were recorded at each eye exam: the date of the eye exam, the highest stage and lowest zone of ROP, presence of plus disease, whether the infant met the criteria for Type 1 ROP. Examinations were continued according to existing ROP screening recommendations. Study eye exam data were recorded until study endpoint: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks postmenstrual age.

**Comment [KKA1]:** Check with Rose about including all these people and the order. Lisa Wrage did all or most of the RTI work for the observational study.

**Comment [rdh2]:** SUPPORT subcommittee needs to be here. ??should there be an author from each site???

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Postmenstrual age was calculated as gestational age at birth in weeks + days (using the best obstetrical estimate) plus the postnatal age in days at the time of each exam. For this observational study, "age of onset" is defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants who had Type 1 ROP on the initial exam or on an exam that was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams was defined as having an uncertain age of onset. Infants who did not complete exams according to the study schedule or had adjudicated ROP outcomes were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the age at which the ROP criteria were met in the first eye.

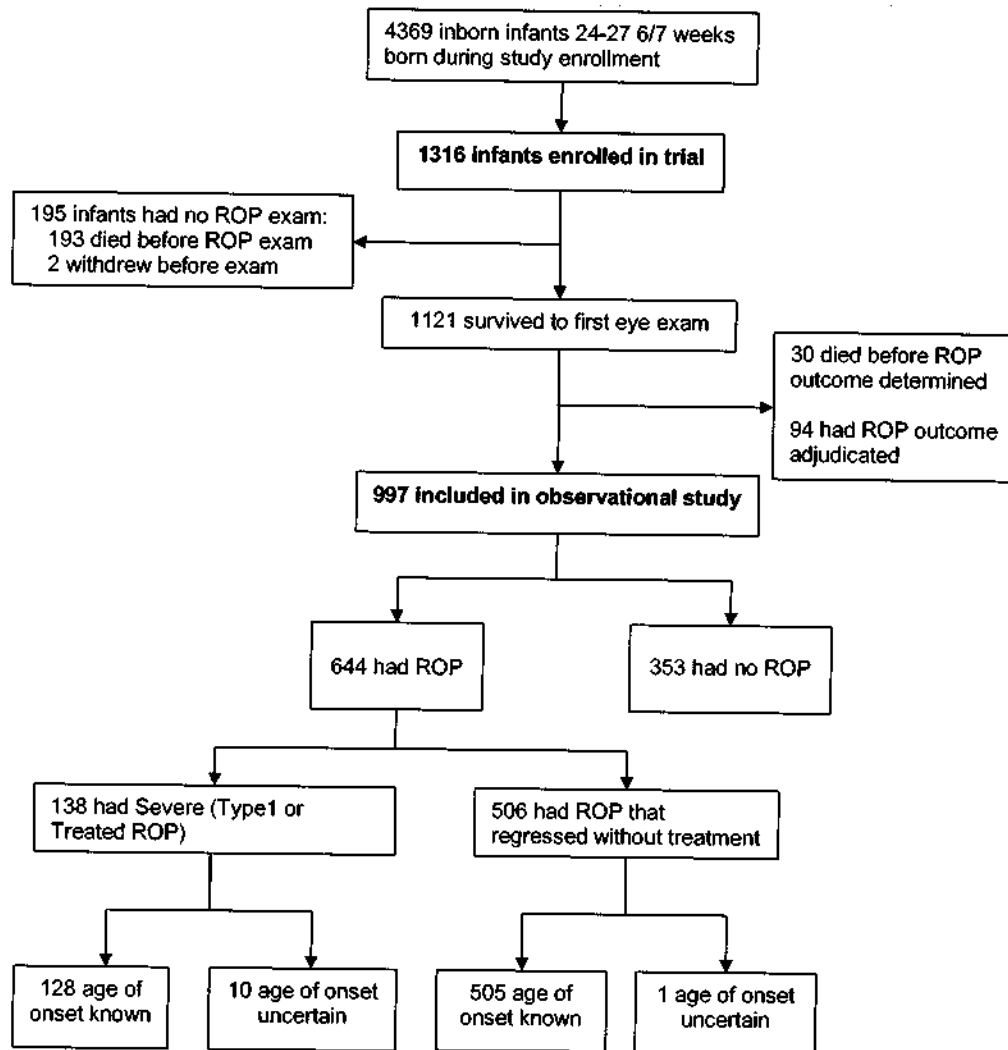
## Results

1316 infants were enrolled in the SUPPORT trial. See Figure 1.

Figure 1. Flow diagram of patient enrollment

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**Comment [rdh5]:** All were inborn



The baseline demographic characteristics of the infants are shown in Table 1.

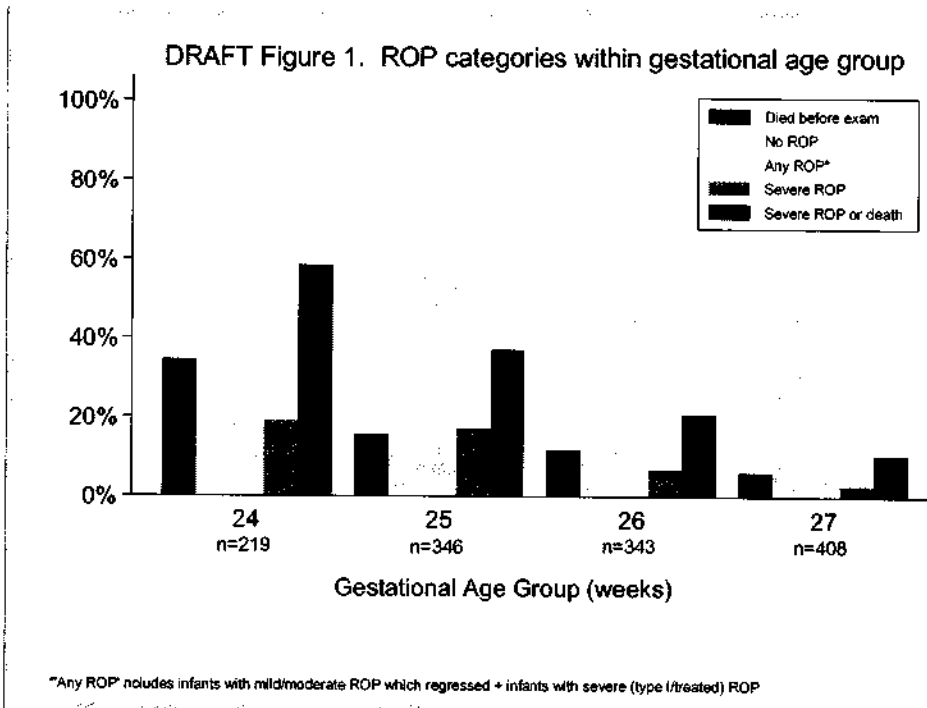
**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP Outcome)			
		All ROP Outcomes	No ROP	Any ROP <sup>1</sup>	Severe (Type 1 or Treated) ROP
<b>n</b>	<b>1316</b>	<b>997</b>	<b>353</b>	<b>644</b>	<b>138</b>
Gestational Age [mean (SD)]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.0 (1.0)	25.5 (0.9)
Birth Weight [mean (SD)]	830 (193)	849 (190)	943 (173)	798 (179)	708 (148)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37.2)	374 (37.5)	153 (43.3)	221 (34.3)	42 (30.4)
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<sup>1</sup> Includes infants with mild/moderate ROP which regressed (n=506) + infants with severe (type 1/treated) ROP (n=138).

As expected, the likelihood of surviving without ROP increased with each increasing week of completed gestation at birth (Figure 2).

**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



**Comment [KKA]** We'll need to get a revised figure without the legend at the top and without the footnote to submit to the journal. I think we should change the x-axis label to "Gestational Age (completed weeks)".

**Comment [rdh]** This graph says it all!!!

The incidence of previously reported risk factors for ROP are shown in Table 2.

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on Oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset Sepsis (+ culture) [(n (%))]	76 (21.5)	250 (38.8)	77 (55.8)
Fungal Sepsis [n (%)]	2/352 (0.6)	23/641 (3.6)	8/137 (5.8)
Grade 3-4 Intraventricular Hemorrhage or Periventricular Leukomalacia [n (%)]	29 (8.2)	98/643 (15.2)	29 (21.0)
Proven Necrotizing Enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent Ductus Arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

**Comment [rdh]** What about race and multiple gestation??

**Comment [KKA]** Yes, who are these denominators not the same?

**Comment [KKA]** Yes, why are these denominators not the same?

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3.

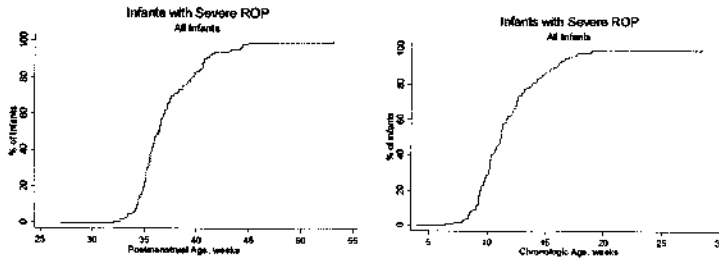
**Table 3. Postmenstrual and postnatal age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Postnatal Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	642	29.3	30.4	31.4	32.7	33.9	35.1	37.9	41.0	46.7	4.0	4.6	5.4	6.7	8.0	9.4	11.9	15.3	19.7
Type II/ ROP2 <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type I/Treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

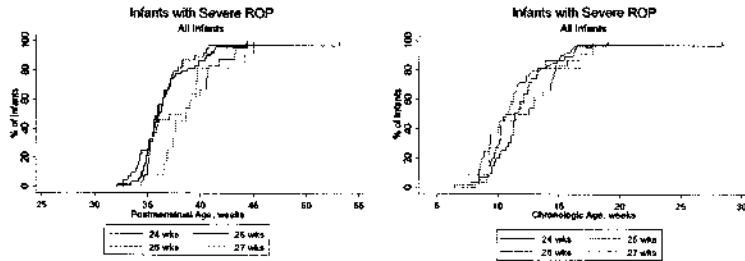
<sup>2</sup> Type II ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease (includes 85 infants who had ROP which regressed and 73 infants who developed severe ROP)

**Figure 3. Postmenstrual and postnatal age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

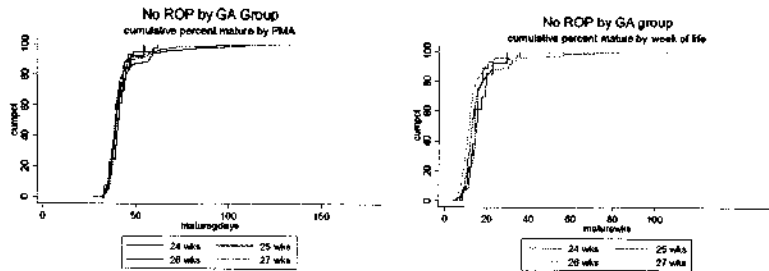
**Figure 4. Postmenstrual and postnatal age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**



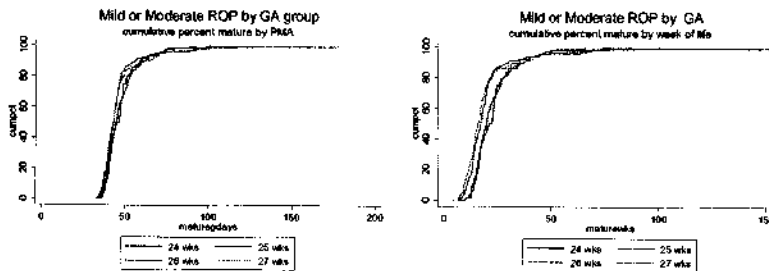
The age at which the retinal vessels became mature (to the ora serrata or two consecutive exams with vessels in zone III) are shown in Figure 5 for infants with no ROP and infants with mild or moderate ROP.

**Figure 5. Postmenstrual and postnatal age of mature vessels**

**No ROP**



**Mild/Moderate ROP**



I think it might be the case that the retinal vessels matured about a week later in infants with mild or moderate ROP as compared to infants with no ROP.



For clinicians caring for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Conclusion**

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore support the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity NICU; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### Discussion

In prior ROP natural history studies,<sup>2,3</sup> less mature infants developed treatable ROP at a later postnatal age than more mature infants, such that the cumulative incidence curves for each week of completed gestation overlapped when they are plotted by postmenstrual age. This relationship was not apparent in our data, possibly because the gestational age range of infants in our study was relatively narrow.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. The SUPPORT Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation who are at highest risk for ROP.

The SUPPORT Trial had an extremely high rate of antenatal steroid administration.

Maternal education was higher than the general NRN population; also more Caucasian women enrolled.

Race?? Is Black race still protective??

Multiples??

SGA??? – doesn't look like we looked at this but might be important.

Comment [KKA]: I need to look at the prior natural history studies again for other comparisons.

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<sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 117: 572-6, 2006. Erratum (screen gestational age of 30 weeks or less) in: Pediatrics 118: 1324, 2006.

<sup>2</sup> Jeffries A. Retinopathy of prematurity: Recommendations for screening. Paediatr Child Health 15: 667-674, 2010.

<sup>3</sup> Palmer EA et al. Incidence and early course of retinopathy of prematurity. Ophthalmology 98: 1628-1640, 1991.

<sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol 120: 1470-6, 2002.

<sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. Pediatrics 81: 697-706, 1988 and Arch Ophthalmol 106: 471-479, 1988.

<sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA et al. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. N Engl J Med 338: 1572-6, 1998.

<sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Ob Gynecol 196(2):147 e1-8, 2007.

<sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 102: 233-250, 2004.

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<sup>8</sup> Early Treatment for Retinopathy of Prematurity Cooperative Group. Then incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 116: 15-23, 2005.

<sup>10</sup> Austeng D, Kallen KBM, Hellstrom A et al. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 128: 1289-1294, 2010.

**From:** [Kennedy, Kathleen A](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)  
**Subject:** Draft of manuscript for SUPPORT ROP Secondary  
**Date:** Wednesday, March 14, 2012 8:09:45 PM  
**Attachments:** [ROP Natural History Study Manuscript.doc](#)

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I've attached a preliminary draft of the manuscript. If you could address the questions in the comments, particularly about the author list, and let me know if you're happy with what's in the tables and figures, revise as needed and then use this to start working on the poster. I haven't done much with the Discussion yet, but I think this is more than we need to proceed with the poster. Once I hear from you, I'll try to get Lisa working on some better looking figures. I'm not sure exactly how that works with RTI. I'm used to making my own.

I'm thinking we could send the manuscript to Pediatrics but, if you have other ideas, let me know.

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  
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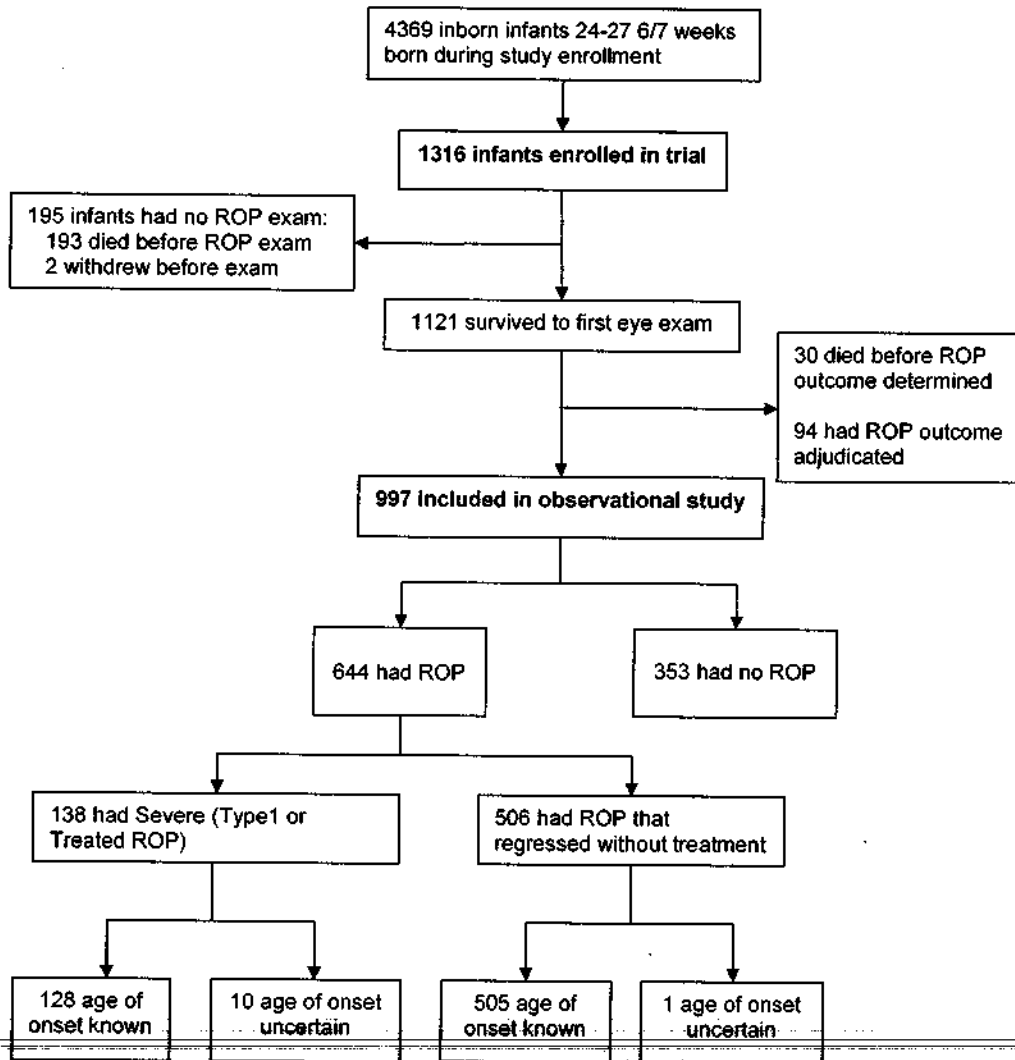
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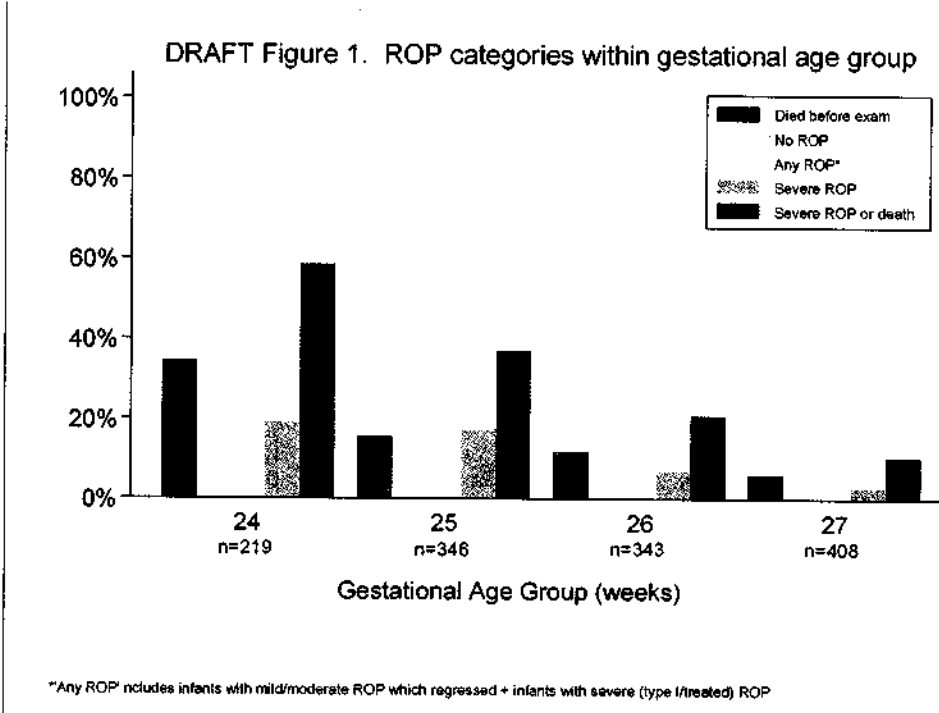
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**Figure 2. Risk of ROP by gestational age at birth (completed weeks) among all 1316 infants in SUPPORT Trial**



Comment [K104] We'll need to get a revised figure without this box at the top and without the footnote to submit to the journal. I think we should change the x-axis label to "Gestational Age (completed weeks)".

The incidence of previously reported risk factors for ROP are shown in Table 2.

**Table 2. Risk factors for ROP**

Risk Factor	No ROP	Any ROP <sup>1</sup>	Severe (Treated or Type 1) ROP
<b>n</b>	<b>353</b>	<b>644</b>	<b>138</b>
Days on Oxygen [mean (SD)]	38.8 (32.1)	67.5 (36.6)	88.2 (29.5)
Late-onset Sepsis (+ culture) [(n (%))]	76 (21.5)	250 (38.8)	77 (55.8)
Fungal Sepsis [n (%)]	2/352 (0.6)	23/641 (3.6)	8/137 (5.8)
Grade 3-4 Intraventricular Hemorrhage or Periventricular Leukomalacia [n (%)]	29 (8.2)	98/643 (15.2)	29 (21.0)
Proven Necrotizing Enterocolitis [n (%)]	20 (5.7)	72 (11.2)	18 (13.0)
Patent Ductus Arteriosus (medical or surgical) [n (%)]	122 (34.6)	366 (56.8)	95 (68.8)

Comment [K105] Lisa, why are these denominators not the same?

Comment [K106] Lisa, why are these denominators not the same?

<sup>1</sup> Includes infants with mild/moderate ROP that regressed (n=506) + infants with severe (type I/treated) ROP (n=138).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3 and Figure 3.

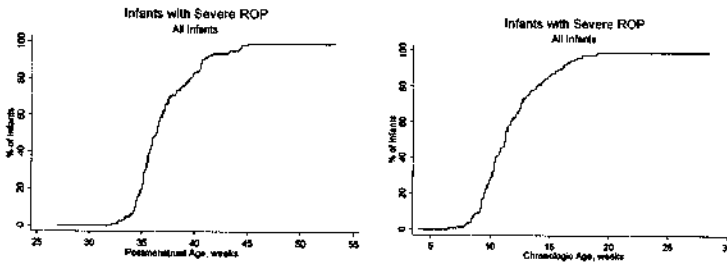
**Table 3. Postmenstrual and postnatal age of onset<sup>1</sup> of ROP (among infants with ROP age of onset determined)**

ROP type	n	Postmenstrual Age (weeks)									Postnatal Age (weeks)								
		min	1%	5%	25%	50%	75%	95%	99%	100%	min	1%	5%	25%	50%	75%	95%	99%	100%
Any ROP	642	29.3	30.4	31.4	32.7	33.9	35.1	37.9	41.0	46.7	4.0	4.6	5.4	6.7	8.0	9.4	11.9	15.3	19.7
Type II ROP <sup>2</sup>	158	29.3	29.7	31.1	34.3	36.1	38.1	40.4	46.4	46.9	4.4	4.6	6.3	8.7	10.8	12.6	15.0	21.0	22.7
Severe (Type I/Treated) ROP	128	32.1	32.7	33.9	35.1	36.4	38.6	43.3	45.0	53.1	6.4	7.1	8.4	9.8	11.3	13.1	17.0	19.0	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol.

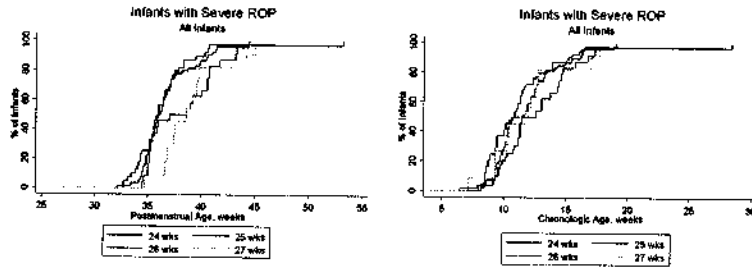
<sup>2</sup> Type II ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease (includes 85 infants who had ROP which regressed and 73 infants who developed severe ROP)

**Figure 3. Postmenstrual and postnatal age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined)**



These distributions were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so the combined data are shown here. The distributions for age of onset for each week of completed gestation at birth are shown in Figure 4.

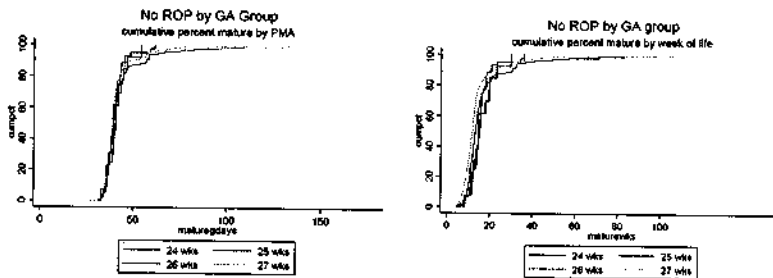
**Figure 4. Postmenstrual and postnatal age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth**



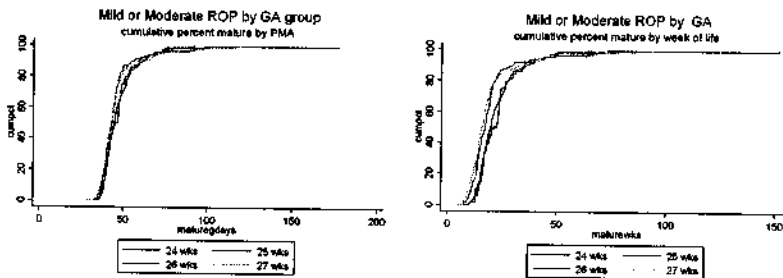
The age at which the retinal vessels became mature (to the ora serrate or two consecutive exams with vessels in zone III) are shown in Figure 5 for infants with no ROP and infants with mild or moderate ROP.

Figure 5. Postmenstrual and postnatal age of mature vessels

No ROP



Mild/Moderate ROP



I think it might be the case that the retinal vessels matured about a week later in infants with mild or moderate ROP as compared to infants with no ROP.

For clinicians caring for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4.

**Table 4. Timing of first exam meeting severe ROP criteria in relation to discharge and transfer**

Infants with Severe ROP N=138	First exam with severe ROP occurred <u>before</u> discharge to home n=124	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks (median, range)	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks (median, range)	42.1 (34.9-78.3)	38.3 (36.4-51.3)
First occurrence after back transfer to lower acuity hospital: n	1	4

To explore whether infants at high risk of developing severe ROP after discharge would be identified before discharge, we compared the worst pre-discharge exams for infants who did and did not develop severe ROP after discharge (among infants whose exams were not mature at the time of discharge).

**Table 5. ROP exam prior to discharge for infants with final ROP status determined after discharge home**

Worst exam findings prior to discharge either or both eyes:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=I and any stage ROP in any zone	10 (71.4%)	196 (37.2%)
Lowest zone of vessels=II and no ROP	2 (14.3%)	126 (23.9%)
Lowest zone of vessels=III and any stage ROP in any zone	1 (7.1%)	81 (15.4%)
Lowest zone of vessels=III and no ROP	0	121 (23%)
Plus disease	0	0
No exam prior to discharge	0	3
Unknown (missing or incomplete information on exam prior to discharge)	0	5

While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge.

**Conclusion**

Current screening guidelines, published in 2006,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III at  $\geq 35$  weeks or, for infants without prethreshold ROP, until 45 weeks postmenstrual age. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks. Only 1 infant developed severe ROP after 45 weeks. Our data therefore support the 2006 screening guidelines.

In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity NICU; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge.

### Discussion

In prior ROP natural history studies,<sup>3</sup> less mature infants developed treatable ROP at a later postnatal age than more mature infants, such that the cumulative incidence curves for each week of completed gestation overlapped when they are plotted by postmenstrual age. This relationship was not apparent in our data, possibly because the gestational age range of infants in our study was relatively narrow.

This observational study had several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants are included. The SUPPORT Trial inclusion criteria also did not allow us to generalize these data to infants < 24 weeks gestation.

Comment [K047]: I need to look at the prior natural history studies again for other comparisons.

<sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 117: 572-6, 2006. Erratum (screen gestational age of 30 weeks or less) in: *Pediatrics* 118: 1324, 2006.

<sup>2</sup> Jeffries A. Retinopathy of prematurity: Recommendations for screening. *Paediatr Child Health* 15: 667-674, 2010.

<sup>3</sup> Palmer EA et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 98: 1628-1640, 1991.

<sup>4</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 120: 1470-6, 2002.

<sup>5</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 81: 697-706, 1988 and *Arch Ophthalmol* 106: 471-479, 1988.

<sup>6</sup> Reynolds JD, Hardy RJ, Kennedy KA et al. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 338: 1572-6, 1998.

<sup>7</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 196(2):147 e1-8, 2007.

<sup>8</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 102: 233-250, 2004.

<sup>9</sup> Early Treatment for Retinopathy of Prematurity Cooperative Group. Then incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. *Pediatrics* 116: 15-23, 2005.

<sup>10</sup> Austeng D, Kallen KBM, Hellstrom A et al. Natural history of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol* 128: 1289-1294, 2010.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Poe, Grace \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)  
**Date:** Thursday, March 08, 2012 12:53:00 PM  
**Attachments:** [Tufts Follow up Study IRB Approval 12,2012.pdf](#)

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For the official grant file  
Rose

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**From:** Testa, Veronika [<mailto:vtesta@tuftsmedicalcenter.org>]  
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**To:** Higgins, Rosemary (NIH/NICHD) [E]; McGowan, Elisabeth C  
**Cc:** Gonsalves, John; Peterson, Theresa  
**Subject:** FW: Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hello Rose,

Here is the IRB approval for the NRN Follow up Study.

Back on January 24<sup>th</sup> and February 14<sup>th</sup> I had sent you a total of 4 emails containing various IRB approvals.

Please let me know that you had received these emails. If not, I'd be happy to resend them to you for your files.

Best regards,

*Veronika*

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**From:** Testa, Veronika  
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